Antiviral Drugs in Children and Adolescents

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Abstract

This article on antiviral drugs is aimed at providing recommendations for treatment of selected viral infections in pediatric population. This article will discuss commonly used antivirals, their pharmacokinetics, pharmacodynamics, mechanisms of action, spectrum of activity, and toxicities. Biologics such as interferons will also be discussed.

Keywords: Antiviral drugs, Acyclovir, CMV infections, Hepatitis, Herpes virus, HIV, RSV infections

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Introduction

Antiviral drugs are used in children to treat herpetic illnesses, viral respiratory ailments, viral hepatitis, and HIV.

The drugs used and their antiviral spectrums are as follows:

- Acyclovir: HSV-1, HSV-2, VZV—chicken pox, herpes zoster
- Ganciclovir/cidofovir: cytomegalovirus (CMV)
- Famciclovir: herpes genitalis and herpes zoster—famciclovir is a prodrug of penciclovir—has greatest bioavailability (OD/BD dose)
- Foscarnet: HSV, VZV, CMV, HIV
- Penciclovir: herpes labialis, CMV—poor bioavailability—only for topical use
- Trifluridine: herpetic keratoconjunctivitis

Acyclovir

Acyclovir in Herpes Labialis with Gingivostomatitis[1]

Herpetic gingivostomatitis may be treated with oral acyclovir; the dose recommended for babies 1 month to 2 years is 100 mg and for 2–18 years 200 mg for 7 days (five times a day) within 4 days of onset.

There is limited evidence on utility of oral acyclovir as compared to placebo. Published data suggest that it reduces duration of pain and fastens time to healing for an initial episode of herpes labialis. Till date, there is no evidence [randomized control trial (RCT)] comparing topical antiviral versus placebo or no treatment. Research in this area is hampered by the fact that it is difficult to suspect and diagnose the first episode.

Currently, there are no recommendations on prophylactic oral antivirals with respect to timing and duration of treatment that reduce the frequency and intensity of episodes compared with placebo. Acyclovir, famciclovir, and valaciclovir may reduce the duration of symptoms and the time to recovery in repeated episodes of herpes labialis. Topical antiviral agents that target pain reduction[2] and healing time in recurrent attacks are not of clinical relevance.

There is some evidence that the duration of illness during recurrences may be shortened in adolescents with the use of valacyclovir (2,000 mg twice a day PO for 1 day), acyclovir (200–400 mg five times daily PO for 5 days), or famciclovir (1,500 mg once daily PO for 1 day).

Acyclovir (400 mg twice a day PO) or valacyclovir (500 mg once daily PO) may be tried for long-term prophylaxis for frequent or severe recurrences.

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Herpetic Keratoconjunctivitis[3]

Application of 1 cm of the acyclovir ointment five times daily, till at least 3 days after complete healing, is the treatment of choice. Topical trifluorothymidine, vidarabine, idoxuridine, and ganciclovir are also useful. Interferon monotherapy has some effect in treating dendritic epithelial keratitis but is not better than other antiviral agents. There are studies that suggest that a combined interferon-nucleoside therapy improves healing.

Recurrent keratitis and amblyopia is a concern in children with HSV. Systemic antiviral prophylaxis for a year may aid to prevent such consequences (1 year acyclovir/valaciclovir).

In view of the pathogenesis in HSV keratitis, which is an immune-mediated phenomenon, there is a valid role of immunoregulatory drugs like cyclosporine.

Herpes Simplex Encephalitis[4]

Early administration of a high-dose IV acyclovir has the best clinical outcomes.

In view of increased frequency of relapses in the newborn period, the current recommendation reiterates the need for 21 days of high-dose IV acyclovir for neonatal HSE.[5] IV acyclovir infusion—neonate—3 months 20 mg/kg 8th hourly for 21 days; 3 months–12 years 250 mg/m^2 8th hourly for 21 days.

At present, there is no common consensus to repeat a lumbar puncture (LP) at the end of treatment of 3 weeks. However, if done so and if the cerebrospinal fluid (CSF) polymerase chain reaction (PCR) is negative it ensures better outcomes. Double the dose is recommended in immunocompromised neonates and children.

