HIV THERAPY

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When to initiate ART

- The optimal time to initiate antiretroviral therapy in adult patients with CD4 count >350 cells/μl is not well defined.
- For HIV-infected patients older than 50 years of age, antiretroviral therapy (ART) is recommended for all, regardless of CD4 cell count.
- Older patients frequently have a blunted immune response
- Older patients have high virologic response rates.
- Older patients have relatively poor CD4 cell increases in response to antiretroviral therapy as measured by an increase of CD4 count by 100 cells/fl

When to initiate ART

- Older HIV-infected patients have a greater risk of developing serious non-AIDS complications.
- Patients >55 years old may be at higher clinical risk even after starting therapy
- The administration of ART during pregnancy or intrapartum significantly reduces the risk of mother-to-child transmission
- A 96% reduction in transmission between sero-discordant heterosexual couples when the positive partner was receiving ART

Necessary testing

- 20-25% drug naïve patients possess resistant strains.
- Reverse transcriptase and protease genotypic resistance testing should be used to guide selection of a regimen
- If transmitted integrase strand transfer inhibitor resistance is a concern, testing should also include the integrase gene
- HLA-B*5701 testing should be performed before initiation of abacavir (ABC).
- Patients should be screened for hepatitis B and hepatitis C virus infection before initiating ART

Necessary testing

- A co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered
- Co-receptor tropism testing is recommended for patients who exhibit virologic failure on a CCR5 antagonist
- A phenotypic tropism assay is preferred to determine HIV-1 co-receptor usage
- A genotypic tropism as an alternative
- A proviral DNA tropism assay can be utilized for patients with undetectable HIV-1 RNA when a CCR5 antagonist is considered for use

Monitor therapy

- HIV screening is recommended to begin at age 13
- Two surrogate markers are used to monitor people with HIV:
- Plasma HIV RNA (viral load) to assess level of HIV viremia
- CD4 T lymphocyte cell count to assess immune function.

Outcomes

- With maximally suppressed viral loads (200 copies/fl), life expectancy approaches that of non-HIV infected population
- Therapy that achieves a plasma viral load of < 50 copies/mL has been shown to provide a durable response to the therapy employed.

Outcomes

- Those with less cumulative time with detectable plasma viremia are less likely to suffer certain complications:
- Cardiovascular disease
- Neurocognitive dysfunction
- Decreased risk of severe bacterial infections
- Malignancies

ART complications

- ART initiation is associated with a risk of immune reconstitution inflammatory syndrome (IRIS).
- IRIS is a clinical syndrome characterized by new or worsening infectious and non-infectious complications observed after the initiation of ART
- The risk of IRIS increases when ART is begun:
- At low CD4 cell counts (<100 cells/fl)
- With the presence of cryptococcal or TB meningitis
- With cutaneous Kaposi’s sarcoma

Monitor therapy

- HIV screening is recommended to begin at age 13
- Two surrogate markers are used to monitor people with HIV:
- Plasma HIV RNA (viral load) to assess level of HIV viremia
- CD4 T lymphocyte cell count to assess immune function.

Initial treatment regimen

- An antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a third active drug from one of three drug classes:
- An integrase strand transfer inhibitor (INSTI)
- A non-nucleoside reverse transcriptase inhibitor (NNRTI)
- A protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (also known as a booster)

Pharmacologic therapy

- Six distinct classes of drugs:
- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI)
- Integrase strand transfer inhibitors (INSTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors (PI)
- CCR5 co-receptor antagonists
- Entry or Fusion inhibitors (EI)

Drug names

- Nucleoside reverse transcriptase inhibitors (NRTI)
- ABC abacavir
- 3TC lamivudine
- FTC emtricitabine
- TAF tenofovir alafenamide
- TDF tenovir disoproxil fumarate
- CCR5 antagonists
- MVC maraviroc
- Entry Inhibitors (EI)
- IBA ibalizumab

Drug names

- Protease Inhibitors (PI)
- DRV/c darunavir with cobicistat
- DRV/r darunavir with ritonavir
- Integrase strand inhibitors (INSTI)
- BIC bictegravir
- DTG dolutegravir
- RAL raltegravir
- EVG/c elvitegravir with cobicistat
- Non-nucleoside reverse transcriptase inhitibots (NNRTI)
- NVP nevarapine

Table 6a. Recommended Antiretroviral Regimens for Initial Therapy

Recommended Initial Regimens for Most People with HIV
Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.
INSTI plus 2 NRTIs: **Note**: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens. • BIC/TAF/FTC **(AI)** • DTG/ABC/3TC **(AI)—if HLA-B*5701 negative** • DTG plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)** • RAL plus (TAF or TDF)[a] plus (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC) **INSTI plus 1 NRTI**: • DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- EVG/c/(TAF or TDF)[a]/FTC **(BI)**

