TABLE 128.4 Approved Protease Inhibitors

AGENT	TRADE NAME	ORAL BIOAVAILABILITY (%)	SERUM HALF-LIFE (hr)	ELIMINATION	ADULT DOSE[a]	DOSAGE FORMS
Saquinavir	Invirase	4	1–2	Hepatic and intestinal metabolism via CYP3A4	1000 mg twice daily with ritonavir 100 mg twice daily	200-mg capsule 500-mg tablet
Ritonavir	Norvir	70	3–5	Hepatic metabolism via CYP3A4 and 2D6	Not recommended as single agent	100-mg capsule and tablet 80-mg/mL solution
Indinavir	Crixivan	60–65	1.8	Hepatic metabolism via CYP3A4	800 mg every 8 h Drink ≥1.5 L of water daily	200- and 400-mg capsules
Nelfinavir	Viracept	70–80	3.5–5	Hepatic metabolism via CYP2C19, CYP3A4, and CYP2D6	1250 mg twice daily or 750 mg three times daily, with meals	250- and 625-mg tablets
Fosamprenavir	Lexiva Telzir[b]	—	7–11	Hepatic metabolism via CYP3A4 Biliary excretion	Treatment-naïve: 1400 mg once daily with ritonavir 100- or 200- mg once daily, or 700 mg twice daily with ritonavir 100 mg twice daily PI-experienced: 700 mg twice daily with ritonavir 100 mg twice daily	700-mg tablet 50-mg/mL suspension
Lopinavir + ritonavir	Kaletra	—	5–6	Hepatic metabolism via CYP3A4	Two tablets twice daily	Lopinavir 100-mg/ritonavir 25-mg and lopinavir 200-mg/ritonavir 50-mg tablets Lopinavir/ritonavir 80-mg/20-mg per mL solution
Atazanavir	Reyataz	—	7	Hepatic metabolism via CYP3A4	Treatment-naïve: 300 mg once daily with ritonavir 100 mg once daily, or cobicistat 150 mg once daily, with food. Treatment-experienced or with TDF: 300 mg once daily with ritonavir 100 mg once daily or cobicistat 150 mg once daily, with food	100-, 150-, 200-, and 300-mg capsules 50-mg packet
Tipranavir	Aptivus	—	5–6	Hepatic metabolism via CYP3A4	500 mg twice daily with ritonavir 200 mg twice daily	250-mg capsule 100-mg/mL solution
Darunavir	Prezista	—	15 (with ritonavir)	Hepatic metabolism via CYP3A4	Treatment-naïve: 800 mg once daily with ritonavir 100 mg once daily, or cobicistat 150 mg once daily, with food. Treatment-experienced: 800 mg once daily with ritonavir 100 mg once daily, or cobicistat 150 mg once daily, with food; or 600 mg twice daily with ritonavir 100 mg twice daily, with food	75-, 150-, 600-, and 800-mg tablets 100-mg/mL suspension

[a]For pediatric dose, see Chapter 127. Consult product monograph for appropriate dose when low-dose ritonavir is used for pharmacokinetic enhancement.
[b]Trade name as marketed in Europe.
CYP, Cytochrome P-450; *PI,* protease inhibitor; *TDF,* tenofovir disoproxil fumarate.

or with mild or moderate hepatic impairment. No data are available on dosing in severe renal failure; the use of darunavir in patients with severe hepatic impairment is not recommended.

In treatment-experienced patients, darunavir is administered with meals as a 600-mg tablet twice daily with ritonavir (100 mg) or as an 800-mg tablet once daily with 100 mg ritonavir for patients with no genotypic darunavir resistance mutations.[137] In treatment-naïve patients, darunavir/r has been studied at an 800-mg/100-mg once-daily dose. The CYP3A inhibitor cobicistat was found to boost darunavir levels in a manner similar to ritonavir,[138] and a fixed-dose combination tablet of darunavir and cobicistat was approved by the FDA in 2015. Darunavir contains a sulfa moiety and should be used with caution in patients with sulfonamide allergies. Darunavir can be used in conjunction with atazanavir, efavirenz and etravirine. It is not recommended for use, however, with lopinavir/r, saquinavir, lovastatin, or simvastatin.

Two randomized phase IIb studies (POWER-1 and POWER-2) in treatment-experienced patients with, on average, three primary PI resistance mutations and an 80-fold or greater baseline change in lopinavir susceptibility demonstrated greater viral load reductions and CD4 lymphocyte increases after 24 weeks of therapy in patients receiving darunavir/r compared with an investigator-selected PI, both with optimized background therapy.[139] At 48 weeks, a greater proportion of darunavir/r-treated than comparator PI-treated subjects had plasma HIV-1 RNA levels less than 50 copies/mL (45% vs. 10%, respectively). In a separate trial comparing darunavir/r to lopinavir/r in lopinavir-naïve, treatment-experienced patients, darunavir/r was noninferior to lopinavir/r in achieving plasma HIV-1 RNA less than 400 copies/mL at 48 weeks.[140] In treatment-naïve patients, darunavir/r was noninferior to lopinavir/r after 48 weeks of treatment in achieving HIV-1 RNA levels less than 50 copies/mL.[141] The dose of darunavir/r studied in treatment-naïve subjects was 800 mg/100 mg once daily, rather than the 600 mg/100 mg twice-daily dose previously studied in treatment-experienced subjects. Adverse effects seen with darunavir include diarrhea, nausea, headache, and nasopharyngitis; 0.5% of subjects enrolled in clinical trials of darunavir/r developed acute hepatitis. Postmarketing cases of liver injury and death have been reported. Coformulated darunavir and cobicistat was evaluated in combination with TAF plus emtricitabine or TDF plus emtricitabine and demonstrated similar, albeit low by modern standards, rates of virologic suppression at 48 weeks (77% vs. 84%, respectively).[141a]

Genotypic data from the screening samples of the POWER studies suggest that several darunavir-associated resistance mutations exist. The I50V mutation, one that is also selected by amprenavir, confers the greatest resistance, with a more than fourfold change increase. However,

a single darunavir-associated resistance mutation, even I50V, does not confer resistance; two or more mutations are required. Mutations V11I, I54L, G73S, and L89V confer the least resistance, with each contributing a less than twofold increase in resistance. Mutations V32I, L33F, I47V, I54M, L76V, and I84V lead to an intermediate twofold to fourfold increase. Treatment-experienced patients should preferably not start darunavir (or tipranavir) without first obtaining a virus-resistance phenotype. This is because the limited clinical experience with these PIs may initially compromise the accuracy of the genotypic algorithms used to predict drug sensitivity.

Ritonavir

Ritonavir was originally marketed and used as a stand-alone PI dosed at 600 mg orally twice daily. Gastrointestinal side effects, particularly diarrhea and nausea, were common and limited the drug's tolerability. Dyslipidemias, vomiting, altered taste, and paresthesias were also reported. Today, ritonavir is usually used at lower doses (100–200 mg twice daily) to inhibit CYP3A4 and improve the bioavailability and increase the half-life of other PIs. These low ritonavir doses decrease, but do not entirely eliminate, its gastrointestinal side effects. Ritonavir inhibits the metabolism of all available PIs but is not used in conjunction with nelfinavir. Ritonavir boosting improves PI efficacy and decreases the occurrence of PI resistance after virologic failure, albeit at a cost of an increased incidence of clinically significant drug-drug interactions.

Drugs Used Less Commonly or of Historical Interest

As ART has evolved and new agents have been introduced, medications and regimens of prior historical importance have now largely been replaced by antiretrovirals with improved efficacy and safety profiles. A compendium of drugs of historical interest follows, together with other drugs more recently approved but of limited utility.

Nucleoside and Nucleotide Reverse-Transcriptase Inhibitors (See Fig. 128.2)

Zidovudine

Zidovudine (ZDV, AZT) is a thymidine analogue that is administered orally as a 300-mg pill twice daily. More commonly, however, zidovudine is coformulated with lamivudine and administered twice daily. For patients with renal impairment necessitating peritoneal dialysis, hemodialysis, or continuous venovenous hemofiltration, zidovudine dosing should be adjusted to 100 mg every 8 hours. Zidovudine can be taken with or without food and has an oral bioavailability of 64%, resulting in part because of first-pass glucuronidation in the liver. Zidovudine is neither a substrate for, nor an inducer of, the CYP enzyme complex. The short plasma half-life and concentrations of zidovudine do not accurately reflect the more robust intracellular concentrations of the zidovudine phosphorylated forms. Zidovudine should never be coadministered with stavudine (d4T) because of antagonism, demonstrated both in vitro and in vivo.[142,143]

As the first antiretroviral agent approved in the United States (in 1987), a wealth of clinical outcomes data has been generated with zidovudine as either monotherapy or dual therapy.[144–148] The use of zidovudine in effective three-drug regimens has been systematically evaluated since 1996.[149] A study that compared the efficacy of six combination regimens demonstrated the superiority of zidovudine in combination with lamivudine and efavirenz and established this zidovudine-containing regimen as the standard for initial ART at the time.[90] Since then, however, tenofovir-containing regimens have largely replaced zidovudine-containing regimens as the preferred first-line regimens because of superior virologic outcomes, reduced drug resistance, and less lipoatrophy.[9,150] If the preferred tenofovir-containing regimens cannot or should not be used, current guideline recommendations also generally do not list zidovudine as an alternative nucleoside backbone choice.[13,14] Zidovudine, used as monotherapy or in combination, has also been widely used to prevent mother-to-child transmission of HIV; rates of transmission in the United States and many other countries are now less than 2%, often using zidovudine-containing regimens.[151–153]

The most common zidovudine adverse effects are headache and malaise. Other common side effects include anorexia, nausea, and vomiting. These symptoms often improve during the first month of therapy. Zidovudine can also cause dose-limiting toxicities of anemia and granulocytopenia. Of greatest long-term concern is the interference of zidovudine with the normal function of mtDNA pol-γ. Lactic acidosis, hepatic steatosis, peripheral neuropathy, lipodystrophic/lipoatrophic changes, and myopathy all appear to be related to the mitochondrial toxicities associated with zidovudine. Because of fewer toxicities and superior clinical outcomes observed with newer NRTIs, zidovudine is no longer frequently used as a first-line antiretroviral agent in developed countries. The combination of zidovudine and lamivudine remains first-line therapy, however, for pregnant persons with HIV.

Two resistance pathways have been described in patients failing zidovudine (or stavudine) therapy, most often when used as monotherapy or dual therapy in the pre–highly active ART era. TAMs accumulate in the *RT* gene either at positions 41, 210, and 215 (TAM1 pathway) or at positions 67, 70, and 219 (TAM2 pathway). Although the factors responsible for the emergence of one pathway over the other remain unclear, the TAM1 pathway confers higher-level zidovudine resistance and greater cross-resistance to other NRTIs than does the TAM2 pathway. Mutations from both pathways can be seen in patients, and TAMs can continue to accumulate over time, especially in those patients who continue zidovudine in the presence of either a partially suppressive or overtly failing regimen.

Stavudine

Stavudine (d4T) is a thymidine analogue that has similar antiretroviral activity as zidovudine but has significant toxicities that limit its clinical use. These include peripheral neuropathy, hyperlactatemia, lactic acidosis, hepatic steatosis, lipoatrophy, and pancreatitis. Stavudine is antagonistic to zidovudine, and also should not be coadministered with didanosine because of concerns for possibly fatal lactic acidosis that appears to have a female predominance.[154] Stavudine offers no advantages in virologic outcome over TDF and should not generally be used as first-line ART.[54] Nevertheless, because of coformulation with other agents and cost concerns, it may still be used as part of initial regimens in some parts of the developing world.

Didanosine

Didanosine (ddI) is functionally an adenosine analogue that is administered in a delayed-release enteric-coated form. Dosing is weight-based and should be reduced commensurate with creatinine clearance. There is no specific recommendation for dosing in the setting of hepatic impairment, although the potential for toxicities in this situation should be closely monitored. Didanosine absorption is decreased in the presence of food, and the drug should be taken 30 minutes before or 2 hours after a meal. As with other dideoxynucleotides, didanosine may be associated with mitochondrial-associated toxicities. Most commonly, didanosine can cause peripheral neuropathy and pancreatitis and should not be coadministered with drugs having similar toxicity profiles. Didanosine use has been associated with a reversible 1.5-fold increased relative risk of myocardial infarction, even after adjustment for baseline cardiovascular risk.[25] However, these data were not confirmed in a second study.[155] Didanosine resistance during the monotherapy and dual-therapy era was most often conferred by the L74V mutation in the *RT* gene. In the era of combination therapy, this mutation is less commonly seen. Resistance to didanosine can also be conferred by the 69 insertion complex and the Q151M complex.[61] Didanosine can also select for the signature tenofovir mutation K65R in vitro, although the significance of this in vivo is unknown.[156] Largely because of associated toxicities and inferior virologic efficacy, current guidelines no longer recommend didanosine-based regimens for initial therapy in antiretroviral-naïve patients.[13–15]

Nonnucleoside Reverse Transcriptase Inhibitors (See Fig. 128.4)

Nevirapine

Nevirapine is administered orally with or without food at 200 mg once daily for the first 2 weeks, then 200 mg twice daily thereafter. Nevirapine

induces it own metabolism via CYP3A4, and the dose increase 2 weeks into therapy is necessary to maintain adequate plasma drug levels. No dose adjustment is needed for renal impairment short of dialysis, and the use of nevirapine in the setting of hepatic dysfunction is not recommended. Nevirapine is a minor substrate for CYP2B6 and 2D6 and a weak inhibitor of CYP1A2, 2D6, and 3A4. It is a major substrate and inducer of CYP3A4 and a strong inducer of CYP2B6. As such, multiple clinically relevant drug-drug interactions are possible. Antibiotics with antimycobacterial activity, such as rifampin, rifabutin, and clarithromycin, should not be coadministered with nevirapine. Inferior virologic outcomes were observed in patients with HIV receiving nevirapine-based ART while on treatment for tuberculosis.[99] Nevirapine decreases serum concentrations of some PIs and decreases plasma concentrations of oral contraceptives and methadone.[157] A careful review of drug-drug interactions on a patient-by-patient basis is warranted before starting nevirapine. Nevirapine crosses the placenta and is known to enter breast milk.[158–160]

Nevirapine can be an effective component of a three-drug antiretroviral regimen.[161,162] Nevirapine has lost favor relative to other NNRTIs, particularly efavirenz, for initial ART, largely because of inferior clinical effectiveness and problematic toxicities that include rash, Stevens-Johnson syndrome, and hepatic necrosis.[163,164] A study of more than 23,000 participants demonstrated an increased risk of death and acquired immunodeficiency syndrome (AIDS)–defining illness in subjects starting a nevirapine-based regimen, relative to efavirenz.[165] After 12 months of combination therapy, participants on nevirapine had smaller CD4 cell count increases and markedly higher rates of virologic failure compared with efavirenz regimens, although disagreement on some of these conclusions exists.[166]

An elevated risk of liver damage contraindicates the use of nevirapine in two subsets of patients: women with CD4 counts greater than 250 cells/mm^3 and men with CD4 counts greater than 400 cells/mm^3.[167,168] Nevirapine use should be avoided in pregnant persons with CD4 counts greater than 250 cells/mm^3.[169–172] Single-dose nevirapine, however, is associated with alarming rates of NNRTI resistance in both mothers and infants, and combination therapies are now generally recommended in these situations.[173–177] In women previously exposed to single-dose nevirapine, combination therapy with lopinavir/r is superior to nevirapine-based therapy.[178]

Resistance to nevirapine is conferred by any of the following mutations in RT: K103N, V106A/M, Y181C, Y188L, and G190A/S. All of these NNRTI mutations reduce nevirapine sensitivity by 50-fold or greater.[97,179] The existence of any of these mutations in a patient's HIV genotype precludes the effective use of nevirapine.

