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Antiviral Therapeutics for Pediatric Primary and Acute Care

Ashley Gyura, DNP, CPNP-PC

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Speaker Disclosure

- I have nothing to disclose

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Learning Objectives

- Explore the current landscape of antiviral drugs available for pediatric populations, emphasizing their safety, efficacy, and age-specific dosing guidelines
- Review common viral infections in pediatric primary and acute care, identifying key targets for antiviral interventions and discussing evidence-based treatment approaches
- Evaluate emerging trends and future directions in antiviral therapeutics for pediatric populations

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Introduction to antiviral medications

- Iododeoxyuridine (IDU) the first effective antiviral agent (1963)
  - used topically to treat herpes simplex keratitis
- Amantadine (1966)
  - First licensed systemic antiviral, for treatment of Influenza A
- Ease symptoms, shorten duration of illness

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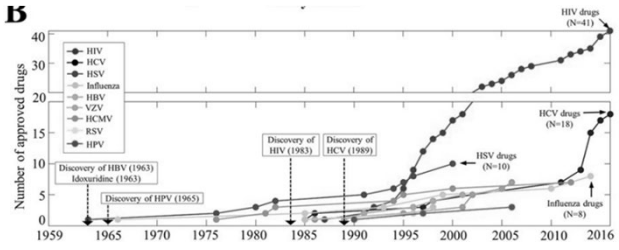
Timeline of approved antiviral drugs, 1963-2016



[1]De Clercq & Li, 2016

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Antibacterials vs antivirals

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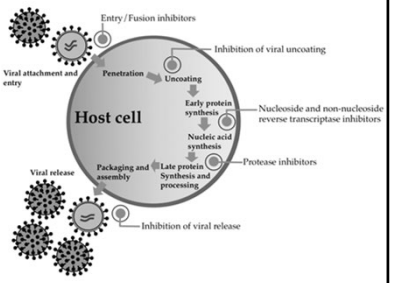
Mechanism of action

- Inhibit viral reproduction by interfering with virus life cycle
- Can target viral or host factors



[2] Suwannarach et al., 2020

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Influenza

- Antiviral therapy can be considered for healthy, non-high-risk outpatients with confirmed or suspected influenza if initiated within 48 hours of illness onset
  - Oseltamivir
  - Baloxavir marboxil
- Antiviral therapy is recommended for patients with confirmed or suspected influenza who are:
  - Hospitalized: oral/enteric oseltamivir
  - Non-hospitalized with complicated or progressive illness of any duration: oral oseltamivir
  - Outpatients at high risk for influenza complications: oral oseltamivir or oral baloxavir

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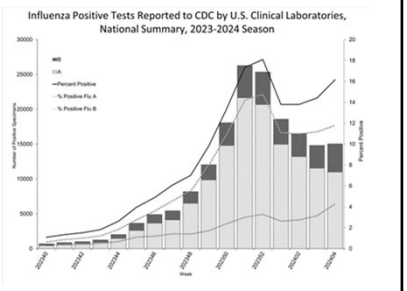
Influenza

- Zanamivir (inhaled, ≥7 years) and Peramivir (intravenous, ≥ 6 months) also FDA approved and have demonstrated efficacy but rarely prescribed in the U.S.
- No evidence of resistance among circulating seasonal influenza A and B viruses for 2023 -2024 seasons



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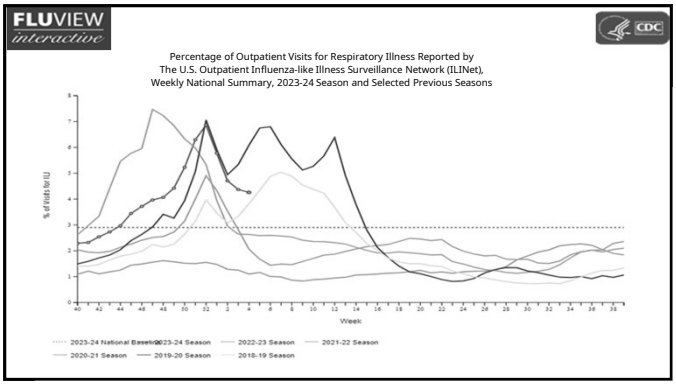