Genital Herpes[6]

Genital herpes is a recurrent and incurable viral disease. The severity and duration of subsequent episodes are reduced by the treatment

of the first episode. This does not alter the course of subsequent recurrent infections. Adolescent—give acyclovir at 400 mg tid; child—10–20 mg/kg/dose qid for 7–10 days—extended if healing incomplete. Topical acyclovir has negligible or no clinical benefit.

For episodic therapy for recurrent genital herpes—adolescent 800 mg tid × 2 days (start within 1st day of onset or in prodrome). In HIV patients, imiquimod may be tried in episodic treatment of lesions thought to be acyclovir-resistant or nonresponsive. Valacyclovir and famciclovir are also effective but clinical experience is lacking.

Herpes simplex prophylaxis in the immunocompromised.

Oral acyclovir—child 1 month–2 years 100–200 mg four times daily and for children 2–18 years 200–400 mg four times daily.

Herpes Simplex Suppression

Prolonged treatment reduces recurrent infections by 70–80%. Oral acyclovir—child 12–18 years 400 mg BD or 200 mg four times daily.

If recurrences are noticed with standard suppressive doses or for genital herpes suppression in late pregnancy (from 36 weeks' gestation), the dose is increased to 400 mg thrice daily. The recurrence frequency is reassessed after 6–12 months of interruption of therapy. The suppression therapy is restarted after two or more recurrences.

Acyclovir in Chickenpox[7]

Antiviral therapy modifies the course in both varicella and herpes zoster.

Neonates—in high risk of severe disease, acyclovir has to be administered even if the immunoglobulins are given and the immune status is normal. Absorption of oral acyclovir is variable and hence not recommended. Healthy children of 1 month–12 years need not be treated. Adolescents—treat within 24 hours.

Immunocompromised children and those at special risk (severe CVS/respiratory disease/chronic skin disorder)—10 days of acyclovir with parenteral therapy for at least 7 days. It is preferable to start therapy for chicken pox within first 24 hours of the onset of illness.

Acyclovir in Herpes Zoster[7]

The treatment is continued for a total of 7–10 days after starting the therapy within 72 hours of the onset of rashes. Published data show that administration of systemic antivirals reduces severity and complications, duration of pain, and viral shedding. Children with immunosuppression are at high risk for severe infection and dissemination and parenteral therapy is indicated among them.

Dose of Acyclovir in Chickenpox and Herpes Zoster Infection

Oral—1 month–2 years 200 mg; 2–6 years 400 mg; 6–12 years 800 mg qid for 5 days; 12–18 years 800 mg (five times daily) × 7 days (to continue for 2 days after crusting of lesions in herpes zoster in the immunocompromised).

IV infusion—neonate—3 months—10–20 mg/kg tid × at least 7 days; 3 months–12 years 250 mg/m^2; 12–18 years 5 mg/kg 8th hourly for 5 days. At all ages—double dose in encephalitis or immunocompromised (10–14 days in encephalitis, longer among immunocompromised). The IV dose is calculated for ideal weight for height to avoid excessive dose in obese. Prophylaxis of chicken pox after delivery IV infusion—neonate 10 mg/kg tid; continued until absence of the virus is confirmed by VZ IgM.

Attenuation of Chickenpox if VZ Immunoglobulin Not Indicated or Not Available

Oral—1 month–18 years 10 mg/kg qid × 7 days started after 1 week of exposure to IV infusion, reconstitute to 25 mg/mL with water for inj. or N saline, then dilute to concentration of 5 mg/mL with N saline or glucose saline and give over 1 hour; OR use an infusion pump and central line to administer the 25 mg/mL solution over 1 hour.

Resistance to Acyclovir

Resistance to acyclovir does occur in immunocompromised. If HSV lesions are unresponsive, is worsening, or there is frequent recurrence, the chances of acyclovir resistance is high. In such conditions, an attempt has to be made to isolate the virus for sensitivity testing. Foscarnet or cidofovir has been used in such situations with success.

Valaciclovir[8]

Herpes Zoster in Immunocompromised

Oral—12–18 years 1 g tid × 7 days (to be continued for 2 days after crusting of lesions).

Herpes Simplex Treatment

Oral—12–18 years, 500 mg BD × 5 days for first episode; recurrent infection, 500 mg BD × 3–5 days for recurrent infection (in immunocompromised or HIV+ve, double dose is given for 5–10 days).