Etravirine

Etravirine is an NNRTI that retains some activity in the presence of certain NNRTI resistance mutations. The drug acts as an allosteric inhibitor of HIV-1 RT.

Etravirine is administered orally as two 100-mg pills (200 mg) twice daily after a meal. Ingestion without food decreases etravirine exposure by 50%. No dose adjustment is required for patients with renal insufficiency or mild-to-moderate hepatic insufficiency. As with other NNRTIs, etravirine has a relatively long half-life (41 ± 20 hours). As a substrate and inducer of CYP3A4 and an inhibitor of other CYP isozymes, etravirine has important drug-drug interactions. The drug cannot be coadministered with tipranavir, fosamprenavir, or atazanavir. Etravirine should not be used with another NNRTI or any unboosted PI and should not be given with rifampin, clarithromycin, erythromycin, or anticonvulsants such as phenytoin or carbamazepine. Etravirine has not been associated with fetal risk in animal studies, and there are no studies to define the risk of etravirine use in pregnant persons.

Two similar randomized, double-blind, placebo-controlled trials of etravirine and darunavir versus darunavir, both with optimized background therapy, demonstrated greater virologic suppression to less than 50 copies/mL after 24 weeks in subjects receiving etravirine and darunavir.[180,181] Subjects in these trials had active or historical genotypic evidence of NNRTI resistance-associated mutations. A smaller randomized, phase IIb placebo-controlled trial of etravirine versus placebo, both with optimized background therapy, however, did not demonstrate a significant reduction in viral loads in etravirine-treated subjects after 48 weeks; in this study, subjects receiving etravirine had a median of one NNRTI resistance mutation at study entry.[182] In PI-naïve subjects with baseline NRTI and NNRTI resistance mutations, an etravirine-containing regimen was inferior to a regimen containing any PI, boosted or unboosted.[183] An etravirine regimen dosed once daily was associated with fewer adverse neuropsychiatric side effects than efavirenz over 48 weeks and similar viral efficacy, although the study was not powered to demonstrate virologic noninferiority.[184]

Resistance to etravirine is associated with up to 17 different mutations in RT.[185] The most important resistance mutations appear to be Y181C and G190A, and these require the presence of other mutations to limit etravirine activity; K103N does not confer etravirine resistance. The most common adverse effects seen with etravirine are rash and nausea. The rash, described as erythema or a papular eruption, usually begins in the second week of therapy and lasts for a median of 10 days.[182] As with other NNRTIs, severe dermatologic reactions have been reported.

Protease Inhibitors (See Fig. 128.5)

Saquinavir

Saquinavir is administered as two 500-mg tablets (1000 mg) along with a ritonavir 100-mg tablet, both twice daily. The use of unboosted saquinavir is not recommended. Saquinavir bioavailability is improved with high-calorie, high-fat meals and should be taken within 2 hours of a full meal. The inhibition of CYP3A4 by saquinavir and ritonavir leads to drug-drug interactions. For example, amiodarone, midazolam, lovastatin, simvastatin, and St. John's wort should not be coadministered. Concurrent use of rifampin is contraindicated because of hepatic toxicity, and levels of oral contraceptives are decreased. A complete review of a patient's medications is warranted before the use of ritonavir-boosted saquinavir (saquinavir/r) therapy.

Early clinical experience with saquinavir was compromised by the poor bioavailability of a hard capsule formulation.[149] A soft gel capsule formulation improved bioavailability and clinical outcomes but has since been replaced by the current 500-mg tablet.[186,187] Twice-daily saquinavir/r was compared with lopinavir/r, both in combination with emtricitabine-TDF, and demonstrated similar virologic and immunologic outcomes.[188] From the perspective of patient adherence, lopinavir/r retains a lower pill burden, can be taken without food, and can be stored above 34°C. A once-daily saquinavir/r dosing schedule has also been tested but demonstrated low drug trough concentrations; this dosing schedule is not currently recommended.[189]

Adverse effects of saquinavir/r are most commonly nausea, vomiting, diarrhea, and abdominal discomfort. Saquinavir/r can prolong the QT and PR electrocardiographic intervals and lead to serious arrhythmias. The major saquinavir resistance mutation is L90M within protease, although G48V can also be selected. Minor mutations can occur at positions 10, 24, 54, 62, 71, 73, 77, 82, and 84.

Indinavir

Indinavir is not recommended for initial ART, boosted or unboosted, because of pill burden and the risk of nephrolithiasis.[14] Unboosted indinavir is administered as two 400-mg capsules every 8 hours. A boosted regimen combines two 400-mg indinavir capsules with 1 to 2 100-mg ritonavir capsule(s), twice daily. Indinavir must be taken with water, either 1 hour before or 2 hours after a meal. Meal requirements do not apply to ritonavir-boosted indinavir (indinavir/r). Indinavir has low solubility at physiologic pH and can crystallize in the kidney and urine.[190,191] Patients should increase their water intake to decrease the risk of nephrolithiasis associated with indinavir/r. CYP3A4 inhibition by indinavir can lead to multiple drug-drug interactions; a thorough review of a patient's medications is warranted before indinavir therapy. The main adverse effects seen with indinavir are nephrolithiasis, unconjugated hyperbilirubinemia without jaundice, abdominal pain, nausea, and dry skin and lips. Indinavir has been used in combination regimens with some success but has been largely replaced in recent years by less toxic and more tolerable PI regimens.[192,193] The major indinavir resistance mutations selected during therapy are M46L, V82A, and I84V. Minor mutations can occur at positions 10, 20, 24, 32, 36, 54, 71, 73, 76, 77, and 90.

Nelfinavir

Nelfinavir is not generally recommended for initial antiviral therapy because of inferior viral efficacy relative to other PIs, notably lopinavir/r, and the NNRTI efavirenz. Nelfinavir is administered as two 625-mg tablets (1250 mg total) twice daily with meals. It is primarily metabolized by CYP2C19 and CYP3A4 and is not boosted with ritonavir. Increasing doses of ritonavir did not necessarily increase the observed area under the curve of nelfinavir.[194] The potential for drug-drug interactions is significant, as for other PIs, and a thorough review of a patient's medications should be undertaken before nelfinavir therapy. Nelfinavir-induced viral suppression, when used in combination with two NRTIs, compares unfavorably with that induced by efavirenz, nevirapine, lopinavir/r, and ritonavir-boosted fosamprenavir (fosamprenavir/r), in antiretroviral-naïve patients.[90,195–198] Nelfinavir should not be used in PI-experienced patients.[199] Adverse effects with nelfinavir include loose stools or diarrhea, hypercholesterolemia, and hypertriglyceridemia. The major nelfinavir resistance mutation is D30N, and L90M is selected less commonly. Minor mutations can occur at amino acid positions 10, 36, 46, 71, 77, 82, 84, and 88 within protease.

Fosamprenavir

Fosamprenavir, the phosphorylated prodrug of amprenavir, has improved oral bioavailability and efficacy compared with the no longer available amprenavir. Pill burden has also been improved but is still greater than with some other PIs. Once ingested, fosamprenavir is converted to amprenavir in the gut. Fosamprenavir is administered as a 700-mg tablet with a 100-mg ritonavir tablet, both twice daily; a once-daily regimen of fosamprenavir 1400 mg with 100 to 200 mg ritonavir has also been used. The twice-daily regimen is preferred; once-daily fosamprenavir/r should not be used in PI-experienced patients and its use in treatment-naïve patients cannot be recommended until efficacy is demonstrated in a sufficiently large randomized clinical trial. Fosamprenavir is metabolized by CYP3A4 and is excreted in feces. The potential for drug-drug interactions is significant. No dose adjustment is required for renal insufficiency but progressive dose reductions are needed in patients with worsening hepatic dysfunction.

Early clinical experience with amprenavir demonstrates viral efficacy in combination regimens.[200] Patients receiving twice-daily fosamprenavir/r demonstrated similar viral load reductions and CD4 cell count increases when compared with those seen in nelfinavir-treated patients.[198] Less virologic failure was seen in fosamprenavir/r-treated patients than in those treated with nelfinavir. A regimen containing twice-daily fosamprenavir/r demonstrated noninferiority to a lopinavir/r-containing regimen in the proportion of patients achieving plasma HIV RNA levels less than 50 copies/mL after 48 weeks of therapy.[116] Similar increases in plasma lipid levels were seen with either therapy.

Adverse effects of fosamprenavir/r therapy include diarrhea, hypertriglyceridemia, and rash. Fosamprenavir contains a sulfonamide moiety that may explain the increased incidence of dermatologic side effects relative to other PIs. Patients with a known sulfonamide allergy should be monitored when starting fosamprenavir/r therapy. The major fosamprenavir resistance mutation is I50V, and I84V is selected less commonly.[97] The valine substitution at position 50 selected by fosamprenavir is different than the leucine substitution selected at the same position by atazanavir (I50L); these mutations do not confer cross-resistance. Minor mutations can occur at amino acid positions 10, 32, 46, 47, 54, 73, 76, 82, and 90.

Lopinavir/Ritonavir

Lopinavir is available only as a coformulation with ritonavir. First-pass metabolism limited lopinavir/r plasma concentrations, whereas ritonavir boosting dramatically improved drug trough concentrations.[201] The most recent formulation of lopinavir-r is a heat-stable tablet that is administered as two lopinavir/r 200-mg/50-mg tablets twice daily. This tablet can be taken without regard to food, although lopinavir/r solution should still be taken with meals. Lopinavir/r can also be given once a day, although not to pregnant persons. Decreased clearance is not expected with renal insufficiency, and some increase in lopinavir/r exposure occurs with worsening hepatic dysfunction. Significant CYP3A4 inhibition occurs, and a patient's medications should be thoroughly reviewed before lopinavir/r therapy.

Lopinavir/r has demonstrated efficacy in combination regimens in treatment-naïve and treatment-experienced patients, and it has been frequently used as the comparator PI in noninferiority trials of new or newly formulated PIs.[196,202] Lopinavir/r is superior to nelfinavir, whereas atazanavir/r, darunavir/r, fosamprenavir/r, and saquinavir/r have demonstrated noninferior virologic outcomes when compared with lopinavir/r in treatment-naïve subjects.[41,116,141,196,203,204] Virologic suppression on a lopinavir/r and two-NRTI regimen can be maintained for at least 7 years.[205] A comparison of lopinavir/r or efavirenz, either with two NRTIs, demonstrated superior virologic efficacy of an efavirenz-containing regimen but greater CD4 cell count gains with the lopinavir/r-containing regimen.[91] Less drug resistance associated with virologic failure was seen in subjects randomized to lopinavir/r.

Adverse effects seen with lopinavir/r are primarily gastrointestinal: diarrhea or loose stools, nausea, and, less commonly, vomiting. Hypercholesterolemia and hypertriglyceridemia are reported in patients taking lopinavir/r. The major lopinavir/r resistance mutation is V82A, although V32I and I47A can also be selected. Lopinavir/r resistance requires the accumulation of multiple mutations, often six or more, before the drug loses clinical effectiveness.[206,207] This is unlikely to occur in treatment-naïve patients receiving lopinavir/r as part of recommended combination therapy. Minor mutations have been documented at positions 10, 20, 24, 33, 46, 50 (I50V), 53, 54, 63, 71, 73, 76, 84, and 90. When mutations V32I and I47A are found together with mutations at position 46, they are associated with high-level lopinavir/r resistance.[208,209]

Tipranavir

Tipranavir is a nonpeptidic PI approved for use in treatment-experienced patients with resistance to multiple other PIs. The drug is administered at 500 mg twice daily with ritonavir 200 mg twice daily, and should be taken with a high-fat meal. No dose adjustments are required for patients with renal or mild hepatic impairment; tipranavir is contraindicated in patients with moderate-to-severe liver dysfunction. Tipranavir capsules are thermally labile and must be kept below 77°F. Complex drug-drug interactions occur as a result of the net effect of tipranavir and ritonavir inducing P-glycoprotein and inhibiting CYP3A4. As a consequence, tipranavir cannot be coadministered with rifampin, several antiarrhythmics, lopinavir, saquinavir, and amprenavir. Numerous other tipranavir interactions exist, including increases in rifabutin levels and significant reductions in the levels of coadministered methadone and oral contraceptives. Tipranavir has been shown to induce adverse fetal effects in animal studies; no studies assessing risk in pregnant persons have been performed.

The efficacy of tipranavir in treatment-experienced subjects with PI-resistant virus was demonstrated in two randomized trials, RESIST-1 and RESIST-2.[210] Subjects enrolled in these trials were required to have at least one primary PI resistance mutation but could not have more than three at codons 33, 82, 84, or 90. After 48 weeks, more subjects randomized to tipranavir-ritonavir plus optimized background therapy achieved viral loads of less than 50 copies/mL than did subjects receiving a ritonavir-boosted comparator PI (23% vs. 10%, respectively).[210] Tipranavir-ritonavir has also shown sustained virologic responses in pediatric and adolescent patients.[211]

Tipranavir has been associated with severe hepatotoxicity and intracranial hemorrhage. Thirteen of 6840 patients receiving tipranavir in clinical trials developed intracranial hemorrhages, and for this reason, patients at risk for bleeding from trauma, surgery, or other medical conditions (e.g., hemophilia), or who are taking other drugs that increase the risk for bleeding, should not receive tipranavir. The most common adverse effects seen with tipranavir are nausea and diarrhea, in part because of the increased dosage of ritonavir required for boosting. Tipranavir contains a sulfonamide moiety; the proportion of patients with a sulfonamide allergy that react unfavorably to tipranavir is unknown.