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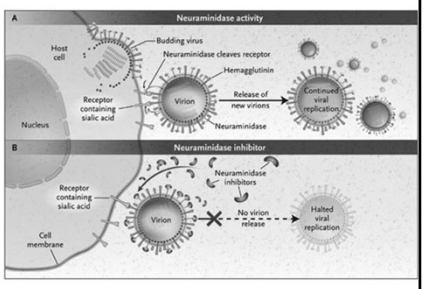
Influenza

- Panel A shows the action of neuraminidase in the continued replication of virions in influenza infection
- The replication is blocked by neuraminidase inhibitors (Panel B), which prevent virions from being released from the surface of infected cells



[15]Moscona, 2005

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Oseltamivir

- Neuraminidase inhibitor
  - Blocks release of influenza virus from infected cells
- Pooled meta-analysis[3] of 5 RCTs in children (outpatients)
  - Reduced illness duration by 18 hours overall and by 30 hours in children without asthma
  - Reduced risk of otitis media by 34%
- Can use for all ages, pregnant woman, recommended for immunocompromised patients

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Oseltamivir Dosing

	Treatment (x5 days)	Prophylaxis
Infants ≤ 8 months	3 mg/kg/dose twice daily	3 mg/kg/ dose once daily
Infants ≥ 9 months	3.5 mg/kg/dose twice daily	3.5 mg/kg/dose once daily
≤ 15 kg	30 mg twice daily	30 mg once daily
>15-23 kg	45mg twice daily	45 mg once daily
>23-40 kg	60 mg twice daily	60 mg once daily
>40 kg	75 mg twice daily	75 mg once daily

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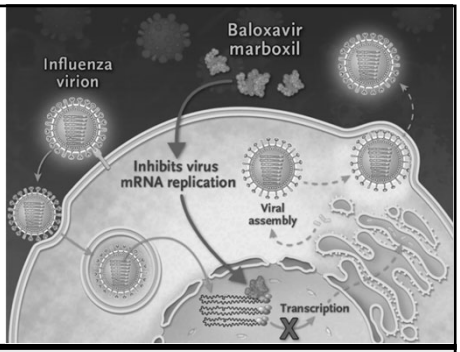
Baloxavir marboxil



[5] Hayden et al, 2018

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Baloxavir marboxil

- Cap-dependent endonuclease inhibitor
  - Inhibits influenza viral replication
- Similar clinical benefit to oseltamivir and significant clinical benefit versus placebo when started within 48 hours after illness onset
  - RCT in non-high-risk children[4, 5] (aged 1 to <12 yrs)
    - Single-dose baloxavir had similar median time to alleviation of influenza signs and symptoms versus 5 days of oseltamivir
  - RCTs in adolescents and adults[6] (aged ≥12 yrs)
    - Single-dose baloxavir significantly reduced illness duration by a median of 26.5 hours vs. placebo in non-high-risk persons
    - Median time to alleviation of symptoms was similar for baloxavir and oseltamivir
    - Baloxavir significantly reduced influenza viral RNA levels at 24 hours, and reduced infectious virus detection versus oseltamivir

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Baloxavir marboxil

- ≥ 5 years (otherwise healthy) or ≥12 years (high-risk)
- Dosing
  - <20 kg: 2 mg/kg PO once as a single dose
  - 20 to <80 kg: 40 mg PO once as a single dose
  - ≥80 kg: Oral: 80 mg PO once as a single dose
- Not recommended for use during pregnancy or in immunocompromised patients

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Sars Cov-2

- Antiviral therapy is recommended for individuals with mild-to-moderate COVID-19 with ≥ 1 risk factor for progression to severe disease
  - Determination based on the provider's assessment of the individual patient
  - https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html
- Preferred therapies
  - Nirmatrelvir/ritonavir (Paxlovid)
  - Remdesivir
- Molnupiravir also available for ≥18 years and only if preferred medications unavailable

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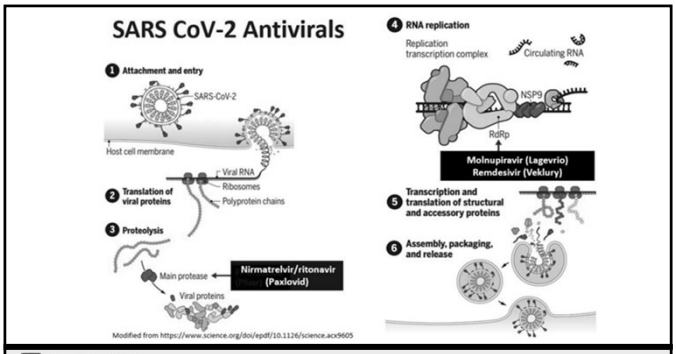