Herpes Labialis Treatment

Oral—12–18 years initial dose 2 g, then 2 g is given BD.

Herpes Simplex Suppression

Oral—12–18 years 500 mg OD or in two divided doses (500 mg BD for immunocompromised or HIV+ve; interrupt every 6–12 months to reassess—restart after 2 or more recurrences.

CMV Prevention Following Solid Organ Transplantation (within 72 Hours)

Oral—12–18 years 2 g qid × 90 days.

Foscarnet[9]

CMV Disease

Retinitis (ganciclovir-resistant/immunocompromised patient)

IV infusion—1 month–18 years induction 60 mg/kg tid × 2–3 weeks then maintenance 60 mg/kg daily, increased to 90–120 mg/kg if tolerated; repeat induction regimen if the disease progresses on the maintenance dose.

Mucocutaneous Herpes Simplex Infection

Acyclovir-resistant/immunocompromised patient

IV infusion—1 month–18 years—40 mg/kg tid × 2–3 weeks or until lesions heal.

IV infusion can be given undiluted via a central venous catheter or after dilution to a concentration of 12 mg/mL with 5% glucose or N saline via a peripheral vein; the infusion is given over at least 1 hour but increased to 2 hours if the dose given is greater than 60 mg/kg.

Ganciclovir[10]

It is the drug of choice for immunocompromised with a life- or sight-threatening CMV infection.

Those on immunosuppressive therapy following organ transplantation for CMV prevention.

IV infusion 1 month–18 years induction with 5 mg/kg BD × 14–21 days for treatment or for 7–14 days for prevention; maintenance, 6 mg/kg daily on 5 days/week or 5 mg/kg daily until adequate recovery of immunity in those at risk of relapse of retinitis; repeat induction treatment if the retinitis progresses.

CMV infection of the CNS.

IV infusion—neonate 6 mg/kg BD for 6 weeks.

Close monitoring of CBC (correction and possibly treatment interruption is required for severe deterioration of CBC).

Other Rare Indications for Antivirals in Children

Orofacial HSV reactivated after cosmetic facial lacer resurfacing—day before procedure start oral valacyclovir/famciclovir.

HSV infection in burns patients—severe/life-threatening—IV acyclovir.

HSV-associated erythema multiforma—antivirals not effective—long-term herpes labialis prophylaxis prevents recurrences of EM.

CMV Retinitis and Acyclovir-resistant HSV 1 and 2 in Immunocompromised Patients

Foscarnet is not to be used for anything except CMV retinitis and/or acyclovir-resistant HSV in an immunocompromised child.

Ganciclovir—reserve for immunocompromised with life- or sight-threatening CMV infection; CMV prevention during immunosuppressive therapy following organ transplantation and CMV infection of the CNS.

Antivirals for Respiratory Viral Infections

Influenza[11]

Amantadine/rimantadine (no longer recommended)

Oseltamivir/zanamivir—these neuraminidase inhibitors prevent the spread from cell to cell by preventing the release of new virions. They are used for both prophylaxis and treatment and are efficacious against influenza A and B. For treatment and postexposure prophylaxis—oseltamivir should be started within 48 hours and zanamivir within 36 hours of symptoms/exposure, respectively. In healthy individuals, it reduces illness duration by about 1–1.5 days. However for severe influenza or in the immunocompromised children, these drugs may be effective even after the ideal time for initiating therapy if viral shedding continues (unlicensed use).

In an epidemic to prevent influenza spread, oseltamivir and zanamivir can be used in certain exceptional circumstances like when the infecting strain is not included in the vaccine. All strains of influenza A retain susceptibility to zanamivir but few strains have reduced susceptibility to oseltamivir. In severely immunocompromised children, oseltamivir resistance is high; hence, zanamivir can be reserved for these children. Zanamivir can be used when oseltamivir cannot be used or when its resistance is suspected. Zanamivir can be used by administering the solution intravenously or as nebulization (unlicensed) when the inhalation of dry powder is not possible.

Prevention of influenza—oral 13–18 years—75 mg OD × at least 7 days after exposure. During an epidemic given for up to 6 weeks.