Entry Inhibitors

HIV entry shares common mechanisms with several other enveloped viruses.[212] The HIV-1 surface glycoproteins gp120 and gp41 mediate

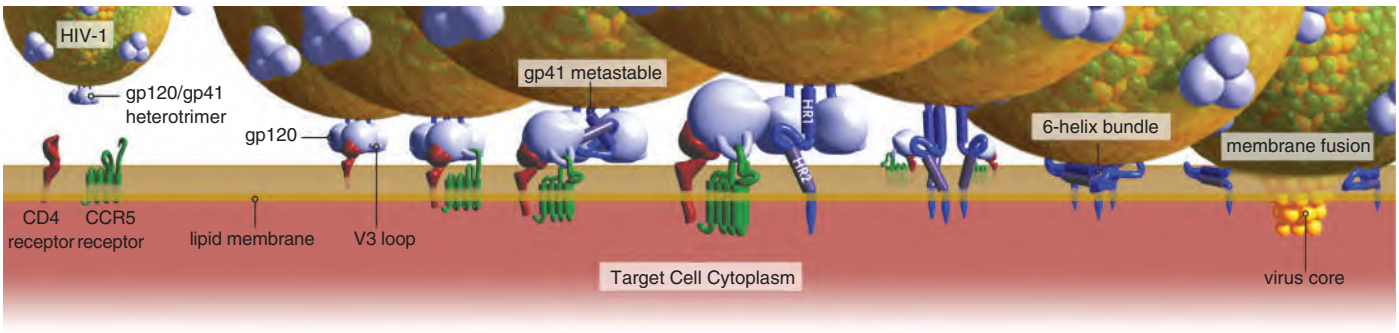

FIG. 128.6 Human immunodeficiency virus entry. Entry *(from left to right)* requires CD4, envelope glycoproteins assembled as a heterotrimer, and a coreceptor, in this case CCR5. Binding of CD4 to glycoprotein gp120 exposes a flexible third hypervariable (V3) loop. The V3 loop interacts with both the N-terminus and the second extracellular loop (ECL2) of CCR5, leading to the release of gp41 by a currently unknown mechanism. Gp41 inserts into the target cell membrane, and rearranges and brings the HR1 and HR2 domains together to form a six-helix bundle. Viral and cellular membranes then approximate, leading to fusion. *CCR5,* C-C motif of chemokine receptor 5; *HR1,* heptad repeat 1; *HR2,* heptad repeat 2. *(Reprinted with permission from Louis B. Henderson, PhD, and the Physicians' Research Network, Inc. See Tsibris A. Update on CCR5 inhibitors: scientific rationale, clinical evidence, and anticipated uses.* https://www.prn.org/images/pdfs/86_tsibris_athe.pdf. *Accessed December 2007.)*

viral binding to and membrane fusion with host target cells (Fig. 128.6 and see Table 128.2). The *ENV* gene product is first translated as gp160 and then cleaved intracellularly into gp120 and gp41. On the viral membrane, there is a noncovalent association of one molecule of gp120 with one molecule of gp41.[213] Three of these units aggregate on the membrane surface to form the gp120/gp41 heterotrimer.[214–216] The association of gp120 with gp41 in the trimer traps gp41 in a conformationally metastable state, the energy from which can later be exploited to accelerate the rate of fusion.[217]

Binding of gp120 to its primary receptor on the cell surface, CD4, is the first step leading to membrane fusion. After CD4 binding, sequential binding of coreceptor occurs, although some interactions of CD4 with gp120 lead to inappropriate shedding of gp120 and inactivation of the fusion reaction.[218] If gp120 is not shed, fusion requires the binding of either the C-C motif of chemokine receptor 5 (CCR5) or C-X-C chemokine receptor 4 (CXCR4) to proceed.[219–223] The interaction of gp120 with CD4 forms the coreceptor binding site.[224] Coreceptor recognition is defined by several structural elements of gp120 that include the V1-V2 hypervariable region, the bridging sheet (an antiparallel, four-stranded β sheet that connects the inner and outer domains of gp120), and most importantly, the V3 hypervariable loop.[224–227] According to current models of HIV-1 entry, sequential binding of gp120 to CD4 and the coreceptor leads to the release of gp41 from its metastable conformation. The hydrophobic N-terminal fusion domain of gp41, now free, inserts into the target membrane.[217,228,229] Two trimeric coiled-coil structures in gp41, termed heptad repeat 1 (HR1) and heptad repeat 2 (HR2), rearrange to form a six-helix bundle that leads to the approximation of the two membranes and eventual fusion.[212] Enfuvirtide is a peptide mimetic of gp41 HR2 that interferes with the HR1-HR2 association, whereas maraviroc binds to CCR5, changes its conformation, and prevents gp120-CCR5 binding (see Table 128.2).[230]

Enfuvirtide

Enfuvirtide is a 36-amino-acid synthetic peptide that is administered as a 90-mg subcutaneous injection twice daily; the location of the injection does not affect bioavailability. No dose adjustment is required for hepatic or renal impairment. No clinically significant drug interactions with enfuvirtide have been reported. Studies in animals demonstrated no teratogenic effects of enfuvirtide, and there are no formal studies in pregnant persons to assess fetal risk from enfuvirtide use.

Two similar randomized, open-label trials in treatment-experienced subjects with advanced HIV disease (median CD4 count <100 cells/μL) demonstrated greater viral load reductions when enfuvirtide was added to an optimized background regimen.[231,232] Enfuvirtide use in enfuvirtide-naïve subjects also adds virologic benefit when used in combination with darunavir, tipranavir, maraviroc, and raltegravir, underscoring the added benefit to patients when at least two active drugs are included in salvage regimens.[68,139,210,233] Enfuvirtide is not currently recommended for treatment-naïve patients.

The need for twice-daily injections, along with the adverse effects that accompany those injections, have limited the clinical use of enfuvirtide. Injection site reactions that include pain, erythema, nodules, cysts, induration, and pruritis are seen in 98% of patients injecting enfuvirtide. Nausea, diarrhea, fatigue, and insomnia have also been reported. Resistance to enfuvirtide is conferred by amino acid substitutions in the HR1 region of gp41, most commonly at positions 36, 38, 40, and 43.[97]

Maraviroc

Maraviroc is a CCR5 antagonist (see Fig. 128.3 and Table 128.2). HIV entry requires viral gp120 to sequentially bind CD4 and a surface coreceptor, either CCR5 or CXCR4. Maraviroc is an allosteric inhibitor of the gp120-CCR5 interaction that blocks HIV attachment to target cells and thereby reduces viral replication.

Maraviroc is typically administered as 300 mg twice daily; the drug has not yet been adequately studied in patients with renal or hepatic dysfunction. Maraviroc is a substrate for CYP3A. This necessitates a dose reduction to 150 mg twice daily during coadministration with CYP3A inhibitors such as PIs (with the exception of ritonavir-boosted tipranavir), ketoconazole, or clarithromycin, and the dose increases to 600 mg twice daily during coadministration with CYP3A inducers, such as efavirenz, nevirapine, and some anticonvulsants. All patients should be screened for viral coreceptor usage before starting maraviroc, and this drug should not be used in patients with evidence of circulating CXCR4-using virus. Phenotypic and genotypic coreceptor usage assays are commercially available, although a phenotypic assay was used to determine coreceptor usage in the major maraviroc clinical trials. A phenotypic tropism assay is therefore generally preferred in routine clinical practice.

Maraviroc may be used in treatment-experienced and treatment-naïve patients in the United States. Two similar clinical trials in treatment-experienced subjects with CCR5-using viruses compared maraviroc versus placebo, both with optimized background therapy.[233,234] After 48 weeks, a greater proportion of maraviroc-treated subjects achieved plasma viral loads less than 50 copies/mL and had greater increases in $CD4^+$ T-cell counts than did placebo recipients. For subjects taking at least three active drugs, similar proportions in the placebo and maraviroc dosing arms achieved undetectable HIV RNA levels. Maraviroc confers no virologic benefit in subjects with dual/mixed virus.[235] In a 48-week study in treatment-naïve subjects, maraviroc was compared with efavirenz, either in combination with zidovudine-lamivudine; the results for HIV RNA levels less than 50 copies/mL did not meet criteria set to demonstrate noninferiority for maraviroc in this study.[236] Adverse effects

seen with maraviroc include cough, fever, upper respiratory infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness. A modest increase in liver-related adverse events was seen in subjects receiving maraviroc, most commonly elevated transaminases and increased bilirubin.

High-level maraviroc resistance can occur by the selection of amino acid substitutions in the third hypervariable (V3) loop of gp120. The intrinsic sequence variability of this region, however, has precluded the identification of canonical genotypic resistance mutations. In clinical trials, genotypic maraviroc resistance has been uncommon compared with escape via selection of minority CXCR4-using viral populations that circulate below the detection limit of coreceptor usage assays. Therefore, changes in coreceptor usage, rather than emergence of true resistance, are the dominant mechanism for virologic escape from maraviroc. In clinical trials to date, discontinuation of maraviroc generally resulted in a loss of detectable CXCR4-using viruses and a reappearance of CCR5-using viral populations.

Ibalizumab

Ibalizumab is a humanized monoclonal antibody that binds CD4 and inhibits postattachment steps in HIV-1 entry. Ibalizumab is not believed to interfere with normal CD4 function and does not prevent HIV-1 gp120 binding to CD4. Ibalizumab is administered intravenously as a single loading dose of 2 g, followed by an 800-mg intravenous infusion every 2 weeks thereafter. The clinical experience with ibalizumab is extremely limited when compared to other antiretroviral medications. The primary and only safety evaluation of ibalizumab comes from a 40-participant study conducted over 25 weeks.[236a] Participants were heavily treatment-experienced, harbored multidrug-resistant HIV-1, and were failing a salvage antiretroviral regimen. Baseline viral loads and CD4 counts were 4.5 $\log_{10}$ copies/mL and 73 cells/mm^3, respectively. In combination with an optimized background regimen that contained at least one drug to which a participant's virus was susceptible, 43% of participants achieved viral load levels less than 50 copies/mL after 25 weeks. Less virus response was observed at lower CD4 counts and higher baseline viral loads. The most common side effects seen in this small study were diarrhea, dizziness, nausea, and rash; creatinine elevations occurred in 10% of participants. Another formulation of ibalizumab was administered intramuscularly, was well tolerated, and reduced viral loads by up to 1.2 logs.[237] The use of ibalizumab should be restricted to patients with multidrug-resistant HIV-1 who are failing a salvage treatment regimen.

Another monoclonal antibody, PRO 140, which binds to CCR5, has been administered subcutaneously to patients with CCR5-topic HIV-1 infection, and was reported to reduce mean viral load activity by 1.65 $\log_{10}$.[238]

INITIATING ANTIRETROVIRAL THERAPY

Recommendations regarding when to initiate ART for HIV infection have varied widely over the years. Overwhelming data now support universal treatment for people with HIV, regardless of CD4 counts. For all patients, regardless of duration of infection or prior treatment experience, the goal of therapy is the reduction of plasma viral load to less than 50 copies/mL. Guidelines from expert panels are published and periodically updated; comprehensive online versions of these recommendations are available.[13–15]

When to Begin Therapy?

The decision to begin ART for any patient must balance the burden and toxicity of the drug regimen against the benefits of decreased HIV-related morbidities and increased life expectancy (Table 128.5). Although clinicians are most comfortable considering the deleterious consequences of HIV infection in discrete quanta of CD4 counts (e.g., <50, <200, >350 cells/mm^3), there is a continuum, without clear demarcation, in the risk of progression to AIDS and death across the range of declining CD4 counts, from 650 cells/mm^3 or more to less than 50 cells/mm^3.[239–242] This includes causes of death not usually attributed to HIV infection itself.[243–249] As the risks associated with ART have decreased because of more potent drug combinations, lower pill burdens that improve adherence, and newer medications with fewer short-term and long-term toxicities, the risk-benefit ratio of initiating ART earlier in the course of disease has shifted toward beginning therapy at higher CD4 cell counts.[250]

TABLE 128.5 When to Initiate Antiretroviral Therapy in Adolescents and Adults

Recommend Initiation of Therapy
All patients with HIV, regardless of CD4 count
Conditions Favoring Early Initiation of Therapy
Acute or recent HIV infection, *or* AIDS-defining conditions, including HIV-associated dementia and AIDS-associated malignancies, *or* Pregnancy, *or* HIV-associated nephropathy, *or* Lower CD4 counts (<200 cells/mm^3), *or* Acute opportunistic infections, *or* HIV RNA >100,000 copies/mL, *or* CD4 decline >100 cells/mm^3/yr, *or* Hepatitis B coinfection, *or* Hepatitis C coinfection

AIDS, Acquired immunodeficiency disease; *HIV,* human immunodeficiency disease; *RNA,* ribonucleic acid.
Modified in part from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: US Department of Health and Human Services. https://aidsinfo.nih.gov/contentfiles/lvguidelines/glchunk/glchunk_11.pdf. Accessed August 4, 2015; and Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society–USA panel. JAMA. *2012;308:387–402.*

Most treatment guidelines now recommend ART for all patients with HIV, regardless of CD4 count.[14] The level of evidence to support therapy initiation guidelines is strongest for CD4 counts less than 200 cells/mm^3. Patients who initiate therapy with CD4 counts between 200 and 350 cells/mm^3 have reduced rates of death, opportunistic infections, and serious non-AIDS events and an increase in rates of maximal virologic suppression and CD4 cell count rises.[241,251–261] Between 350 and 500 cells/mm^3, cohort studies and randomized controlled trials have demonstrated a decreased risk of HIV-related disease progression, relative to patients who initiated therapy at CD4 counts less than 350 cells/mm^3.[262–266]

A randomized controlled trial of 4685 participants (the Strategic Timing of AntiRetroviral Treatment [START] study) recently demonstrated that early initiation of ART in patients with a CD4 count greater than 500 cells/mm^3 was associated with reduced disease progression and mortality when compared with delayed therapy.[267] In this study, individuals were randomized to start ART immediately or to defer until the CD4 count decreased to 350/mm^3 or AIDS developed. The primary end point (development of a serious AIDS or non-AIDS event) occurred in 42 participants in the immediate group versus 96 participants in the deferred group (hazard ratio, 0.43; 95% confidence interval, 0.30–0.62; $P < .001$). The majority of primary end points in both groups occurred when the CD4 count was greater than 500/mm^3. A second study, the Temprano trial, enrolled 2056 individuals in Côte d'Ivoire with CD4 cell counts greater than 500/μL and demonstrated that ART started at CD4 cell counts greater than 500/μL reduced the risk of serious infection and death by 44% when compared with ART initiation using World Health Organization guidelines at the time.[268] Together these two clinical end point trials provide convincing evidence that ART should be started as soon as possible in nearly all patients with HIV once the diagnosis is made.