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Nirmatrelvir/ritonavir (Paxlovid)

- Nirmatrelvir (SARS CoV-2 main protease inhibitor) +Ritonavir (HIV-1 protease inhibitor and CYP3A inhibitor- "booster")
- 83-88% relative risk reduction in mortality, hospitalization[7]
- ≥12 years and ≥40 kg (EUA) within 5 days of symptom onset
  - FDA approved for ≥18 years
- Dosing: nirmatrelvir 300 mg and ritonavir 100 mg PO BID x5 days
  - eGFR 30 to <60 mL/minute: Nirmatrelvir 150 mg and ritonavir 100 mg, administered together twice daily for 5 days
- Drug-drug interactions, not recommended in severe liver disease or eGFR<30 mL/minute

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Liverpool COVID-19 Drug Interaction Database

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Nirmatrelvir/ritonavir Resistance

- Mechanism[8]
  - Alterations at the S1 and S4 subsites substantially decrease the level of inhibitor binding
  - Alterations at the S2 and S4′ subsites increase protease activity
  - The virus suffers when it develops resistance, unlikely to see resistant variants spread widely
- Clinical correlates of resistance
  - Immunocompromised people whose infections may persist for months
    - patients may initially experience a decrease in viral load, but as these mutations arise, the virus can return unimpeded by the drug

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Remdesivir

- SARS-CoV-2 nucleotide analog RNA polymerase inhibitor
- 87% relative risk reduction in mortality, hospitalization [9]
- Approved for patients ≥ 28 days and ≥ 3 kg
- Dosing (intravenous)
  - ≥ 3kg up to 40 kg: 5mg/kg on Day 1 followed by 2.5 mg/kg daily from day 2
  - ≥40 kg: 200 mg on Day 1 followed by 100 mg daily from Day 2
  - Duration
    - Non-hospitalized patients: 3 days, start within 7 days of symptom onset
    - Hospitalized patients: 5-10 days depending on severity
- No renal adjustments, few to no drug interactions

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Human Herpesviruses

Alpha-herpesvirinae	Herpes simplex virus types 1 and 2 (HSV1, HSV2)	Mucocutaneous ulcerative disease, keratitis, encephalitis, and severe neonatal disease
	Varicella Zoster Virus (VZV)	Varicella (chickenpox) as the primary infection and shingles as the reactivated infection
Betaherpesvirinae	Human cytomegalovirus (CMV)	Congenital infection, immunocompromised
	Human herpesvirus 6 (HHV6)	Roseola, posttransplant complications- encephalitis and interstitial pneumonitis
	Human herpesvirus 7 (HHV7)	Posttransplant complications- encephalitis and interstitial pneumonitis
Gammaherpesvirinae	Epstein-Barr virus (EBV)	Infectious mononucleosis, multiple malignancies, posttransplant lymphoproliferative disorders
	Kaposi's sarcoma-associated herpesvirus (KSHV)	Kaposi sarcoma and 2 lymphoproliferative disorders

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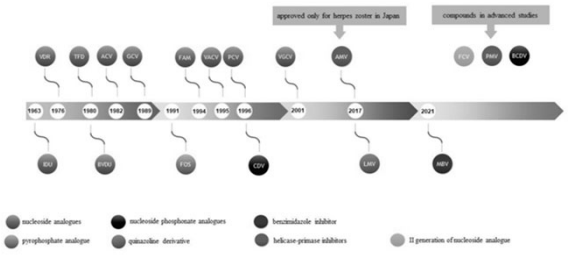
Antiviral drugs approved for use in herpes infections in humans



[10] Majewska & Mlynarczyk-Bonikowska, 2022

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Activity of Nucleoside Analogues against Herpesviruses

TABLE 295-4

Relative in vitro Activity of Nucleoside Analogues Against Herpesviruses

Virus	Acyclovir	Penciclovir	Vidarabine	Foscarnet	Ganciclovir
HSV-1	+++	++	++	++	+++
HSV-2	+++	++	++	++	+++
VZV	+++	+++	++	++	++
CMV	+/–	+/–	+/–	++	++
EBV	+	–	–	+	++

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; VZV, varicella-zoster virus; +++, high degree of activity; ++, moderate degree of activity; +, minimal degree of activity; +/–, minimal to no activity; –, no useful activity.