Influenza treatment—oral—for children above 1 year age—up to 16 kg–30 mg, 16–23 kg–45 mg, 23–40 kg—60 mg, and >40 kg–75 mg—every 12 hours for 5 days.

Oseltamivir

Prevention of influenza—oral 13–18 years—75 mg OD × at least 7 days after exposure or for up to 6 weeks during an epidemic.

Influenza treatment—oral—for children above 1 year age—up to 16 kg–30 mg, 16–23 kg–45 mg, 23–40 kg–60 mg, and >40 kg–75 mg—every 12 hours for 5 days.

Zanamivir—by inhalation of powder

Postexposure prophylaxis of influenza—5–18 years 10 mg OD × 10 days

Influenza prevention during an epidemic—5–18 years 10 mg OD × up to 28 days.

Influenza treatment—5–18 years 10 mg BD × 5 days (10 days if resistance to oseltamivir suspected).

Peramivir, a novel neuraminidase inhibitor, is recently approved by the U.S. Food and Drug Administration for intravenous administration.

There is a risk of bronchospasm with use of zanamivir.

Respiratory Syncytial Virus Bronchiolitis[12]

Ribavirin is a guanosine analog. Many DNA and RNA viruses are inhibited by ribavirin. In infants with severe bronchiolitis caused by respiratory syncytial virus (RSV) especially in those with other serious diseases, ribavirin is licensed for administration by inhalation but there is no evidence of clinically relevant benefit by ribavirin in RSV bronchiolitis.

Palivizumab is a monoclonal antibody. It is licensed in children at high risk of the disease for preventing serious lower respiratory tract disease caused by RSV; specialist supervision is recommended for prescribing and is prescribed based on the likelihood of hospitalization. Palivizumab is recommended for:

- Infants born preterm, under 9 months of age with chronic lung disease (oxygen requirement for at least 28 days from birth).
- Infants born preterm, under 6 months of age with hemodynamically significant, acyanotic congenital heart disease.

Palivizumab should be considered for:

- Severe combined immunodeficiency syndrome in those children under 2 years of age.
- Long-term ventilation for children under 1 year of age.
- Long-term ventilation with additional comorbidity (cardiac disease or pulmonary hypertension for children 1–2 years of age).

In treatment of chronic hepatitis C infection, ribavirin may also be used orally with peginterferon alfa/interferon alfa; oral ribavirin can be used for Lassa fever. It can be used intravenously in immunocompromised for the treatment of life-threatening RSV, parainfluenza virus, and adenovirus infections (unlicensed indications).

Anemia and jaundice are adverse effects to be watched out for when ribavirin is administered.

Hepatic Viral Infections

The drugs used are the following:

Interferons

Lamivudine—cytosine analog—HBV

Entecavir—guanosine analog—HBV—lamivudine resistance strains

Ribavirin—hepatitis C (with interferons)

Chronic Hepatitis B (CHB)

Recommendations are still in evolution. Reliable complete eradication of the virus is not achieved by any of the available drugs. Factors like effectiveness, adverse events, potential for viral resistance, cost, patients' preference and values, and availability in the care setting have to be considered in framing the treatment recommendations.

Tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are the most effective agents for virologic suppression in both HBeAg-positive and HBeAg-negative populations—and of the two, the most consistent performance is seen with TAF.[13] This is tenofovir's prodrug. It is a safe drug with respect to renal function and bone mineral density when compared to TDF.

The oral drugs recommended for CHB prior to 2017 were TDF and entecavir (ETV). Renal complications (nephropathy and Fanconi syndrome) and osteomalacia have been reported with TDF. Resistance has not been detected with TDF till date. Lactic acidosis is seen with ETV. A slowly emerging resistance pattern is observed with ETV.

The synthetic cytokine pegylated interferon-α (PEG-IFN) is believed to act on the cell-mediated immunity. It has a finite treatment duration, with a higher rate of HBeAg and HBsAg seroconversion, and no drug resistance, but the adverse events (flu-like symptoms, neutropenia, anemia, thrombocytopenia, depression, neuropathy, and dermatological side effects) are more than any of the oral drugs. It has a low preference and compliance as they have to be administered parenterally. Pegylated interferon-α is reserved for select cases and is hardly used in clinical practice nowadays for the above reasons. A synergistic therapeutic effect is demonstrated with certain combinations including nucleos(t)ide and PEG-IFN. Greater viral suppression and higher rates of HBeAg loss and HBsAg loss are shown by these combination.