Boosted PI plus 2 NRTIs:

- In general, boosted DRV is preferred over boosted ATV
- (DRV/c or DRV/r) plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- (ATV/c or ATV/r) plus (TAF or TDF)[a] plus (FTC or 3TC) **(BI)**
- (DRV/c or DRV/r) plus ABC/3TC—**if HLA-B*5701 negative (BII)**

NNRTI plus 2 NRTIs:

- DOR/TDF[a]/3TC **(BI)** or DOR plus TAF[a]/FTC **(BIII)**
- EFV plus (TAF or TDF)[a] plus (FTC or 3TC)
  - EFV 600 mg plus TDF plus (FTC or 3TC) **(BI)**
  - EFV 400 mg/TDF/3TC **(BI)**
  - EFV 600 mg plus TAF/FTC **(BII)**
- RPV/(TAF or TDF)/FTC **(BI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**

Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available
- DRV/r plus RAL twice a day **(CI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**
- DRV/r once daily plus 3TC[a] **(CI)**

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children

Preferred Regimens			
Age	**Regimens**		**FDC Available** (see Appendix A, Table 1)
Infants, Birth to Age <14 Days[a,b]	Two NRTIs **plus** NVP		No
	Weight ≥2 kg	Two NRTIs **plus** RAL[c]	No
Children Aged ≥14 Days to <3 Years	Two NRTIs **plus** LPV/r[b]		No
	Weight ≥2 kg	Two NRTIs **plus** RAL[c]	No
Children Aged ≥3 Years	Weight <25 kg	Two NRTIs **plus** ATV/r	No
		Two NRTIs **plus** twice-daily DRV/r[d]	No
		Two NRTIs **plus** RAL[c]	No
	Weight ≥25 kg	Two NRTIs **plus** DTG[e]	Yes
		Two NRTIs **plus** EVG/c[f]	Yes
Adolescents Aged ≥12 Years with SMRs of 1–3	Weight ≥25 kg	Two NRTIs **plus** BIC[g]	Yes

Once daily dosing

Available as a Multi-Tablet Regimen with Once-Daily Dosing		
Tenofovir alafenamide/ emtricitabine *and* dolutegravir* (TAF 25 mg/FTC *and* DTG; Descovy *and* Tivicay)	•Initiate ***only*** in patients with CrCl ≥30 mL/min. •Documented DTG resistance after initiation in treatment-naive patients is rare. •Contains 25 mg of TAF, unboosted. •Magnesium- or aluminum-containing antacids may be taken 2 hours before or 6 hours after DTG; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food.	A1
Tenofovir alafenamide/ emtricitabine *and* raltegravir (TAF 25 mg/FTC *and* RAL HD; Descovy *and* Isentress HD)	•Initiate ***only*** in patients with CrCl ≥30 mL/min. •To date, no clinical trials have been conducted with TAF and RAL; data are based on bioequivalence pharmacokinetic studies. •Contains 25 mg of TAF, unboosted. •Administer as TAF/FTC once daily and RAL HD 1200 mg once daily, dosed as two 600 mg HD tablets. •Magnesium- or aluminum-containing antacids are contraindicated; co-administration of calcium-containing antacids is not recommended with RAL HD.	

Nucleoside reverse transcriptase inhibitors

- Competitively inhibit nucleotide binding to reverse transcriptase and terminate the DNA chain
- Lack a 3’-OH group
- Require phosphorylation to be active
- Tenovir is a nucleotide reverse transcriptase inhibitor and does not require phosphorylation to be active
- Adverse effects include bone marrow suppression and peripheral neuropathy
- Lactic acidosis (nucleosides only)

Nucleoside reverse transcriptase inhibitors

- Emtricitabine has few adverse effects
- Selects for the M184V resistance mutation which confers high-level resistance
- Improves susceptibility to tenofovir.
- 5-8% of patients who begin abacavir have hypersensitivity reactions (HSRs).
- Risk highly associated with the presence of the HLA-B*5701 allele.
- Triple NRTI regimens are biologically inferior.