If ART should begin as soon as possible, how soon is too soon? Immediate ART initiation following HIV diagnosis has recently been studied in both resource-limited and resource-rich settings. An unblinded randomized controlled trial of single-visit ART initiation in Johannesburg, South Africa, enrolled 377 participants and demonstrated greater rates of virologic suppression, defined as HIV-1 RNA levels less than 400 copies/mL within 10 months of study enrollment, in participants randomized to "rapid" ART when compared to standard ART initiation (64% vs. 51%,

respectively).[268a] Approximately 70% of patients in the rapid ART arm initiated same-day therapy, with 96% of rapid arm participants starting within 1 month. A 703-participant study of same-day ART initiation in Haiti demonstrated greater proportions of those participants randomized to same-day ART retained in care and virologically suppressed at 12 months, when compared to participants who initiated ART within 3 weeks of diagnosis.[268b] In San Francisco, California, participants enrolled in a program that offered ART initiation on the same day of diagnosis had faster times to virologic suppression when compared to participants offered standard-of-care ART initiation, and median time from care to ART was reduced by 96% (27 days vs. 1 day).[268c,268d] A rapid-entry program of economically and socially disenfranchised people with HIV in Atlanta, Georgia, reduced the time to ART initiation and the time to virus suppression.[268e] The accumulating data suggest that ART initiation on the same day as HIV diagnosis is feasible and demonstrates benefits at the individual- and population-based levels.

Treatment of HIV infection across CD4 strata may play an important role in limiting HIV transmission, a strategy known as "treatment as prevention." An observational study of nearly 3400 heterosexual patients with HIV and their uninfected partners (i.e., serodiscordant couples) demonstrated a 92% reduction in HIV transmission rates when the partner with HIV received ART.[269] In the HPTN 052 study, serodiscordant heterosexual couples in which the partner with HIV had a median CD4 count of approximately 450 cells/mm^3 were randomized to immediate or delayed ART and followed prospectively.[270] A 96% reduction in HIV transmission was observed in participants who received early ART. Early ART participants had increased CD4 counts and decreased rates of extrapulmonary tuberculosis. These data were the first from a randomized controlled trial to definitively demonstrate both a personal benefit to patients with HIV from early ART initiation and a public health benefit from a reduction in the rates of HIV transmission.

Although treatment guidelines play a useful role in helping physicians decide when to start therapy, patient willingness and readiness to start lifelong therapy are critical, and the role of meticulous adherence in ART success is undeniable.[271–273] The deferral of therapy until adherence can be maximized is preferable to suboptimal or incomplete therapy.

What to Begin With?

Several patient and virus factors need to be considered when choosing an initial regimen (Table 128.6). These include existing comorbidities (e.g., cardiovascular, renal, or psychiatric disease), potential adverse drug effects and interactions with other medications the patient may be receiving, pill burden, pregnancy or pregnancy potential, convenience, resistance testing results, access, cost, and potential patient adherence. Determining the drug susceptibility of a patient's HIV isolate is also an important step in constructing a combination antiretroviral regimen. Based on the results of genotypic testing, a regimen can be constructed that maximizes the probability of virologic suppression while minimizing adverse effects, toxicities, and pill burden for the patient. Fixed-dose combinations have become a mainstay of initial therapeutic regimens and have simplified the available choices. Most regimens in the United States will consist of a dual-NRTI backbone in combination with an INSTI.

TABLE 128.6 What Antiretroviral Regimens to Start

RECOMMENDED REGIMENS
Dolutegravir-abacavir-lamivudine[b,c]
Dolutegravir + tenofovir (TDF or TAF)-emtricitabine[b,c]
Raltegravir + tenofovir (TDF or TAF)-emtricitabine
Bictegravir-TAF-emtricitabine

[a]Recommendations from the 2018 U.S. Department of Health and Human Services (HHS) Antiretroviral Guidelines Panel.[14]
[b]Only for patients who are HLA-B*5701 negative.
[c]Dolutegravir may be associated with a risk of neural tube defects.[87h–87j] See reference 14 for HHS guidance regarding use.
TAF, Tenofovir alafenamide fumarate; *TDF,* tenofovir disoproxil fumarate.

Dual-NRTI Backbone

Three two-NRTI fixed-dose combinations are commercially available: tenofovir prodrug (TDF or TAF) plus emtricitabine, abacavir plus lamivudine, and zidovudine plus lamivudine. When considering TAF versus TDF, in general TAF has less bone and kidney toxicity, whereas TDF is associated with lower lipid levels. The combination of zidovudine and lamivudine, long the most widely used fixed-dose NRTI combination, has been replaced by tenofovir prodrug (TDF or TAF) and emtricitabine in the developed world as the most commonly used dual-NRTI combination.

Two studies have directly compared abacavir-lamivudine and TDF-emtricitabine, either in combination with lopinavir/r (the HEAT study) or in conjunction with a comparison of efavirenz and atazanavir/r (ACTG 5202). In the HEAT study, a similar proportion of patients in either treatment arm had achieved viral loads of less than 50 copies/mL after 48 weeks, regardless of initial screening viral loads.[18] In the larger ACTG 5202 trial, however, abacavir-lamivudine-treated subjects with initial viral loads greater than 100,000 copies/mL had an elevated hazard ratio of virologic failure compared with subjects receiving TDF-emtricitabine, forcing an independent data safety monitoring board to recommend that this arm of the study be discontinued.[16] Abacavir-lamivudine should therefore be used with caution in patients with viral loads greater than 100,000 copies/mL, pending further data in this population. Similar viral efficacy was observed in a study of abacavir-lamivudine in combination with dolutegravir, regardless of pretreatment plasma HIV-1 RNA levels.[87] Concerns have also been raised about a possibly increased cardiovascular risk associated with concomitant abacavir use, although more data are needed.[25,155] Until such information is available, caution is advised regarding abacavir use in patients with preexisting cardiac risk factors.[14]

Regimens containing a single NRTI in combination with an NNRTI and a PI, or NRTI-sparing regimens have been studied, generally with inferior results. Subjects randomized to receive an NRTI-NNRTI-PI combination discontinued treatment more frequently because of side effects than subjects receiving either a dual-NRTI–NNRTI or dual-NRTI–PI combination regimen.[274] An NRTI-sparing regimen of efavirenz and lopinavir/r was more likely to be associated with drug resistance, had increased frequencies of lipid elevations, and showed greater rates of virologic failure in patients with viral loads greater than 100,000 copies/mL when compared with a dual-NRTI–efavirenz or dual-NRTI–lopinavir/r combination regimen.[91] An NRTI-sparing regimen of raltegravir plus darunavir/r resulted in high rates of virologic failure.[275] Based on these findings, combination therapy without a dual nucleoside backbone is not generally recommended for initial ART, although trials of NRTI-sparing regimens continue.

Initial INSTI-, NNRTI-, or PI-Based Therapy

NNRTI-, PI-, and INSTI-based therapies, in combination with a dual-NRTI backbone, all provide effective suppression of HIV-1 replication and reconstitution of CD4 cell counts. The use of NNRTIs in initial therapy has been largely eclipsed by the successful development of more effective PI- and INSTI-based combination therapies. In general, integrase inhibitor–based regimens have demonstrated either noninferiority (raltegravir and elvitegravir) or superiority (dolutegravir) to some NNRTI- or PI-based regimens when tolerability and virologic and immunologic outcomes were compared. While the choice of whether to use an NNRTI, a boosted PI, or an INSTI in combination with two NRTIs as initial therapy needs to be individualized, INSTI options are preferred.[13–15]

Initial Integrase Inhibitor–Based Therapy

Treatment with integrase inhibitor–based therapy represents all of the regimens currently recommended by the HHS Antiretroviral Guidelines Panel.[14] Dolutegravir is dosed once daily while raltegravir is administered once or twice daily; bictegravir is coformulated into one once-daily pill. Although raltegravir and elvitegravir have not been directly compared as initial therapy in a clinical trial, raltegravir may be considered over fixed-dose coformulated elvitegravir in settings in which fewer drug-drug interactions, no food requirement, and no association with proximal renal tubulopathy or inhibition of creatinine secretion are relevant. One

study has demonstrated the noninferiority of dolutegravir when compared with raltegravir.[81]

Initial PI-Based Regimens

Several clinical trials have evaluated which PIs to use initially. Darunavir/r is preferred in certain clinical scenarios unless patients are intolerant to ritonavir-associated side effects. Atazanavir/r, darunavir/r, fosamprenavir/r, and saquinavir/r have all demonstrated noninferiority to lopinavir/r.[116,141,203,276] Atazanavir/r has fewer gastrointestinal side effects and may induce fewer changes in lipid profiles than lopinavir/r but is associated with more hyperbilirubinemia than other regimens, a toxicity that increases treatment discontinuation when compared with darunavir/r.[129,276] Nelfinavir and indinavir no longer have important roles in initial therapy.[196,198]

Alternative NNRTI-Based Regimens

Depending on comorbidities, in certain clinical situations alternative (e.g., efavirenz-based) regimens may be preferable to recommended regimens, recognizing the low genetic barrier to resistance of this class. Efavirenz is preferred over nevirapine for therapy in most treatment-naïve patients because of less toxicity and possibly greater efficacy. In pregnant persons and persons of child-bearing age who might become pregnant, alternatives to efavirenz should be considered, and nevirapine may be preferable. Similarly, in individuals with preexisting psychiatric disturbances, some prefer nevirapine or rilpivirine over efavirenz because of efavirenz-associated neuropsychiatric side effects. Rilpivirine may be considered in patients with pretreatment HIV-1 RNA level loads less than 100,000 copies/mL and CD4 counts greater than 200 cells/mm^3.

Triple NRTI and Four-Drug Therapy

Three-drug NRTI therapy has been compared with other regimens in clinical trials and is not generally recommended.[92,277] A comparison of TDF versus efavirenz, both combined with abacavir-lamivudine, resulted in a high rate of virologic nonresponse in treatment-naïve TDF-treated subjects, together with high rates of the M184V (98% of subjects tested) and K65R (54%) resistance mutations.[47]

No advantages have been demonstrated for four-drug versus three-drug initial regimens. In early trials, the addition of a PI to a three-drug regimen of two NRTIs plus an NNRTI provided no additional benefit.[90] The addition of a fourth drug to two-class, three-drug therapy confers no additional benefit. In a randomized, double-blind trial, standard three-drug therapy (zidovudine-lamivudine-efavirenz) had similar efficacy to four-drug therapy (zidovudine-lamivudine-efavirenz-abacavir), even in subjects with initial viral loads greater than 100,000 copies/mL.[20] In subjects with virologic suppression on a zidovudine-lamivudine-abacavir regimen, the addition of either TDF or efavirenz resulted in similar rates of virologic suppression maintenance; treatment failures were also similar.[278]

Two-Drug Therapy

While combinations of three active drugs remain the mainstay of ART, researchers have begun to explore the role of initial two-drug therapy in investigational regimens. An 805-participant study in France of treatment-naïve participants randomized to raltegravir twice daily or coformulated TDF and emtricitabine once daily, both with darunavir/r, demonstrated noninferior rates of virologic and clinical failure with raltegravir plus darunavir/r over 96 weeks, when compared to the more standard three-drug regimen of TDF, emtricitabine, and darunavir/r.[278a] There were caveats, however. Participants with baseline CD4 counts below 200 cells/mm^3 had more failures in the two-drug arm and there was a trend toward more failure in the two-drug arm in patients with viral loads greater than 100,000 copies/mL, a finding noted in two other studies that evaluated ritonavir-boosted darunavir plus raltegravir.[275,278b] A two-drug combination of lopinavir/r and lamivudine had noninferior rates of virologic suppression when compared to lopinavir/r and two NRTIs at 48 weeks.[278c] While this regimen is impractical due to pill burden, the side effect profile of lopinavir/r, and the need for twice-daily dosing, it does highlight the general point that some two-drug regimens may hold promise as initial ART. Studies are currently ongoing to evaluate additional two-drug combinations, specifically dolutegravir plus lamivudine and darunavir/r plus lamivudine.

Interrupting Therapy

Temporary discontinuations of antiretroviral treatment, whether referred to as structured treatment interruptions or intermittent therapy, have been studied in patients with HIV infection as a strategy to minimize drug toxicities and cost, decrease treatment fatigue, improve quality of life, stimulate HIV-specific immune responses, or minimize the emergence of drug-resistance viruses. In many of these respects, interruptions of therapy have been unsuccessful. The body of available evidence suggests a lack of benefit to structured treatment interruptions, and a large study demonstrated potential harm with this approach.[240,279] Several other studies have also supported the proposition that discontinuing therapy has detrimental effects on outcome.[280–282] Taken together, the available evidence on the use of treatment interruptions in HIV infection suggests a lack of benefit and the potential for harm with treatment interruption. Treatment interruptions are, thus, not a recommended strategy, and their use should generally be limited to the research setting as part of a clinical trial.

LABORATORY TESTING DURING ANTIRETROVIRAL THERAPY

CD4-based criteria are most widely used to determine when ART should be initiated. Resistance testing, HLA-B57 typing, and plasma viral RNA load monitoring are also important laboratory tests that assist the clinician in designing the most effective and patient-specific antiretroviral regimen. When CCR5 antagonist therapy is being considered, coreceptor tropism testing is essential. Routine monitoring of hepatic and renal function, along with serum lipids, fasting glucose, and hematologic parameters, should be undertaken when appropriate (Table 128.7).