[11] Long, 2023

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Acyclovir and Valacyclovir

- Nucleoside DNA polymerase inhibitor
  - Valacyclovir converts to acyclovir in vivo with first-pass intestinal and hepatic metabolism
- Only 15-30% of oral acyclovir is absorbed
  - Absorption of valacyclovir is 3-5x greater than acyclovir
- Generally favorable side effect profile
  - Most serious side effect is neurotoxicity
- For long term suppressive therapy, monitor BUN, SCr, liver enzymes, CBC monthly

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Acyclovir and Valacyclovir

- Effective for the treatment of infections caused by HSV and VZV in immunocompetent and immunocompromised
  - IV vs oral equally efficacious, topical has less benefit
  - Valacyclovir is equally effective to acyclovir with advantage of less frequent dosing
- Treatment indicated for life-threatening infections (HSV encephalitis, neonatal HSV infections, and VZV infections in ICH), mucocutaneous HSV infections in ICH, disseminated HSV and VZV infections, symptomatic primary genital HSV

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Acyclovir and Valacyclovir

- Less dramatic for healthy patients with herpes labialis, recurrent genital herpes, varicella, and herpes zoster
- Can still have significant benefit in symptom reduction!
  - Shorten the duration of illness and viral shedding in primary or recurrent genital infection,
  - Decrease the frequency of recurrences if using as suppressive therapy for genital infection
  - Small benefit for primary gingivostomatitis or recurrent herpes labialis

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Acyclovir Dosing (HSV)

Neonatal herpes simplex virus (HSV) infection	IV	Birth to ≤4 mo	Tx: 60 mg/kg per day, in 3 divided doses for 14 days (SEM disease) or 21 days (CNS or Disseminated disease) (durations >21 days are necessary if CSF PCR remains positive near end of treatment course)
	Oral	2 wk to 8 mo	Oral suppressive dosing following completion of IV treatment; dosing: 300 mg/m^2, 3 times per day for 6 mo
Genital HSV infection: first episode	Oral	≥12 y	1000–1200 mg/day, in 3–5 divided doses for 7–10 days.
			Oral pediatric dose: 40–80 mg/kg per day, divided in 3–4 doses (maximum 1000 mg/day)
	IV	≥12 y	15 mg/kg per day, in 3 divided doses for 5–7 days
Genital HSV infection: recurrence	Oral	≥12 y	1000 mg in 5 divided doses for 5 days, or 1600 mg in 2 divided doses for 5 days, or 2400 mg in 3 divided doses for 2 days
Chronic suppressive therapy for recurrent genital and cutaneous (ocular) HSV episodes	Oral	≥12 y	800 mg/day, in 2 divided doses for as long as 12 continuous months; decisions to continue suppressive therapy should be revisited annually
Recurrent herpes labialis	Oral	All ages	80 mg/kg per day, in 4 divided doses, for 5 to 7 days (max 3200 mg/day)

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Valacyclovir Dosing (HSV)

Genital HSV infection, first episode	Oral	Adolescent dose	2 g/day, in 2 divided doses for 10 days (5–14 days in HIV infected patients); longer duration if lesions incompletely healed
		Children	<45 kg: 40 mg/kg/day in 2 divided doses ≥45 kg: 2 g/day, in 2 divided doses 7–10 days of treatment
Episodic recurrent genital HSV infection	Oral	Adolescent dose	1 g/day, in 2 divided doses for 3 days; HIV-infected patients should receive 2 g/day for 5–14 days
Daily suppressive therapy for recurrent genital HSV infection	Oral	Adolescent	500 mg or 1 g, once daily (the lower dose is less effective if frequent recurrences (eg, ≥10/y); HIV: 500 mg twice daily for indefinite duration; acyclovir for young children
Recurrent herpes labialis	Oral	≥12 y	4 g/day, in 2 divided doses for 1 day

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Acyclovir Dosing (VZV)

Varicella (chickenpox)	Oral	All ages	20 mg/kg/dose 4 times daily for 5 days (Max 3,200/day)
	IV	All ages	10 mg/kg/dose every 8 hours
Herpes Zoster (shingles)	Oral	≥12 y	800 mg q4h (5 doses per day) for 5 to 7 days
	IV	<2 y	10 mg/kg/dose q8h for 7-10 days
		≥ 2 y	500 mg/m2/dose q8H for 7-10 days

Valacyclovir Dosing (VZV)