Non-nucleoside reverse transcriptase inhibitors

- Bind to reverse transcriptase at a site that differs from NRTIs.
- Do not require phosphorylation to be active
- Do not compete with nucleotides
- Rash and hepatotoxicity as common adverse events
- CNS symptoms common with efavirenz
- Not for use in pregnancy either
- Resistance mutations affect all NNRTIs

Integrase strand inhibitors

- INSTI-based regimens have quickly become the recommended regimens because of their virologic efficacy, lack of drug interactions, and favorable toxicity profile.
- Prevent viral integration into host genome
- BIC and DTG, the second-generation INSTIs, have higher barriers to resistance than the first-generation INSTIs RAL and EVG and may have more activity against non-B subtypes of HIV
- TDF has higher renal and bone adverse effects than does TAF
- Hypercholesterolemia may be seen

Protease inhibitors

- Advantages include excellent virologic potency and a high barrier to drug resistance (since multiple mutations are required for a patient to develop resistance).
- Because PIs are metabolized via hepatic enzymes, these drugs have the potential for multiple drug interactions.
- They may also be associated with metabolic complications such as dyslipidemia, fat maldistribution, and insulin resistance.
- CYP34A inhibitors

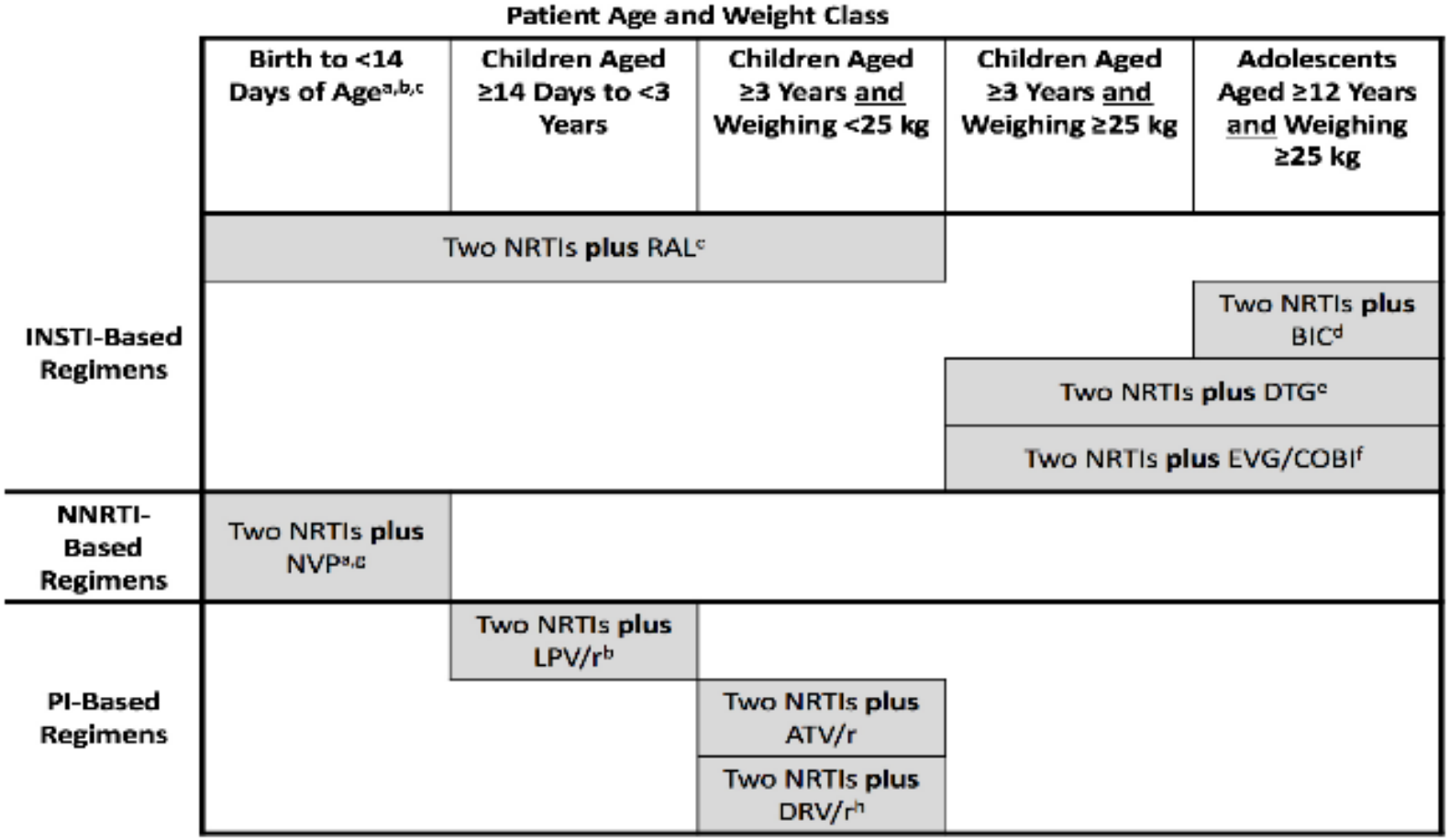
Other inhibitors

- CCR5 antagonists
- Maraviroc binds to CCR5, preventing an interaction with gp120.
- CD4 post-attachment inhibitors
- Ibaluzimab is a monoclonal antibody that binds to domain 2 of CD4 and interferes with post-attachment steps required for the entry of HIV-1 virus particles into host cells and prevents the viral transmission that occurs via cell-cell fusion.