CD4 T-Cell Counts

CD4 T-cell counts should be determined when an HIV diagnosis is made and monitored at intervals thereafter. However, the value of frequent (every 3–4 months) CD4 count monitoring in HIV clinical management has been called into question.[283] Patients with plasma viral loads less than 200 copies/mL and CD4 counts greater than 300 cells/mm^3 had a greater than 97% chance of maintaining durable CD4 counts greater than 200 cells/mm^3 for 4 years. Once combination ART is started, the CD4 count may reasonably be expected to increase between 50 to 150 cells/mm^3 in the first year and 50 to 100 cells/mm^3 in the second year.[284,285] In patients initiating therapy when CD4 counts fall below 200 cells/mm^3, only a minority reconstitute their CD4 counts to greater than 500 cells/mm^3 after 4 years.[284] CD4 counts can often reach levels considered normal in patients who initiate therapy with CD4 counts greater than 350 cells/mm^3.[286] For patients with consistently suppressed viral loads who have been on ART for 2 years or more, the HHS guidelines recommend yearly testing for those with CD4 counts of 300 to 500 cells/mm^3 and optional testing for those with CD4 counts greater than 500 cells/mm^3.[14]

HLA-B*5701 Screening

Prospective screening for the HLA-B*5701 allele reduces substantially, but does not eliminate, the risk of an abacavir hypersensitivity reaction.[24,287] All patients being considered for an abacavir-containing regimen should first undergo HLA-B*5701 testing. Patients who test positive for this allele should not receive abacavir therapy. Abacavir skin patch testing is not recommended.

Plasma Viral Load Monitoring

Viral load monitoring is necessary to assess the response to ART and the durability of virologic suppression. The goal of all ART, whether in treatment-naïve or treatment-experienced patients, living in developed or developing countries, is suppression of plasma HIV RNA to undetectable levels (<50 copies/mL). Viral load should be measured before starting therapy, 2 to 8 weeks later, and then at 4- to 8-week intervals until HIV RNA is no longer detectable. At least a 1 $\log_{10}$ reduction in viral load should be expected at 4 weeks, with a decline in plasma HIV RNA to less than 50 copies/mL by 16 to 24 weeks of therapy. More

TABLE 128.7 Laboratory Monitoring Before and During Antiretroviral Therapy

	ENTRY INTO CARE	STARTING[a] OR MODIFYING ART	2–8 WEEKS POST-ART	EVERY 3–6 MONTHS	EVERY 6 MONTHS	EVERY 12 MONTHS	TREATMENT FAILURE
CD4 T-cell count	✔	✔		✔[b]		✔[c] (after 2 yr)	✔
HIV viral load	✔	✔	✔[d]	✔[e]	✔[e]		✔
Resistance testing	✔	✔[f]					✔
HLA-B*5701 testing		✔[g]					
Tropism testing		✔[h]					✔[h]
Hepatitis B serology (HBsAb, HBsAg, HBcAb)[i,j,k]	✔	✔				✔	
Hepatitis C screening (HCV Ab or RNA)[l]	✔					✔[m]	
Basic chemistries[n]	✔	✔	✔	✔			
ALT, AST, total bilirubin	✔	✔	✔	✔			
CBC with differential	✔	✔			✔		
Fasting lipid profile[o]	✔	✔				✔	
Fasting glucose or hemoglobin A_{1c}	✔	✔		✔[p]		✔[p]	
Urinalysis[q]	✔	✔			✔[r]	✔	
Pregnancy test		✔[s]					

[a]If ART initiation occurs soon after the HIV diagnosis and entry into care, then repeat baseline testing is not needed.
[b]During the first 2 years of ART or if viremia develops while the patient is on ART or the CD4 count is <300 cells/mm^3.
[c]After 2 years on ART with consistently suppressed viral load, check every 12 months for CD4 count 300–500 cells/mm^3; for CD4 count >500 cells/mm^3, CD4 monitoring is optional.
[d]If HIV RNA is detectable at 2–8 weeks, repeat testing every 4–8 weeks until viral load is <200 copies/mL.
[e]For patients on ART, viral load is typically measured every 3–4 months. This interval may be extended to every 6 months for adherent patients with stable CD4 counts and consistently suppressed viral loads.
[f]Resistance testing should include genotypic drug resistance testing for mutations in the reverse transcriptase and protease genes. If there is a clinical concern for transmitted INSTI resistance, integrase resistance mutation testing may be included.
[g]If considering abacavir.
[h]If considering a CCR5 antagonist or for failure of a regimen that includes a CCR5 antagonist.
[i]ART regimens for patients with HIV and HBV infection should include TAF or TDF plus either lamivudine or emtricitabine.
[j]If HBsAb, HBsAg, and HBcAb are negative, administer HBV vaccine series.
[k]An isolated positive HBcAb is most consistent with resolved HBV infection and loss of HBsAb. Consider HBV viral load testing for confirmation.
[l]HCV antibody testing may be inadequate to screen for HCV infection acquired in the past 6 months or HCV infection of any duration in patients with CD4 counts <100 cells/mm^3.
[m]Repeat screening for at-risk patients: injection drug users, MSM, jailed persons, and people with percutaneous/parenteral exposure to blood in unregulated settings.
[n]Serum sodium, potassium, chlorine, bicarbonate, BUN, creatinine, fasting glucose, and creatinine-based estimated glomerular filtration rate. Measure serum phosphorus in patients with chronic kidney disease on a TAF- or TDF-containing regimen.
[o]If normal at baseline test, check yearly. If borderline or abnormal, check every 6 months.
[p]If normal, check every 12 months. If abnormal at last measurement, check every 3–6 months.
[q]Urine glucose and protein should be checked before starting a TAF- or TDF-containing regimen
[r]If on a TAF- or TDF- containing regimen, check every 6 months. Otherwise, check urinalysis yearly.
[s]In woman with child-bearing potential.
ALT, Alanine aminotransferase; *ART,* antiretroviral therapy; *AST,* aspartate aminotransferase; *BUN,* blood urea nitrogen; *CBC,* complete blood count; *HBcAb,* hepatitis B core antibody; *HBsAb,* hepatitis B surface antibody; *HBsAg,* hepatitis B surface antigen; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HCV Ab,* hepatitis C virus antibody; *HIV,* human immunodeficiency virus; *HLA,* human leukocyte antigen; *INSTI,* integrase strand transfer inhibitor; *MSM,* men who have sex with men; *TAF,* tenofovir alafenamide fumarate; *TDF,* tenofovir disoproxil fumarate.
Modified from US Department of Health and Human Services, Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed April 13, 2018.

rapid virus decay kinetics may be observed with INSTI-based therapy, although the clinical significance of this is unknown.[87] Viral blips, or transient viral load increases to between 50 and 1000 copies/mL in a patient with previously suppressed plasma HIV RNA, are occasionally seen but do not appear to be associated with eventual virologic failure and do not necessitate a change in therapy.[288,289] In some cases, blips may be the results of temporary lapses in patient adherence to antiretroviral regimens.[290] True virologic failure is defined as a persistently detectable viral load in a patient with previously suppressed HIV RNA or the inability to achieve an undetectable viral load after 24 to 48 weeks of therapy. Although multiple causes of virologic failure are possible, a detectable viral load in either scenario should prompt HIV drug resistance testing. The term *low-level viremia* specifically refers to confirmed detectable plasma HIV-1 RNA levels less than 200 copies/mL.

The initiation of effective ART in developing countries can result in initial treatment outcomes that are similar to those seen in resource-rich nations.[291] The lack of available viral load monitoring in many resource-poor countries, however, can complicate efforts to achieve and sustain durable virologic suppression on ART.[292,293] One potential consequence of using CD4- or clinically based criteria to guide treatment decisions is the emergence of HIV-1 drug resistance in patients who may unknowingly continue a partially suppressive antiretroviral regimen. High rates of HIV resistance have been observed in some developing countries that institute ART programs without frequent viral load monitoring.[294–297] The accumulation of resistance carries the risk of compromising both first- and second-line therapeutic regimens, and efforts to bring cost-effective viral load monitoring to patients with HIV worldwide should be encouraged.

HIV Drug Resistance Testing

Virologic failure that results from resistance to antiretroviral agents is a major cause of treatment failure.[298–301] The clinical significance of antiretroviral drug resistance was demonstrated not long after the

introduction of the nucleoside analogues.[302,303] Subsequent studies have shown an increased risk of virologic failure when patients are treated with drugs to which the virus shows genotypic or phenotypic resistance.[304,305] Resistance testing for HIV protease and RT mutations is cost-effective under several clinical circumstances and is currently recommended at the time of HIV diagnosis, before initiating therapy in pregnant persons, and whenever a treatment regimen fails with HIV RNA levels greater than 1000 copies/mL.[120,306–311] The resistance test should, if possible, be performed while the patient is still on the failing regimen. The role of testing for integrase inhibitor resistance in patients with newly diagnosed HIV is less clear. A recent modeling study suggested that, with the currently low base case prevalence of transmitted integrase inhibitor resistant virus (around 0.1%), integrase resistance testing of patients newly diagnosed with HIV would result in worse clinical outcomes and would not be cost-effective.[311a]

Genotypic resistance assays sequence HIV genes from patient isolates and report the presence of mutations that confer resistance; these assays are generally preferred for antiretroviral-naïve patients. Phenotypic resistance assays rely on cultured patient HIV isolates and report fold changes in sensitivities in the presence or absence of drugs. Phenotypic tests are usually more expensive than genotypic tests but can be useful in the interpretation of more complex resistance patterns. Virtual phenotypic resistance assays make use of a library of known matched genotypes and empirically tested phenotypes to predict a patient's phenotype based on known genotype results. All resistance assays have limitations when determining resistance to recently approved antiretrovirals. Clinical experience is often helpful to evaluate the number and type of genotypic mutations and the magnitude of phenotypic fold changes in drug susceptibility that are clinically meaningful and correspond to a loss of in vivo drug activity. Technical issues can sometimes prevent successful resistance testing when plasma HIV RNA levels are less than 500 to 1000 copies/mL.

Determining HIV Coreceptor Usage

The coreceptor tropism assay used most widely in clinical trials is a phenotypic assay that requires the amplification of *env* sequences from plasma HIV-1 RNA.[312] A commercial genotypic assay is available and can be used to determine coreceptor usage but has not been validated with clinical outcomes, making it more challenging for the practicing clinician to interpret. Currently, the HHS Antiretroviral Guidelines Panel recommends phenotypic testing as the preferred assay for measuring tropism.[14] As with resistance testing, viral loads greater than 1000 copies/mL are needed to most accurately perform coreceptor usage testing. Test results supplied to the clinician will indicate whether a virus is R5, X4, or dual/mixed. The term *dual/mixed* refers to the fact that the current coreceptor usage assay cannot distinguish between the presence of one virus that uses either receptor for viral entry (dual-tropic) or mixed viral populations in the same patient sample—populations that use either CCR5 or CXCR4. For clinical purposes, this distinction is not as important as knowing whether the sample contains any X4 virus. Although the initially approved phenotypic assay only detected X4 viruses if they constituted 5% to 10% of the "quasipecies" present, assays with improved sensitivity for detection of CXCR4, using or dual/mixed virus, are now available.[313] Changes in coreceptor usage, rather than emergence of true resistance, represent the dominant mechanism of virologic escape from CCR5 antagonists.[233]

CHANGING THERAPY

Clinical assessment, together with measurement of HIV RNA levels and CD4 cell counts, should be used to assess the need to change therapy. If the patient experiences drug toxicity or intolerance or is unable to adhere to therapy, a change in regimens may be required. In these situations, it may be appropriate simply to replace the offending drug by another that is better tolerated and exhibits similar potency.

Clinical situations that should prompt consideration for changing therapy include a poor early virologic response to therapy, failure to suppress plasma HIV-1 RNA to undetectable levels by 4 to 6 months after initiation, repeated detection of virus in plasma after initial suppression to undetectable levels, a persistent and significant decline in the CD4 T-cell count, and clinical deterioration.

The selection of a new regimen in patients with virologic, immunologic, and clinical failure should involve consideration of the history of previous antiretroviral drug exposure, current drug resistance patterns, other drugs with the potential for drug interactions, and individual comorbid conditions. At least two, and preferably three, fully active drugs should be included in the new regimen, ideally using agents from at least one new class. With the multiple drugs available, the goal of the new regimen should always be to durably suppress plasma HIV RNA levels to below detectable limits of the most sensitive available assay.

SPECIAL CIRCUMSTANCES

Preexposure Prophylaxis

ART has been studied as possible HIV prevention for at-risk, HIV-uninfected populations. The effectiveness of a 1% TDF-containing vaginal gel was studied in a randomized controlled trial of South African women, where its use before and after potential HIV exposures was associated with a 39% reduction in HIV incidence.[314] Greater risk reduction was observed in women with high levels of gel adherence. A study of 2499 HIV-uninfected men and transgender women who have sex with men demonstrated a 44% risk reduction of HIV infection over 1 year of follow-up in participants randomized to receive oral TDF-emtricitabine daily, compared with placebo.[315] This risk reduction was strongly tied to adherence and varied from 73% in participants with 90% or greater adherence to 32% when adherence was less than 50%. A large study of serodiscordant heterosexual Kenyan and Ugandan couples found that daily oral TDF use reduced the incidence of HIV infection by 62% and that daily TDF-emtricitabine reduced HIV incidence by 73%.[316] Similar findings were reported in a 1200-person Botswanan study where daily oral TDF-emtricitabine reduced HIV incidence by 63%.[317] In general, preexposure prophylaxis reduces the risk of HIV infection and on-demand preexposure prophylaxis reduces HIV infection risk specifically in men who have sex with men.[318,319]

Not all studies have demonstrated benefits to preexposure prophylaxis. A study of daily oral TDF-emtricitabine in African women did not demonstrate reduced HIV incidence rates and was associated with increased rates of side effects.[320] A separate study of African women showed no HIV incidence reduction with the use of oral TDF or daily TDF vaginal gel; adherence to study drugs was low.[321] The Centers for Disease Control and Prevention has issued interim guidelines on the use of HIV chemoprophylaxis.[322,323] These guidelines emphasize that patients considered for preexposure prophylaxis should be at an ongoing high (for men having sex with men) or very high (for heterosexuals) risk for HIV acquisition. Subjects receiving preexposure prophylaxis should be treated with the fixed-dose combination TDF-emtricitabine once daily. Regular HIV antibody testing, counseling, sexually transmitted infection screening, and serum creatinine measurements should be performed. There are currently insufficient data to recommend TAF-containing regimens for preexposure prophylaxis.

Postexposure Prophylaxis

Exposures to HIV can occur both inside and outside of the health care setting. For health care personnel, the risk of HIV exposure results from percutaneous or mucous membrane exposure to HIV-infected body fluids, most commonly blood. Nonoccupational exposure can occur with any exchange of body fluids, most commonly sexual activity (voluntary or forced) or intravenous drug use. Saliva that does not contain blood is associated with a negligible risk of HIV transmission.[324] Few data exist in humans regarding optimal postexposure prophylaxis (PEP), so in many cases, treatment decisions will be based on guidelines from national advisory panels, anecdotal clinical experiences, and patient preferences.