Lamivudine—lamivudine was found to have good activity in terms of lowering HBV DNA levels with improvements in serum enzyme levels along with hepatic histology in a study initiated 20 years earlier, before the availability of oral nucleoside therapies of hepatitis B and long before the availability of the more potent agents like tenofovir and entecavir with a higher barrier to resistance.[14] Development of antiviral resistance was a major shortcoming, with this HBV DNA levels generally rose and there was worsening of biochemical and histologic features.

Chronic Hepatitis C[15]

Published data from the World Health Organization recommend initiation of therapy in all individuals 12 years of age or older diagnosed with HCV infection, irrespective of the disease stage.

The WHO recommends the use of pan-genotypic direct-acting antivirals (DAAs) regimens for the treatment of persons with chronic HCV infection aged 18 years and above.

In adolescents aged 12–17 years or weighing at least 36 kg with chronic HCV infection, the current regimen includes (based on the genotype):

- Sofosbuvir/ledipasvir for 12 weeks in genotypes 1, 4, 5, and 6
- Sofosbuvir/ribavirin for 12 weeks in genotype 2
- Sofosbuvir/ribavirin for 24 weeks in genotype 3

In children aged less than 12 years with chronic HCV infection, the WHO recommends:

- Defer treatment until 12 years of age.
- Interferon-based regimens should no longer be used for treatment.
- New highly effective short-course oral pan-genotypic DAA regimens are likely to become available for children under 12 years of age in late 2019 or 2020, thus providing access to advanced treatment and cure to a vulnerable group.

Antiretroviral Drugs[16]

Antiretroviral (ART) medicines:

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Nucleotide reverse transcriptase inhibitors (NtRTIs)
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Entry inhibitors
- Integrase inhibitors

Uses of ART:

- Prevention of mother-to-child transmission (PMTCT)
- Postexposure prophylaxis (PEP)
- Preexposure prophylaxis (PrEP)
- Treatment of established case of HIV/AIDS

ART

Till date none of the ARTs offer viral clearance or promise clinical cure. They merely suppress viral replication for extended periods and change the course of disease along the drawn time frame. Decisions about ART for pediatric HIV is based on viral load/replication, CD4 count or percentage, and clinical conditions.

ART—reason for combining at least three ARVs from at least two different classes is for its synergistic effect and to prevent the development of resistance; possible when used in monotherapy.

Although combination therapy offers the best course of action, it increases the rate of local and systemic toxicity and the potential complex drug–drug interactions that are present within the ARTs pose potential toxicity. Classically, the protease inhibitor drugs are inducers or inhibitors of the cytochrome P450 system and are therefore likely to have serious interactions with multiple drug classes. The inhibitory effect of ritonavir (a protease inhibitor) on the cytochrome P450 system has been exploited, and small doses of the drug are added to several other protease inhibitors (lopinavir, tipranavir, atazanavir) of what is known as the boosted regimen.

The preferred ART combination is two NRTIs (replication in both active and resting cells is suppressed) and one NNRTI or one protease inhibitor (for prolonged viral suppression).
Additional alternate regimens:

- Triple NRTIs (i.e., abacavir, zidovudine, and lamivudine)
- Boosted PI—lopinavir/ritonavir in combination with two NRTIs
- One NRTI and one NNRTI

PMTCT—zidovudine (ZDV)

Zidovudine to the pregnant woman (100 mg five times/24 hours PO). A combination antiretroviral therapy (cART) containing zidovudine

should be preferred. At 14 weeks of gestation, the therapy should be started with a combination ART preferably containing ZDV. It should be continued during delivery or till exclusive breastfeed is given or till the first 6 weeks of life (2 mg/kg q 6 hours PO). In the developed world, this decreases perinatal HIV transmission rate to <1%.

A short-term regimen (300 mg BD from 36 weeks gestation and 300 mg every 3 hours during delivery) resulted in almost 50% reduction in transmission. Even if a mother receives no ART during gestation or delivery, ZDV prophylaxis given immediately after the delivery or within 6 hours of birth for 6 weeks reduces the transmission rate.