When to initiate ART therapy in children

- Antiretroviral therapy is initiated in infants <12 months of age regardless of clinical status, CD4 count, or viral load.
- The 1-year risk of AIDS or death is substantially higher in younger than older children at any given level of CD4 count, particularly for infants age <12 months.
- Always test for drug resistance.

Figure 1. Preferred Regimen by Age, Weight, and Drug Class



Pediatric therapy

- When combined with two NRTIs, the following drugs and drug combinations are considered Preferred regimens for children:
- Children aged <14 days: NVP
- NVP is associated with rare occurrences of significant hypersensitivity reactions (HSRs).
- Low barrier to viral resistance.
- Switch to another regimen at 15 days of age
- Children aged <14 days and weighing ≥2 kg: Raltegravir (RAL)
- Children aged ≥14 days to <3 years: LPV/r or RAL

Pediatric therapy

- RAL plus a two-NRTI backbone is recommended as a Preferred INSTI-based regimen for infants and children from birth to age 3 years who weigh ≥2 kg and for children aged ≥3 years and weighing <25 kg
- Viral mutation affects all NNRTI drug class

Pediatric therapy

- BIC/FTC/TAF is recommended as a Preferred INSTI-based regimen for adolescents aged ≥12 years and weighing ≥25 kg
- DTG plus a two-NRTI backbone is recommended as a Preferred INSTI-based regimen for children and adolescents aged ≥3 years and weighing ≥25 kg
- Under 20kg, PK varies
- EVG/c/FTC/TAF is recommended as a Preferred INSTI-based regimen for children and adolescents weighing ≥25 kg who have creatinine clearance (CrCl) ≥30 mL/min

Pediatric therapy

- Children aged ≥3 years and
- Weighing <25 kg: Atazanavir/ritonavir (ATV/r), twice-daily darunavir/ritonavir (DRV/r), or RAL
- Weighing ≥25 kg: Dolutegravir (DTG)
- Weighing ≥25 kg: Elvitegravir/cobicistat (EVG/c). Adolescents aged ≥12 years and weighing ≥25 kg: Bictegravir (BIC).

Pediatric therapy

- ATV/r plus a two-NRTI backbone is recommended as a Preferred PI-based regimen for children aged ≥3 years and weighing <25 kg.
- DRV/r plus a two-NRTI backbone is recommended as a Preferred PI-based regimen for children aged ≥3 years and weighing ≥10 kg but <25 kg
- Dosing frequency depends upon age and viral mutations
- LPV/r plus a two-NRTI backbone is recommended as a Preferred PI-based regimen for infants with a postmenstrual age ≥42 weeks and postnatal age ≥14 days to <3 years

Other combinations

- ABC plus 3TC or FTC is recommended as the Preferred dual-NRTI combination for children aged ≥3 months
- FTC/TAF is recommended as a Preferred dual-NRTI combination in children and adolescents weighing ≥25 kg who have estimated CrCl ≥30 mL/min when this combination is used with an INSTI or NNRTI
- FTC/ATF is considered a Preferred dual-NRTI combination when used with a PI in children and adolescents weighing ≥35 kg who have estimated CrCl ≥30 mL/min
- EVG/c/FTC/TAF for children and adolescents weighing ≥25 kg

Pregnancy

- Zidovudine/lamivudine remains as the preferred option in pregnant women.
- This dual-NRTI has the most safety and efficacy data for both mother and newborn.
- Infants who are identified as HIV-infected during the first 6 weeks of life while receiving zidovudine chemoprophylaxis should have zidovudine discontinued and initiate treatment with combination therapy with at least 3 drugs.
- Trimethoprim-sulfasoxazole prophylaxis.