Occupational HIV Exposures

Prospective studies have suggested a roughly 0.3% and 0.09% risk of HIV transmission from percutaneous and mucous membrane exposure, respectively.[325,326] The risk of HIV transmission increases with the severity of the exposure; a deep puncture from a hollow-bore needle containing HIV-infected blood with a high viral load confers greater risk than a superficial cut from a suture needle in a patient with an undetectable

viral load. Transmission can occur in both settings, however, and prompt evaluation by occupational health services is imperative. If the source person is known to be HIV positive, PEP should be considered.[326] For blood or fluid sources with unknowable HIV status (e.g., from a disposed needle in a sharps container), PEP is generally not recommended. The absolute and relative risk reductions in HIV transmission from the use of PEP are unclear, but PEP should begin as soon as possible after exposure. Animal studies suggest the optimal duration of PEP may be approximately 4 weeks, although the tolerability of regimens can limit patient adherence.[327–333] Because of toxicities and tolerability, older guidelines had recommended a tiered approach for health care workers needing PEP, wherein more severe exposures received combination three-drug therapy and less severe exposures receive two-drug therapy. However, with the improved dosing schedules and tolerability of newer medications, all PEP regimens should now contain at least three drugs regardless of the severity of the exposure.[326] Any PEP regimen should attempt to maximize adherence (e.g., low pill burdens, no food restrictions), limit toxicities, and account for any drug resistance in the source HIV. The delay associated with HLA-B*5701 typing before abacavir use should generally preclude its inclusion in PEP regimens. Consultation with persons with expertise in HIV ART is advised.

Nonoccupational HIV Exposures

Nonoccupational postexposure prophylaxis (nPEP) is recommended for patients presenting within 72 hours of exposure to known HIV-infected body fluids. Under these circumstances, nPEP should consist of combination three-drug ART for 28 days.[334] HIV seroconversion on nPEP, when used for voluntary sexual and intravenous drug use exposures, has been reported to occur at a rate of 1% in one nonrandomized study; the availability of nPEP does not appear to increase risk behavior.[335–337] The use of prophylaxis in sexual assault victims is recommended, but the acceptance of and adherence to nPEP in this group may be low.[338] A decision to offer nPEP when the source patient is unavailable, and thus has an unknown HIV status, should be made on an individual basis. HIV postexposure prophylaxis is not generally recommended in the setting of bombings or other mass-casualty events.[339]

CONCLUSIONS AND FUTURE DIRECTIONS

Remarkable progress has been made since the advent of ART for HIV infection in the mid-1980s, turning a once almost uniformly fatal disease into a generally treatable infection. Newer regimens offer greater convenience and less toxicity than ones previously used, and emerging data suggest that ART should be initiated earlier during the natural history of HIV infection than was previously recommended.

Many challenges remain for patients on therapy, including adherence to complex regimens, emergence of drug-resistant virus variants, and the development of complications of therapy. Close monitoring of patients on therapy remains essential, using available laboratory tests, such as CD4 cell counts and viral load measurements, to evaluate success or failure. Progress is also being made in the rollout of ART in the developing world, although major challenges remain because of the costs and infrastructure needs required for sustainable programs. As the rollout and optimization of antiretroviral treatment programs continue in the developing world, viral load testing and resistance monitoring will be increasingly important to minimize the morbidity associated with suboptimal treatment regimens.

The successes of ART have permitted a consideration of the possibility of HIV cure. The experience of the "Berlin patient," a man with HIV presumably cured after allogeneic stem cell transplantation from a CCR5 Δ32-homozygous donor, provided the proof-of-concept that the HIV reservoir could be eradicated.[340] The best research approach to pursue HIV cure on a broader scale remains unsettled. Research efforts currently focus on eradication approaches to evaluate the roles of latency reversal agents, broadly neutralizing antibodies, and compounds with novel mechanisms of action, with the hope of ushering in a new era of potent and selective eradication therapeutics.

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129 Management of Opportunistic Infections Associated With Human Immunodeficiency Virus Infection

Henry Masur

SHORT VIEW SUMMARY

Definition
- Acquired immunodeficiency syndrome (AIDS) is an immunologic disease caused by human immunodeficiency virus (HIV), a retrovirus that is characterized by declining immunity and increased susceptibility to characteristic opportunistic infections and cancers.
- AIDS-related opportunistic infections are defined as infections that occur with increased frequency or severity in patients with HIV infection.

Epidemiology
- The incidence of HIV-related opportunistic infections in an individual patient depends on the patient's degree of immunosuppression and environmental and person-to-person exposures.
- Occurrence of specific infections may be due to primary infection (initial acquisition of the pathogen), reinfection, or reactivation of latent infection (secondary infection).

Microbiology
- The organisms that cause HIV-related opportunistic infections include bacteria, fungi, viruses, and protozoa.
- The constellation of infections that occur in AIDS is characteristic of this syndrome: *Pneumocystis* pneumonia, *Toxoplasma* encephalitis, cytomegalovirus retinitis, pneumococcal pneumonia, disseminated *Mycobacterium avium* complex, cryptosporidiosis, cryptococcal meningitis, and tuberculosis. The occurrence of these infections individually or in a cluster should prompt consideration of underlying HIV infection in any patient without another clear predisposing condition.

Diagnosis
- Given the broad range of pathogens that can cause infectious syndromes in patients with HIV infection and the potential toxicities of therapeutic agents, specific microbiologic diagnoses should be established in preference to empirical treatments when possible.

Therapy
- Specific agents can successfully treat most, but not all, HIV-related opportunistic infections (see Table 129.2). Prognosis depends on the severity of the acute illness, the presence of comorbidities, and availability of effective and well-tolerated therapies. For a few HIV-related opportunistic infections such as cryptosporidiosis and JC virus encephalitis, there is no effective specific therapy; effective treatment relies on improving immune response by initiating effective antiretroviral therapy (ART).

Prevention
- ART is the most effective preventive strategy for reconstituting immunity and reducing (but not eliminating) the risk of opportunistic infections.
- Primary prophylaxis regimens for *Pneumocystis jirovecii* and *Toxoplasma gondii* are effective for patients not on ART (admittedly a rare group who would take prophylaxis but not ART) with $CD4^+$ T-lymphocyte counts less than 200 cells/mm^3 or for patients starting ART with $CD4^+$ T-lymphocyte counts less than 100 cells/mm^3.
- Long-term suppressive therapy is important for preventing relapse and recurrence of certain infections while awaiting ART-induced immune reconstitution.
- Immunization is an important strategy for preventing viral and bacterial diseases in patients with HIV infection.

The quality and duration of survival for patients with human immunodeficiency virus (HIV) infection has improved remarkably since acquired immunodeficiency syndrome (AIDS) was first recognized in the early 1980s.[1–5] Much of the early improvement in prognosis before the availability of potent antiretroviral therapy (ART) was the result of anti-*Pneumocystis* prophylaxis and effective management of individual acute opportunistic infections.[6–9] Since 1995 the expanding number of well-tolerated and highly effective antiretroviral drugs has permitted the development of multidrug regimens that have durably improved $CD4^+$ T-cell counts and reduced HIV viral load, thus reducing the incidence of opportunistic infections and neoplasms and prolonging survival. For patients who are linked to care and who manifest durable responses to long-term ART, survival of patients with HIV infection is currently almost equal to that of individuals without HIV infection.[4,5]

HIV-related opportunistic infections and neoplasms continue to occur in the United States and abroad. In the United States and globally, many HIV-infected persons are not receiving ART and thus continue to develop the complications of untreated HIV infection. In the United States despite efforts to provide everyone with access to ART, substantial numbers of patients are unaware of their HIV infection or have not been able to access ART.[10–13] In Washington, D.C., for example, it was estimated that in 2016, 10% to 15% of HIV-infected persons had not been tested for HIV and were thus unaware that they were infected. Among individuals who were tested, 34% had a $CD4^+$ count <200 cells/mm^3 at the time they were first tested, and some presented with an acute opportunistic infection as the initial manifestation of HIV infection. Among persons who were aware of their HIV infection, 26% were not retained in care, and 37% did not achieve durable viral suppression.[14]

Thus in the United States a substantial number of HIV-infected individuals are susceptible to opportunistic infections and neoplasms. Such HIV-related complications are seen regularly in health care facilities throughout the United States including urban and rural areas in all geographic regions.

HIV-related opportunistic infections do not behave clinically exactly like opportunistic infections seen in other immunosuppressed populations. For example, cytomegalovirus (CMV) manifests in HIV-infected persons primarily as retinitis or colitis (and almost never as pneumonitis), whereas in stem cell transplant recipients CMV manifests as pneumonitis or colitis. Toxoplasmosis manifests mainly as encephalitis in patients with HIV infection, but in patients with cancer or organ transplants it is more likely to manifest as visceral or disseminated disease. *Pneumocystis* pneumonia is far more likely to be an acute illness in organ transplant recipients than in HIV-infected persons, who often develop indolent disease (which ultimately becomes life threatening or fatal if untreated). Trimethoprim-sulfamethoxazole (TMP-SMZ) is associated with much more frequent allergic responses in patients with HIV infection compared

with patients with cancer or patients who have received stem cell or solid-organ transplants.

The management of HIV-related opportunistic infections continues to evolve as new diagnostic tests and new therapies are developed. The current guidelines for management of HIV-related opportunistic infections from the National Institutes of Health, Centers for Disease Control and Prevention, and Infectious Diseases Society of America are updated multiple times per year.[8]

As patients with HIV infection live longer, new clinical syndromes are emerging. The additional years of survival permit hepatitis C virus (HCV), hepatitis B virus (HBV), and human papillomavirus (HPV), for example, to have more impact. More patients with HIV and either HCV or HBV are living long enough to develop cirrhosis, decompensated liver disease, and hepatocellular carcinoma.[15–21] More patients with HPV are living long enough to develop HPV-related cancers of the cervix, rectum, and oropharynx.

In the current era, the causes of death for patients with HIV have changed.[17–19] Patients have an enhanced inflammatory state despite durable viral suppression.[22–24] This advanced inflammatory state appears to accelerate cardiovascular, hepatic, and renal disease and appears to have a role in enhancing the development of cancers. Liver disease has become a major cause of death in patients with HIV in the United States.[17–19] Malignant neoplasms other than Kaposi sarcoma and lymphoma, most of which are associated with chronic viral infection, are also more frequent causes of death than in the past.[25–28] Patients may also be affected by concurrent health risks involving opioids, alcohol, tobacco, and obesity, which also affect their long-term survival.

Efforts to recognize HIV infection early and to initiate ART before immunosuppression is substantial are the most important approaches to prevention of HIV/AIDS–related opportunistic infections. Similarly, early recognition of opportunistic infections and prompt initiation of appropriate treatment will minimize the impact of opportunistic infections when they do occur. Health care resources used to manage opportunistic infections are unequivocally well spent if applied with a strategy that emphasizes prevention and that provides aggressive recognition of and therapy for acute syndromes.[29,30]

IMMUNOLOGIC MONITORING

Patients with HIV infection differ from most other populations of immunosuppressed patients in that there is a highly sensitive and highly specific laboratory test to determine susceptibility to individual opportunistic pathogens. The $CD4^+$ T-cell count is a valuable marker to determine when patients are at increased risk for development of a specific opportunistic infection.[31–35] For example, for patients with HIV infection, *P. jirovecii* pneumonia (PCP) occurs rarely in patients who have $CD4^+$ T-cell counts greater than 200 to 250 cells/mm^3,[8,31,32] and disseminated *Mycobacterium avium-intracellulare* complex (MAC) occurs rarely in patients with $CD4^+$ counts greater than 50 cells/mm^3.[8,36,37] The $CD4^+$ T-cell count is helpful for focusing a diagnostic evaluation. For instance, if a patient with a $CD4^+$ count of 700 cells/mm^3 develops cough, fever, and diffuse interstitial pulmonary infiltrates, the likelihood that this syndrome is caused by PCP is extremely low (but not zero). Therefore sputum examination or bronchoalveolar lavage for *Pneumocystis* is not initially indicated for such a patient, and most attention when processing respiratory secretions and choosing empirical therapy should be directed at common bacterial and viral pathogens. In contrast, if the $CD4^+$ count were 25 cells/mm^3 in the same patient, the search for *Pneumocystis* in sputum or bronchoalveolar lavage would be an important focus because PCP is so common in this patient population. If a patient with HIV infection develops chronic fever and weight loss without focal findings, disseminated MAC becomes a more important consideration if the $CD4^+$ T-cell count is less than 50 cells/mm^3 than if the $CD4^+$ count is more than 300 cells/mm^3, in which case tuberculosis (TB), endemic mycoses, and HIV-related malignant neoplasms (especially lymphoma) would be more appropriate considerations.

Although current $CD4^+$ T-cell counts provide a useful estimate of susceptibility to infections, they are not perfect predictive tools. For example, although more than 90% of cases of PCP occur in patients with $CD4^+$ T-cell counts less than 200 cells/mm^3, some cases occur in patients with $CD4^+$ counts in the range of 200 to 300 cells/mm^3, and a few occur in patients with $CD4^+$ counts greater than 300 cells/mm^3.[31–34] Moreover, if the most recent $CD4^+$ count and viral load were obtained many months before the patient's presentation or if the patient's adherence to ART is uncertain, it will be difficult to judge the patient's current immune status.

A possible concern has been that $CD4^+$ T-cell counts in patients receiving ART may not accurately reflect the clinical susceptibility to opportunistic infections. Evaluation of several large databases demonstrated that ART does not alter the relationship between $CD4^+$ T-cell counts and the occurrence of opportunistic infections in any substantial manner, regardless of how low the nadir $CD4^+$ count was before initiation of ART.[38]

When ART is initiated, it is important to recognize that some syndromes that may appear to be infectious are immunologic or inflammatory reactions induced by the initiation of ART—that is, immune reconstitution inflammatory syndrome (IRIS). Most of these syndromes that occur soon after ART initiation, especially in patients with low $CD4^+$ T-cell counts, appear to be reactions to latent organisms or residual antigen, rather than active infections due to replicating organisms.