Varicella (chickenpox)	Oral	≥3 months	20 mg/kg/dose q8H for 5 days (max 1gr/dose)
Herpes Zoster (shingles)	Oral	≥2 y	20 mg/kg/dose q8H (max 1 gr/dose) for 7-10 days or untile lesions crusted over

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Acyclovir and Valacyclovir Resistance

- Mechanism
  - Usually due to mutations in thymidine kinase gene, resulting in absent or altered thymidine kinase; rarely due to mutation in DNA polymerase gene
- Clinical correlates of resistance
  - Persistent or progressive infection due to resistant strains isolated from patients with severely compromised immunity (e.g., bone marrow transplant recipients, those with AIDS)
  - Isolates of HSV from healthy people described in those receiving long-term suppressive therapy
- Alternative – Foscarnet

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Famciclovir and Topical Penciclovir

- Nucleoside analogue
  - Famciclovir is the inactive prodrug of penciclovir
  - Penciclovir is approximately 100-fold less potent than acyclovir in inhibiting herpesvirus DNA polymerase activity but remains effective because of high intracellular concentrations and long half-life
- Overall good efficacy in reducing time to crusting, well tolerated, but generally only recommended for ≥ 12 years of age d/t lack of data
- Topical penciclovir for the treatment of recurrent herpes labialis reduces the time to healing and the duration of pain by about one half of a day
  - Apply ASAP, preferably during prodromal phase, and continue q2 hours during waking hours for 4 days

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Famciclovir Dosing

Genital HSV infection, recurrent episodes	Oral	Adult dose, adolescents	Immunocompetent: 2000 mg/day, in 2 divided doses for 1 day; CDC regimens featuring smaller incremental doses and greater number of treatment days are available. HIV-infected patients: 1000 mg, in 2 divided doses for 7 days (CDC and NIH guidelines provide range of 5–14 days)
Daily suppressive therapy	Oral	Adult dose, adolescents and children	Immunocompetent: 500 mg/day, in 2 divided doses for 1 y, then reassess for recurrence of HSV infection; HIV: 1000 mg/day, in 2 divided doses for minimum of 1 y; same dosage for children and adolescents old enough to receive adult doses
Recurrent herpes labialis	Oral	Adult dose, adolescents	Immunocompetent: 1500 mg as a single dose HIV-infected patients: 1000 mg/day, in 2 divided doses for 7 days (CDC and NIH guidelines provide range of 5–10 days); comparatively slower resolution seen in adolescent patients
Herpes zoster	Oral	Adult dose, adolescents	1500 mg/day, in 3 divided doses for 7 days (7–10 days in HIV patients with localized lesions, longer if lesions resolving slowly, or to complete 10–14 days total course with initial IV acyclovir if more severe skin or visceral infection)

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Famciclovir and Topical Penciclovir Resistance

- Mechanism
  - Usually due to mutations in thymidine kinase gene, resulting in absent or altered thymidine kinase; also can result from mutation in DNA polymerase gene
- Clinical correlates of resistance
  - Persistent or progressive infection due to resistant strains isolated from patients with severely compromised immunity (e.g., bone marrow transplant recipients those with AIDS)
  - Isolates of HSV from healthy people described in those receiving long-term suppressive therapy
- Alternatives- Foscarnet, Acyclovir

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Cytomegalovirus (CMV)

- Symptomatic* congenital CMV (cCMV) disease
  - Improved audiologic and neurodevelopmental outcomes at 2 years of age when treated with oral valganciclovir for 6 months*
  - Currently, treatment is recommended to start by 28 days of age*
- Treatment also recommended for “life and sight” threatening infections in immunocompromised
  - Disseminated CMV and retinitis
  - Prophylaxis of CMV in high-risk host (eg, post-transplant)
  - Preemptive therapy of CMV in high-risk host

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Ganciclovir and Valganciclovir

- Nucleoside analogue
  - Greatest in vitro activity is against CMV
  - Valgancyclovir is an L-valine ester prodrug of ganciclovir
- cCMV dosing
  - IV ganciclovir 6 mg/kg/dose every 12 hours if c/o poor gut absorption
    - Weight adjust monthly, ideally transition to valganciclovir when possible
    - Monitor CBC with differential weekly for 6 weeks, at 8 weeks, then monthly; ALT monthly
  - Oral valganciclovir 16 mg/kg/dose every 12 hours for 6 months
    - Weight adjust monthly
    - Monitor CBC with differential weekly for 6 weeks, at 8 weeks, then monthly; ALT and sCr monthly
    - Take with food- increases absorption by 30%