Exposure prophylaxis

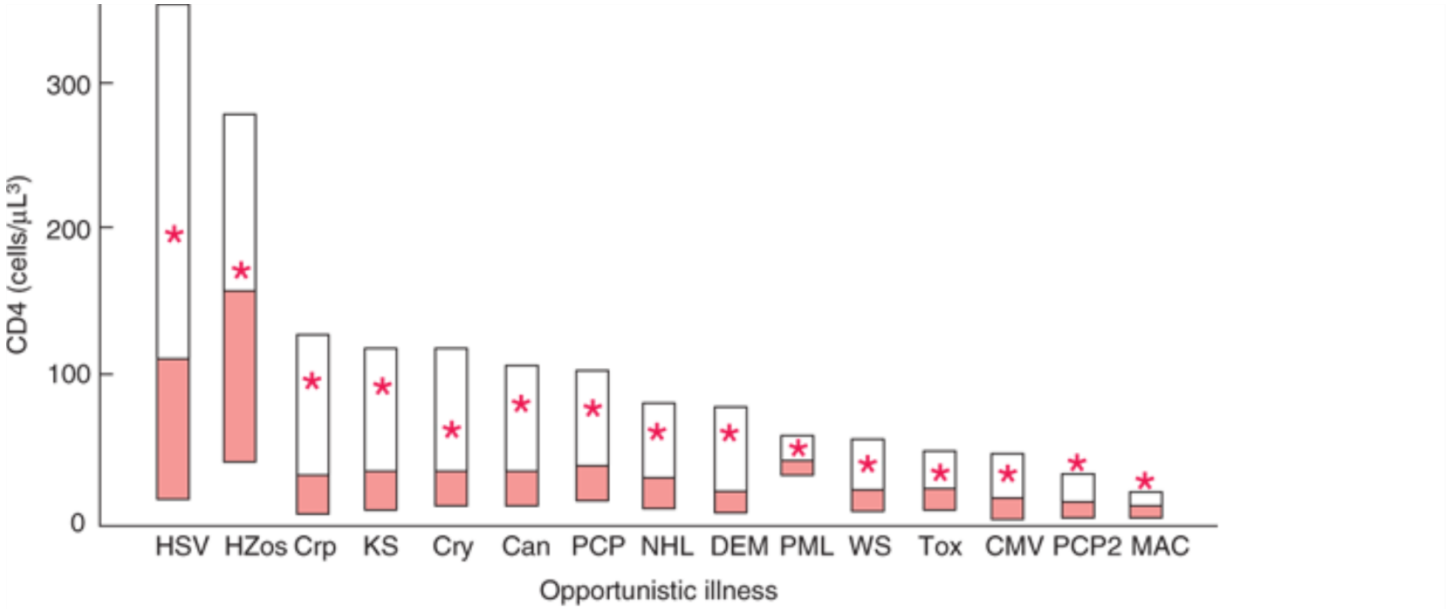
- Pre-exposure prophylaxis with tenofovir and emtricitabine.
- Post-exposure prophylaxis with a 28 day course of ART therapy.
- This is not 100% effective in blocking HIV infection.

Pre-exposure protection

Table 10: Recommended Oral PrEP Medications

Generic Name	Trade Name	Dose
Tenofovir disoproxil fumarate (TDF)	Viread	300 mg
Emtricitabine (FTC)[a]	Emtriva	200 mg
TDF + FTC	Truvada	300mg/200 mg

CD4 counts and development of opportunistic infections



Boxplot of the median (line inside the box), first quartile (bottom of the box), third quartile (top of the box), and mean (asterisk) CD4+ lymphocyte count at the time of the development of opportunistic disease. Can, candidal esophagitis; CMV, cytomegalovirus infection; Crp, cryptosporidiosis; Cry, cryptococcal meningitis; DEM, AIDS dementia complex; HSV, herpes simplex virus infection; HZos, herpes zoster; KS, Kaposi's sarcoma; MAC, Mycobacterium avium complex bacteremia; NHL, non-Hodgkin's lymphoma; PCP, primary Pneumocystis jiroveci pneumonia; PCP2, secondary P. jiroveci pneumonia; PML, progressive multifocal leukoencephalopathy; Tox, Toxoplasma gondii encephalitis; WS, wasting syndrome. (From RD Moore, RE Chaisson: Ann Intern Med 124:633, 1996.)

Accessed 02/03/2016

Opportunistic infections

- CD4 <250 Coccidiomycosis
- Endemic in Sonoran life zone
- Fluconazole prophylaxis
- CD4 <200 Pneumocystis jiroveci
- Trimethoprim-sulfamethoxazole prophylaxis
- CD4 <150 Histoplasma capsulatum (Ohio valley)
- Itraconazole prophylaxis
- CD4 <100 Toxoplasma gondii
- Trimethoprim-sulfamethoxazole prophylaxis

Opportunistic infections

- CD4 <100 Penicillosis
- Endemic in SE Asia
- Fluconazole prophylaxis
- CD4 <50 Mycobacterium avium complex
- Azithromycin prophylaxis