$CD4^+$ T-cell counts are not the only laboratory predictors of opportunistic infection. HIV viral load in the peripheral blood is an independent predictor. For patients with detectable HIV viremia, with each log increase in titer, the likelihood of occurrence of an opportunistic infection increases. For patients with HIV viral loads that are below the level of assay detection (e.g., <50 copies/μL), the risk of opportunistic infection is reduced substantially at any $CD4^+$ T-cell count compared with patients with measurable viremia.[39–43]

Pathogen-specific assays are also useful for predicting or recognizing the occurrence of opportunistic infections. Assays for TB (purified protein derivative skin test or interferon-γ release assay), *Cryptococcus* (serum cryptococcal antigen), *Toxoplasma* (serum antibody), HBV (hepatitis B surface antigen [HBsAg], hepatitis B surface [HBs] antibody, hepatitis B core antibody [HBc]), and HCV (HCV serology and polymerase chain reaction [PCR]) are examples of tests that help inform prevention and management strategies.[8,44–48]

Although prospective monitoring for risk of opportunistic infection focuses on laboratory-based measures, clinical findings can be useful predictors of opportunistic infection susceptibility as well. For example, the development of otherwise unexplained oropharyngeal candidiasis or oral hairy leukoplakia, wasting, and any type of pneumonia can each be indicators of current susceptibility to PCP or other opportunistic infections.[8]

SPECTRUM OF OPPORTUNISTIC PATHOGENS

Many of the opportunistic diseases that characterize HIV-induced immunosuppression occur in patients with HIV infection much more frequently than in almost any other patient group. For example, without prophylaxis or effective ART, PCP ultimately develops in at least 80% of HIV-infected patients in North America.[8,33] The annual attack rate for patients with $CD4^+$ T-cell counts less than 100 cells/mm^3 is about twice that for patients with severe combined immunodeficiency syndrome and more than 10 times the rate for patients with organ transplantation, solid tumors, or most hematologic malignant neoplasms.[49] Disseminated MAC was rarely recognized in humans before the advent of HIV infection, yet it occurred in 30% to 50% of patients with advanced HIV infection in North America before ART and specific chemoprophylaxis became standard of care.[8,36,37]

Cerebral toxoplasmosis, chronic cryptosporidiosis, chronic microsporidiosis, and Kaposi sarcoma are examples of other processes that occur only rarely in individuals other than patients with HIV infection. Their presence should strongly suggest that HIV testing be performed unless there is another obvious cause of severe immunosuppression.

Environmental exposure is an important determinant of the infectious complications of HIV infection. Thus management of HIV-infected patients benefits from careful assessment of geographic and occupational exposures. HIV-infected patients likely have enhanced susceptibility to certain pathogens if they work in certain occupations such as child care (cryptosporidia, *Streptococcus pneumoniae,* and enteric bacterial pathogens), correctional facilities or homeless shelters (TB), and veterinary

facilities (cryptosporidia). Geography is also important (*Histoplasma* in the Midwest, *Coccidioides* in the Southwest, *Trypanosoma cruzi* in Brazil, TB in South Africa and South East Asia). Some pathogens are ubiquitous, such as *Streptococcus pneumoniae, Candida,* herpes simplex virus type 1 (HSV-1), and CMV. Other pathogens are not so universal and occur only because of specific exposure to an infected individual or an environmental source. These exposures may be respiratory (e.g., TB, endemic mycoses, and *Pneumocystis*), enteric (e.g., *Salmonella, Cryptosporidium,* and *Microsporida*), vector-borne (e.g., *Leishmania, Bartonella,* trypanosomes), contact mediated (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA]), or sexual (e.g., HSV-2, human herpesvirus 8 [HHV-8], *Treponema pallidum*).[8,50–59]

Traditionally, most HIV-associated opportunistic infections were thought to be caused by reactivation of latent infection, but this conclusion was based primarily on speculation rather than data. Some episodes of opportunistic infection in adults clearly represent primary infection rather than reactivation. Moreover, for some patients, second episodes of disease such as TB and PCP have been caused by strains that are clearly different from the strain causing the initial episode, suggesting that acquisition of a new strain rather than reactivation of the initial disease-causing strain can produce acute infection.[60–66]

INFECTIONS DUE TO PATHOGENS THAT ARE NOT OPPORTUNISTIC

Patients with HIV infection develop nonopportunistic as well as opportunistic infections. HIV-infected patients are just as likely to acquire common, community-acquired, or hospital-acquired pathogens as non–HIV-infected patients. Therefore if a patient with HIV infection develops a respiratory syndrome, diagnostic considerations should include common causes of disease in the community including influenza virus, *Mycoplasma pneumoniae,* and *Legionella* infections. Diarrhea is more likely caused by nonopportunistic viruses, microbial toxins, and bacteria that are circulating in the community than by cryptosporidia or microsporidia.[67–70]

Behavioral factors can influence the relative frequency of causative pathogens. *S. aureus* (especially MRSA) is more common among men who have sex with men[50,51] and persons who inject drugs compared with the general population. Enteric pathogens are overrepresented among men who have sex with men compared with the general population. Thus in considering the differential diagnosis of various syndromes, common community-acquired pathogens and pathogens associated with certain lifestyles or exposures should not be overlooked.

MANAGEMENT OF ANTIRETROVIRAL THERAPY FOR PATIENTS WITH ACUTE OPPORTUNISTIC INFECTION

If a patient who has not been on ART develops an acute opportunistic infection, providers must decide when to initiate ART, as all patients with HIV infection should be treated expeditiously with ART. The immune augmentation that ART produces may help facilitate recovery from an acute opportunistic infection, but definitely will ultimately be beneficial in preventing HIV-related opportunistic complications and prolonging survival.[71] However, complications are associated with initiation of ART, which must factor into the decision about when to initiate ART.

For ART-naïve patients, the initiation of ART may produce a clinically apparent, enhanced inflammatory response (IRIS) to the presenting clinical syndrome that can cause considerable morbidity.[8,72–74] For instance, in terms of the site of clinical disease that is being treated, initiating ART after PCP therapy is started can exacerbate pulmonary dysfunction when the enhanced immune and inflammatory responses interact with remaining *Pneumocystis* organisms or antigen in the lung. Similarly a patient with cryptococcal or tuberculous meningitis may develop dangerously increased intracranial pressure (ICP) when ART is initiated and the inflammatory response to meningeal organisms or antigen is enhanced.[72–78]

ART-induced IRIS may also unmask a subclinically infected site that had latent organisms or residual antigen due to an infection the patient was known to have or due to a pathogen that was not known to be present. For example, for a patient being treated for pulmonary TB, ART-associated IRIS may manifest as meningitis, pericarditis, or lymphadenitis, as the IRIS involves sites that did not initially appear clinically to be infected. For an HIV-infected patient not known to have an opportunistic infection, for example, when ART is started, IRIS may manifest as retinitis due to CMV that was not clinically apparent before ART or lymphadenitis due to MAC that was not known to be present. Some of these IRIS presentations may be mild and self-limiting. Others can be life threatening, can be difficult to distinguish from new opportunistic infections, and may warrant therapy with corticosteroids or immunosuppressive biologic agents.

Delivering ART to a patient who is seriously or critically ill presents special pharmacologic challenges. Patients may be unable to absorb oral drugs because they are intubated, they have severe nausea, or they have poor gastrointestinal absorption due to cryptosporidiosis or microsporidiosis. In such cases, clinicians must decide whether to try to optimize pharmacokinetics to reach targeted serum levels, given uncertainty about absorption, or to withhold therapy until ingestion and absorption are more predictable.

The current recommendation for patients not already receiving ART is that ART should be initiated within the first 2 weeks of treatment of the opportunistic infection.[8,71] This recommendation is based on studies that showed waiting longer was associated with the development of additional opportunistic infections and decreased survival. Exactly when in that window period ART should be started depends on clinical judgment related to the severity of the patient's infectious syndrome, the projected ability to absorb oral drugs, and potential drug interactions. For patients with severe disease and complicated management, longer intervals to initiation of ART may be appropriate.

There are notable exceptions to the general recommendation to start ART within 2 weeks of diagnosing an opportunistic infection. For opportunistic infections that have no effective specific therapy such as cryptosporidiosis and JC encephalitis, initiating ART is the only intervention likely to provide benefit, and thus ART should be started as soon as feasible.[79–83] For cryptococcal or tuberculous meningitis, ART should not be initiated until 2 to 10 weeks of therapy for the opportunistic infection have been completed, especially if patients have increased ICP or low cerebrospinal fluid (CSF) white blood count at time of diagnosis.[8] Clinically apparent pericardial disease warrants similar considerations.

For patients already receiving ART when an opportunistic infection is diagnosed, ART should generally be continued if possible. However, as discussed earlier, drug absorption issues or potential drug interaction complexities may be sufficiently compelling that temporary ART interruption may be the best management strategy.

DRUG INTERACTIONS

Some drugs used for treatment or prevention of opportunistic infections can interact with each other, with drugs used to treat concurrent conditions such as seizures or depression or anxiety, or with antiretroviral agents.[8] Such interactions can alter the efficacy and toxicity of prescribed drugs. This most often occurs with drugs that share the same hepatic cytochrome metabolic pathway. Protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs) and boosting agents (e.g., cobicistat and ritonavir) as well as rifampin, rifabutin, azoles, atovaquone-proguanil, and quinolones need special attention because they all are metabolized by hepatic enzymes. For example, darunavir, ritonavir, and lopinavir-ritonavir can each increase the rifabutin area under the concentration-time curve (AUC) substantially. Ritonavir decreases the AUC of voriconazole. Coadministration of voriconazole and efavirenz leads to decreased voriconazole AUC and increased efavirenz AUC.[8] Useful tables are available in the US Department of Health and Human Services Guidelines for Antiretroviral Therapy in Adolescents and Adults as well as websites, package inserts, and published investigations of specific drug-drug interactions.[8]

PREVENTION OF OPPORTUNISTIC INFECTIONS

Antiretroviral Therapy

The optimal approach to prevention of opportunistic infections is to initiate effective ART. As noted earlier, ART can probably never restore

immune function to normal, and some pathogens such as *Mycobacterium tuberculosis,* herpes zoster, and *Streptococcus pneumoniae* will still cause more frequent disease in HIV-infected patients than in non–HIV-infected patients, even with comparable $CD4^+$ T-cell counts. However, the lower the $CD4^+$ T-cell count, the higher the incidence is of each of these opportunistic infections.

Ideally all patients with HIV infection start ART within a few days of establishing their HIV diagnosis. Chemoprophylaxis without ART was shown to be effective and extends survival modestly. However, very few patients who do not take ART would take chemoprophylaxis for PCP or toxoplasmosis. Thus chemoprophylaxis without ART is rarely clinically relevant in this era.

Patients who start ART with $CD4^+$ T-cell counts less than 200 cells/mm^3 should take PCP prophylaxis and *Toxoplasma* prophylaxis (patients who are anti-*Toxoplasma* immunoglobulin G [IgG] positive) until their $CD4^+$ counts exceed 200 cells/mm^3 and 100 cells/mm^3, respectively, although admittedly their risk of these opportunistic infections is substantially decreased once HIV viral loads fall below the limit of assay detection, regardless of $CD4^+$ count. Chemoprophylaxis against MAC for patients with $CD4^+$ counts below 50 cells/mm^3 was previously recommended but is no longer recommended due to the rarity of MAC infection in the United States since effective ART regimens were introduced.[8]

Ensuring currency of immunizations for HIV-related pathogens is also important. Being up-to-date for pneumococcal and *Haemophilus* vaccines, zoster vaccine (if age appropriate), hepatitis B vaccine, and influenza vaccine are important strategies.[8]

Empirical Versus Specific Therapy

An issue that frequently arises when patients have acute infectious processes is whether to use immediate empirical antimicrobial regimens or to withhold therapy until a specific diagnosis is established by invasive techniques. Such decisions require clinical judgment. Evidence of substantial immunosuppression or clinically severe disease would logically indicate the need to start empirical therapy quickly rather than waiting for diagnostic test results. In addition, there may be situations in which the diagnosis is so predictable (e.g., retinitis with hemorrhage and exudates in a patient with a $CD4^+$ T-cell count <50 cells/mm^3; a cerebral mass lesion in a patient who is *Toxoplasma* IgG positive and has a $CD4^+$ count <50 cells/mm^3; or a patient with dysphagia, oral candidiasis, and a $CD4^+$ count <50 cells/mm^3) that expensive or invasive diagnostic tests are not mandatory if the patient responds as expected to empirical therapy.

Many AIDS-related opportunistic infections relapse within weeks or months after acute therapy is stopped if effective ART cannot be initiated and maintained.[8] Experience during the first decade of AIDS clearly documented that PCP, toxoplasmosis, cryptococcosis, disseminated MAC infection, and CMV retinitis would relapse if lifelong suppressive pathogen-specific therapy was not maintained. For a few opportunistic infections such as mucosal candidiasis, herpes simplex infections, and herpes zoster infections, such secondary prophylaxis has not been indicated because the disease is not life threatening; recurrences could be easily treated; and pill burden, cost, drug toxicity, and potential drug interactions appear to outweigh the small potential benefit.

Patients who respond to ART, as manifested by sustained increases in $CD4^+$ T-cell counts, are very unlikely to experience opportunistic infection relapse (with the exception of coccidioidomycosis) and thus do not need to receive prolonged long-term maintenance therapy beyond what is recommended in current guidelines.[84–88] There are sufficient data to recommend that for patients who have $CD4^+$ T-cell counts above the thresholds suggested in well-established, evidence-based guidelines,[8] primary prophylaxis (preventing a first episode of disease) or secondary prophylaxis (preventing relapse or recurrence) can be discontinued. Prophylaxis should be restarted if the $CD4^+$ T-cell count subsequently falls below the threshold indicated in the guidelines.[8]

Tables 129.1, 129.2, and 129.3 summarize current recommendations from the National Institutes of Health, Centers for Disease Control and Prevention, and Infectious Diseases Society of America for prophylaxis to prevent first episodes (Table 129.1); to treat acute opportunistic infections (Table 129.2); and to start, discontinue, and restart prophylaxis (Table 129.3).

MANAGEMENT OF SPECIFIC OPPORTUNISTIC INFECTIONS

Pneumocystis jirovecii Pneumonia

PCP was the clinical manifestation that originally suggested to clinicians that a new syndrome, AIDS, was occurring in patients who appeared to be previously healthy.[89,90] Until those cases, PCP had been infrequently recognized in the United States in any population because immunosuppressive regimens were not as intense as current approaches and diagnostic tools were less developed.

PCP continues to be a commonly recognized complication of HIV infection in North America and Western Europe. As more patients are receiving ART and as the $CD4^+$ T-cell count at ART initiation rises, PCP is not as common as it was in the pre-ART era. However, there are many HIV-infected patients who have not been prescribed ART or in whom the virus is not durably suppressed, and thus PCP continues to occur. PCP occurs worldwide, although in some areas of the world it is rarely documented (see Chapter 269).