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Ganciclovir Toxicity

- Significant myelosuppression with dose-related neutropenia
  - Incidence during a 2-week course is about 40%
  - Phase III RCT of ganciclovir therapy in neonates with cCMV, 2/3 of patients developed neutropenia and 1/2 required dose modification
- In preclinical test systems, ganciclovir is mutagenic, carcinogenic, and teratogenic, and causes irreversible reproductive toxicity in animals
  - BLACK BOX WARNINGS
- Valgancyclovir can have neutropenia but is less prevalent than with ganciclovir

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Ganciclovir and Valganciclovir Resistance

- Mechanism
  - Decreased intracellular phosphorylation due to mutations in the CMV ul97 gene with decreased expression of CMV phosphotransferase enzymes or mutation in viral DNA polymerase gene [12]
- Clinical correlates of resistance
  - Responsible for severe, rapidly progressive infection in patients with severely compromised immunity (e.g., bone marrow transplant recipients, those with AIDS)
- Alternative – Foscarnet, cidofovir

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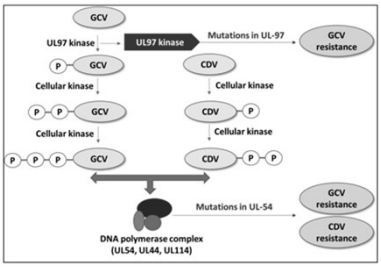
Mechanism of CMV resistance



[12] Panda et al, 2023

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HIV for perinatally exposed newborns

- Zidovudine (ZDV)
  - Minimal toxicity, primarily transient hematologic toxicity (anemia), generally resolves by 12 weeks of age
- Lamivudine (3TC), Nevirapine (NVP)
  - ZDV+3TC+NVP - Neonatal hematologic toxicity is common (anemia, neutropenia)
- Raltegravir (RAL)
  - Only for infants ≥ 37 weeks gestation weighing ≥2 kg
  - Hyperbilirubinemia observed otherwise safe and well tolerated

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All newborns perinatally exposed to HIV should receive appropriate antiretrovirals ASAP, preferably within 6 hours

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HIV for perinatally exposed newborns

Risk Category	Medication	Duration
Low risk of perinatal HIV transmission	ZDV	Birth to 2 to 6 weeks depending on gestational age and other factors*
High Risk of Perinatal HIV Transmission *Or* Presumed newborn exposure	ZDV, 3TC, and NVP *or* ZDV, 3TC, and RAL	Birth to 2 to 6 weeks For 3 drug regimen- ZDV will be continued to 6 weeks regardless
Newborn with HIV	ZDV, 3TC, and NVP *or* ZDV, 3TC, and RAL	-

*This table is oversimplified, for more details on categories and definitions please see guideline [13]

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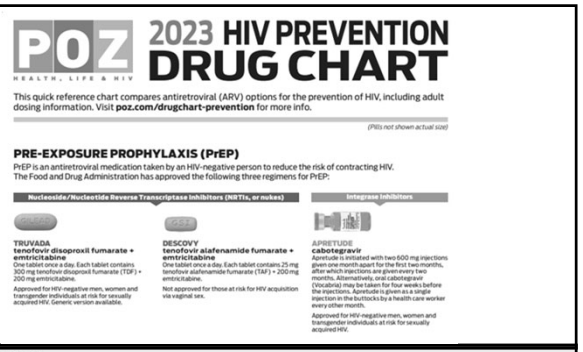

POZ HEALTH, LIFE & HIV

2023 HIV PREVENTION DRUG CHART

This quick reference chart compares antiretroviral (ARV) options for the prevention of HIV, including adult dosing information. Visit **poz.com/drugchart-prevention** for more info.

(Pills not shown actual size)

PRE-EXPOSURE PROPHYLAXIS (PrEP)

PrEP is an antiretroviral medication taken by an HIV-negative person to reduce the risk of contracting HIV. The Food and Drug Administration has approved the following three regimens for PrEP:

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs, or nukes)

TRUVADA
tenofovir disoproxil fumarate + emtricitabine
One tablet once a day. Each tablet contains 300 mg tenofovir disoproxil fumarate (TDF) + 200 mg emtricitabine.
Approved for HIV-negative men, women and transgender individuals at risk for sexually acquired HIV. Generic version available.