Full-term infants—ZDV—2 mg/kg qid for 6 weeks. Preterm infants—1.5 mg/kg PO or IV Q12H for first 14 days (if available) and then increased to 2 mg/kg tid.

PMTCT—niverapine (NVP)

Oral nevirapine: Perinatal transmission is reduced by 50% with one dose to women in labor and one to infant in first 48–72 hours of life; this regimen is simple and effective because of the prolonged half-life and also very cost-effective for developing countries. But if ART is required for children more than 6 months of age, a NVP-based regimen was found to have a high failure rate.

Indications of ART

Start before the immune system is irreversibly damaged.

All infants, regardless of clinical or immunological, must receive ART.

Child 36–59 months: if CD4 <350 cells/mm^3 (15%).

Adult guidelines to be followed for child >5 years old.

Adult and adolescents

The WHO clinical stage 1 or 2 and a CD4 count ≤350 cells/mm^3—ART has to be initiated before CD4 drops below 200 cells/mm^3.

The WHO clinical stage 3 or 4 regardless of CD4 count.

HIV and TB coinfection regardless of the CD4 count.

HIV/HBV coinfection with evidence of active liver disease.

What to start (NACO)

Pediatric formulations will be provided at all ART centers. The drugs supplied are fixed-dosed combinations (FDC) available in India, which are stavudine-based regimens. It has been recommended that in order to scale up the treatment of children, this will be used as long as zidovudine (AZT)-based regimens are available and recommended globally, as the preferred choice for children (Table 1).

Choice of ART drug

With the concerns about persistence of resistant mutants to NVP, the boosted PI-based regimen (lopinavir/ritonavir, LPV/r) has to be started in <2 years old exposed to nevirapine in the mother or in infancy.

>3 years—HIV + TB—2NRTI + efavirenz (avoid nevirapine/rifampicin interaction); if EFZ not possible—triple NRTI regimen.

>12 years—HIV + hepatitis B—tenofovir (TDF) + emtricitabine (FTC)/lamivudine (3TC) + NVP/EFV. This combination provides a dual benefit of acting against two viruses, i.e., hepatitis B and HIV.

In <3-year-olds, efavirenz (EFV) is not suitable because of inadequate information on dosage and in adolescent girls due to its known teratogenic nature in the first trimester of pregnancy during which organogenesis occurs.

Table 1: Formulations of FDCs available for pediatric HIV use in India

Formulation	*Stavudine (d4T) (mg)*	*Lamivudine (3TC) (mg)*	*Nevirapine (NVP) (mg)*
FDC 6 (baby tab)	6	30	50
FDC 10 (tab)	10	40	70
FDC 12 (junior tab)	12	60	100
FDC 30 d4T (adult tab)	30	150	200
FDC—30 AZT (adult tab)	300	150	200

Toxicity of ARV drugs

Hematological: with AZT (anemia, neutropenia, and thrombocytopenia).

Mitochondrial dysfunctions: with other NRTI drugs: include lactic acidosis, hepatic toxicity, pancreatitis and peripheral neuropathy.

Lipodystrophy and other metabolic abnormalities: frequently with stavudine (d4T) and protease inhibitors, and to a lesser degree with other NRTI drugs. Abnormalities include fat maldistribution and body habitus changes, hyperlipidemia, hyperglycemia, insulin resistance, diabetes mellitus, osteopenia, osteoporosis, and osteonecrosis.

Allergic reactions: including skin rashes and hypersensitivity reactions. These are more common with the NNRTI drugs, but also seen with certain NRTI drugs, such as abacavir (ABC).

Hepatic dysfunctions: in children with hepatic dysfunction of any etiology, NVP requires careful consideration because of its potential life-threatening hepatotoxicity.

Conclusion

A review of drugs used to treat viral illnesses is needed as new recommendations are now available and drugs used previously are no longer used. However, acyclovir remains the mainstay of treatment of herpes virus infections.

Points to Remember

- Antiherpes virus agents—know all about the prototype/first-line drug—ACYCLOVIR. Other anti-HSV drugs are rarely required.
- Antivirals for respiratory viral infection—oseltamivir.
- Antivirals for hepatic viral infections—used sparingly.
- ART—those dealing with HIV/AIDS need to know all the issues involved—drug resistance, issues with compliance/monitoring, dosages, etc.

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