DESCOVY
tenofovir alafenamide fumarate + emtricitabine
One tablet once a day. Each tablet contains 25 mg tenofovir alafenamide fumarate (TAF) + 200 mg emtricitabine.
Not approved for those at risk for HIV acquisition via vaginal sex.

Integrase Inhibitors

APRETUDE
cabotegravir
Apretude is initiated with two 600 mg injections given one month apart for the first two months, after which injections are given every two months. Alternatively, oral cabotegravir (Vocabria) may be taken for four weeks before the injections. Apretude is given as a single injection in the buttocks by a health care worker every other month.
Approved for HIV-negative men, women and transgender individuals at risk for sexually acquired HIV.

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POST-EXPOSURE PROPHYLAXIS (PEP)

PEP involves taking a short course of ARV drugs, usually for a month, after a high-risk exposure. For maximum effectiveness, PEP should be started immediately—and no more than 72 hours—after possible exposure. The Centers for Disease Control and Prevention recommends the following preferred HIV PEP regimen:

Alternative PEP regimens can be found online in the CDC's PEP Guidelines.

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Hepatitis B

- Antiviral therapy recommended in HBeAg-positive children (ages 2 to <18 years) with both elevated ALT and measurable HBV DNA levels, with the goal of achieving sustained HBeAg seroconversion
  - Entecavir (2y+)
    - Lower risk of viral resistance compared to lamivudine
    - Dosage based on weight and treatment naiveté
    - HIV status (prior to initiation of therapy); periodic renal and hepatic function tests, lactic acid if concerned
  - Tenofovir dipovoxil fumarate (12y+)
  - Interferon-α-2b (1y+) x24 weeks
  - Lamivudine (2y+)
    - Nonpreferred

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Hepatitis C

HCV Antiviral Therapy for Children and Adolescents,

Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

Recommended regimens listed by pangenotypic, evidence level and alphabetically for Treatment-Naive or Interferon-Experienced Children and Adolescents Without Cirrhosis or With Compensated Cirrhosis[a]		
RECOMMENDED	DURATION	RATING
Combination of glecaprevir/pibrentasvir (weight-based dosing; see Table 1) for children aged ≥ 3 with any genotype[b]	8 weeks	I, B
Combination of sofosbuvir/velpatasvir (weight-based dosing; see Table 2) for children ≥3 of age with any genotype	12 weeks	I, B
Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 3) for children aged ≥3 years with genotype 1, 4, 5, or 6	12 weeks	I, B

[a] Child-Pugh A.
[b] A longer duration of therapy (ie, 16 weeks) may be needed for genotype 3 interferon-experienced patients.

[14] Bhattacharya et al., 2023

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Future antiviral agents

- As viral pathogenesis and mechanisms of viral replication are further understood, novel targets for antivirals can be developed
  - Can then understand how viruses develop resistance and provide a target for design of the next generation of antivirals
- Although each virus is unique, similarities can be identified within and across viral families
  - For example, with the herpesvirus family, analogous proteins and replication pathways have been identified

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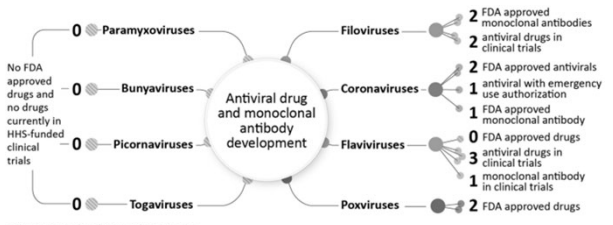
Future pandemics?



FDA = U.S. Food and Drug Administration
HHS = Department of Health and Human Services

Source: GAO analysis of HHS and other documentation; GAO (icons). | GAO-23-105847

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2023 Report: GAO Policy Options for Pandemic Preparedness

- Create a strategy to focus on developing diverse antiviral drugs to respond to pandemics caused by the most dangerous pathogens
- Assign to a new or existing entity the authority to lead, implement, and be accountable for identifying and developing antiviral drugs for pathogens or pathogen families of greatest risk
- Implement economic incentives to develop antiviral drug candidates and spur new drug-development technologies
  - New technologies spurred by investment in pandemic antiviral drugs may allow for the treatment of alternative or nonpandemic infectious diseases (e.g. remdesivir)

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Questions?

Ashley.Gyura@childrensmn.org

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