PCP can be almost completely prevented by either ART-induced immune reconstitution or specific chemoprophylaxis. As noted previously, many patients do not recognize that they have HIV infection until they develop PCP. Some patients are aware of their HIV infection but do

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TABLE 129.1 Prophylaxis to Prevent First Episode of Opportunistic Disease

OPPORTUNISTIC INFECTIONS	INDICATION	PREFERRED	ALTERNATIVE
Pneumocystis pneumonia (PCP)	$CD4^+$ count <200 cells/mm^3, *or* $CD4^+$ <14%, *or* $CD4^+$ count >200 but <250 cells/mm^3 if monitoring $CD4^+$ cell count every 3 mo is not possible *Note:* Patients who are receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis	TMP-SMZ 1 DS PO daily, *or* TMP-SMZ 1 SS daily	TMP-SMZ 1 DS PO 3 times weekly *or* Dapsone 100 mg PO daily or 50 mg PO bid, *or* Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly, *or* (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly, *or* Aerosolized pentamidine 300 mg via Respirgard II nebulizer every mo, *or* Atovaquone 1500 mg PO daily, *or* (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily
Toxoplasma gondii encephalitis	*Toxoplasma* IgG-positive patients with $CD4^+$ count <100 cells/mm^3 *Note:* All regimens recommended for primary prophylaxis against toxoplasmosis are also effective as PCP prophylaxis	TMP-SMZ 1 DS PO daily	TMP-SMZ 1 DS PO 3 times weekly, *or* TMP-SMZ 1 SS PO daily, *or* Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly, *or* (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly, *or* Atovaquone 1500 mg PO daily, *or* (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily

TABLE 129.1 Prophylaxis to Prevent First Episode of Opportunistic Disease—cont'd

OPPORTUNISTIC INFECTIONS	INDICATION	PREFERRED	ALTERNATIVE
Mycobacterium tuberculosis infection (i.e., treatment of LTBI)	(+) screening test for LTBI, with no evidence of active TB, and no prior treatment for active TB or LTBI, *or* Close contact with a person with infectious TB, with no evidence of active TB, regardless of screening test results	(INH 300 mg + pyridoxine 25–50 mg) PO daily × 9 mo, *or* INH 900 mg PO biw (by DOT) + pyridoxine 25–50 mg PO daily × 9 mo	Rifampin 600 mg PO daily × 4 mo, *or* Rifabutin (dose adjusted based on concomitant ART) × 4 mo, *or* (Rifapentine [see dose below] PO + INH 900 mg PO + pyridoxine 50 mg PO) once weekly × 12 wk *Rifapentine dose:* 32.1–49.9 kg: 750 mg *or* 50 kg: 900 mg Rifapentine recommended only for patients receiving raltegravir- or efavirenz-based ART regimen For patients exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or public health authorities
Streptococcus pneumoniae infection	For individuals who have not received any pneumococcal vaccine, regardless of $CD4^+$ count, followed by: If $CD4^+$ count ≥200 cells/mm^3 If $CD4^+$ count <200 cells/mm^3 For individuals who have previously received PPV23 Revaccination: If age 19–64 yr and ≥5 yr since first PPV23 dose If age ≥65 yr and ≥5 yr since previous PPV23 dose	PCV13 0.5 mL IM × 1 PPV23 0.5 mL IM at least 8 wk after PCV13 vaccine PPV23 can be offered at least 8 wk after receiving PCV13 or can wait until $CD4^+$ count is increased to ≥200 cells/mm^3 One dose of PCV13 should be given at least 1 yr after last receipt of PPV23 PPV23 0.5 mL IM or SQ × 1 PPV23 0.5 mL IM or SQ × 1	PPV23 0.5 mL IM × 1
Influenza A and B virus infection	All HIV-infected patients	Inactivated influenza vaccine annually (per recommendation for the season) Live-attenuated influenza vaccine is *contraindicated* in HIV-infected patients	
Syphilis	For individuals exposed to a sex partner with a diagnosis of primary, secondary, or early latent syphilis within past 90 days, *or* For individuals exposed to a sex partner >90 days before syphilis diagnosis in the partner, if serologic test results are not available immediately and the opportunity for follow-up is uncertain	Benzathine penicillin G 2.4 million U IM for 1 dose	For penicillin-allergic patients: Doxycycline 100 mg PO bid for 14 days, *or* Ceftriaxone 1 g IM or IV daily for 8–10 days, *or* Azithromycin 2 g PO for 1 dose: *not recommended* for MSM or pregnant women
Histoplasma capsulatum infection	$CD4^+$ count ≤150 cells/mm^3 and at high risk because of occupational exposure or living in a community with hyperendemic rate of histoplasmosis (>10 cases/100 patient-yr)	Itraconazole 200 mg PO daily	
Coccidioidomycosis	New positive IgM or IgG serologic test in patients who live in disease-endemic area and with $CD4^+$ count <250 cells/mm^3	Fluconazole 400 mg PO daily	
Varicella virus	Preexposure prevention: Patients with $CD4^+$ counts ≥200 cells/mm^3 who have not been vaccinated, have no history of varicella or herpes zoster, or are seronegative for VZV *Note:* Routine VZV serologic testing in HIV-infected adults and adolescents is not recommended Postexposure prevention: Close contact with a person with chickenpox or herpes zoster and is susceptible (i.e., no history of vaccination or of either condition or known to be VZV seronegative)	Preexposure prevention: Primary varicella vaccination (Varivax), 2 doses (0.5 mL SQ each) administered 3 mo apart If vaccination results in disease because of vaccine virus, treatment with acyclovir is recommended Postexposure prevention: Varicella-zoster immune globulin (VariZIG) 125 IU per 10 kg (maximum 625 IU) IM, administered as soon as possible and within 10 days after exposure *Note:* VariZIG is exclusively distributed by FFF Enterprises (Temecula, CA) Individuals receiving monthly high-dose IVIG (>400 mg/kg) are likely to be protected if last dose of IVIG was administered <3 wk before exposure	Preexposure prevention: VZV-susceptible household contacts of susceptible HIV-infected patients should be vaccinated to prevent potential transmission of VZV to their HIV-infected contacts Alternative postexposure prevention: Acyclovir 800 mg PO 5 times per day for 5–7 days, *or* Valacyclovir 1 g PO TID for 5–7 days These alternatives have not been studied in patients with HIV If antiviral therapy is used, varicella vaccines should not be given until at least 72 h after last dose of the antiviral drug
Hepatitis A virus (HAV) infection	HAV-susceptible patients with chronic liver disease or who are injection drug users or MSM	Hepatitis A vaccine 1 mL IM × 2 doses at 0 and 6–12 mo IgG antibody response should be assessed 1 mo after vaccination; nonresponders should be revaccinated when $CD4^+$ count >200 cells/mm^3	For patients susceptible to both HAV and hepatitis B virus (HBV) infection: Combined HAV and HBV vaccine (Twinrix), 1 mL IM as a 3-dose (0, 1, and 6 mo) or 4-dose series (0, 7, and 21–30 days and 12 mo)

Continued

TABLE 129.1 Prophylaxis to Prevent First Episode of Opportunistic Disease—cont'd

OPPORTUNISTIC INFECTIONS	INDICATION	PREFERRED	ALTERNATIVE
Hepatitis B virus (HBV) infection	Patients without chronic HBV or without immunity to HBV (i.e., with anti-HBs <10 IU/mL) Patients with isolated anti-HBc: vaccinate with 1 standard dose of HBV vaccine and check anti-HBs 1–2 mo after; if >100 IU, no further vaccination needed; if titer is <100 IU, vaccinate with full series Early vaccination is recommended before $CD4^+$ count falls below 350 cells/mm^3 In patients with low $CD4^+$ cell counts, vaccination should not be deferred until $CD4^+$ count reaches >350 cells/mm^3 because some patients with $CD4^+$ counts <200 cells/mm^3 do respond to vaccination	HBV vaccine IM (Engerix-B 20 µg/mL or Recombivax HB 10 µg/mL), 0, 1, and 6 mo, *or* HBV vaccine IM (Engerix-B 40 µg/mL or Recombivax HB 20 µg/mL), 0, 1, 2, and 6 mo Combined HAV and HBV vaccine (Twinrix), 1 mL IM as 3-dose (0, 1, and 6 mo) or 4-dose series (0, 7, and 21–30 days and 12 mo) or Heplisav 2-dose series (0, 1 mo) 0.5 mL IM Anti-HBs should be obtained 1–2 mo after completion of vaccine series Patients with anti-HBs <10 IU/mL are considered nonresponders and should be revaccinated with another 3-dose series	Some experts recommend vaccinating with 4 doses of double dose of either HBV vaccine
Herpes zoster	Age 50 yr or older	2-dose series of recombinant zoster vaccine (RZV) 0.5 mL IM 2–6 mo apart	
Human papilloma virus (HPV)		Recombinant 9-valent vaccine 0.5 mL IM (0, 1, and 6 mo)	

ART, Antiretroviral therapy; *bid,* twice daily; *DOT,* directly observed treatment; *DS,* double-strength; *HBs,* hepatitis B surface antibody; *HIV,* human immunodeficiency virus; *Ig,* immunoglobulin; *IM,* intramuscular; *INH,* isoniazid; *IVIG,* intravenous immune globulin; *LTBI,* latent tuberculosis infection; *MSM,* men who have sex with men; *PCV13,* 13-valent pneumococcal conjugate vaccine; *PO,* per os (oral); *PPV23,* 23-valent pneumococcal polysaccharide vaccine; *SQ,* subcutaneous; *SS,* single-strength; *TB,* tuberculosis; *TMP-SMZ,* trimethoprim-sulfamethoxazole; *VZV,* varicella-zoster virus.
From Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/guidelines. Accessed March 1, 2019.

TABLE 129.2 Treatment of AIDS-Associated Opportunistic Infections

OPPORTUNISTIC INFECTION	PREFERRED THERAPY	ALTERNATIVE THERAPY	OTHER COMMENTS
Pneumocystis pneumonia (PCP)	Patients who develop PCP despite TMP-SMZ prophylaxis can usually be treated with standard doses of TMP-SMZ Duration of PCP treatment: 21 days <u>For moderate-to-severe PCP:</u> TMP-SMZ: (TMP 15–20 mg and SMZ 75–100 mg)/kg/day IV given q6h or q8h; may switch to PO after clinical improvement <u>For mild-to-moderate PCP:</u> TMP-SMZ: (TMP 15–20 mg and SMZ 75–100 mg)/kg/day, given PO in 3 divided doses, *or* TMP-SMZ: 160 mg/800 mg or DS 2 tablets PO tid <u>Secondary prophylaxis, after completion of PCP treatment:</u> TMP-SMZ DS: 1 tablet PO daily, *or* TMP-SMZ (80 mg/400 mg or SS): 1 tablet PO daily	<u>For moderate-to-severe PCP:</u> Pentamidine 4 mg/kg IV daily infused over ≥60 min; can reduce dose to 3 mg/kg IV daily because of toxicities, *or* Primaquine 30 mg (base) PO daily + (clindamycin 600 mg q6h IV or 900 mg IV q8h) or (clindamycin 450 mg PO q6h or 600 mg PO q8h) <u>For mild-to-moderate PCP:</u> Dapsone 100 mg PO daily + TMP 5 mg/kg PO tid, *or* Primaquine 30 mg (base) PO daily + (clindamycin 450 mg PO q6h or 600 mg PO q8h), *or* Atovaquone 750 mg PO bid with food <u>Secondary prophylaxis, after completion of PCP treatment:</u> TMP-SMZ DS: 1 tablet PO 3 times weekly, *or* Dapsone 100 mg PO daily, *or* Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly, *or* (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly, *or* Aerosolized pentamidine 300 mg monthly via Respirgard II nebulizer, *or* Atovaquone 1500 mg PO daily, *or* (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily	

TABLE 129.2 Treatment of AIDS-Associated Opportunistic Infections—cont'd

OPPORTUNISTIC INFECTION	PREFERRED THERAPY	ALTERNATIVE THERAPY	OTHER COMMENTS
Toxoplasma gondii encephalitis	Treatment of acute infection: Pyrimethamine 200 mg PO 1 time, followed by weight-based therapy: If <60 kg, pyrimethamine 50 mg PO once daily + sulfadiazine 1000 mg PO q6h + leucovorin 10–25 mg PO once daily, *or* If ≥60 kg, pyrimethamine 75 mg PO once daily + sulfadiazine 1500 mg PO q6h + leucovorin 10–25 mg PO once daily Leucovorin dose can be increased to 50 mg daily or bid Duration for acute therapy: At least 6 wk; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 wk After completion of acute therapy, all patients should be initiated on long-term maintenance therapy	Treatment of acute infection: Pyrimethamine (leucovorin)[a] + clindamycin 600 mg IV or PO q6h, *or* TMP-SMZ (TMP 5 mg/kg and SMZ 25 mg/kg) IV or PO bid, *or* Atovaquone 1500 mg PO bid with food + pyrimethamine (leucovorin)[a], *or* Atovaquone 1500 mg PO bid with food + sulfadiazine 1000–1500 mg PO q6h (weight-based dosing, as in preferred therapy), *or* Atovaquone 1500 mg PO bid with food	Refer to http://www.daraprimdirect.com for information regarding how to access pyrimethamine If pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMZ should be used in place of pyrimethamine-sulfadiazine For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies Atovaquone should be administered until therapeutic doses of TMP-SMZ are achieved Adjunctive corticosteroids (e.g., dexamethasone) should be administered only when clinically indicated to treat mass effect associated with focal lesions or associated edema; discontinue as soon as clinically feasible Anticonvulsants should be administered to patients with a history of seizures and continued through acute treatment but should not be used as seizure prophylaxis If clindamycin is used in place of sulfadiazine, additional therapy must be added to prevent PCP
	Long-term maintenance therapy: Pyrimethamine 25–50 mg PO daily + sulfadiazine 2000–4000 mg PO daily (in 2–4 divided doses) + leucovorin 10–25 mg PO daily	Long-term maintenance therapy: Clindamycin 600 mg PO q8h + (pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily, *or* TMP-SMZ DS 1 tablet bid, *or* TMP-SMZ DS 1 tablet once daily, *or* Atovaquone 750–1500 mg PO bid + pyrimethamine 25 mg + leucovorin 10 mg PO daily, *or* Atovaquone 750–1500 mg PO bid + sulfadiazine 2000–4000 mg PO daily (in 2–4 divided doses), *or* Atovaquone 750–1500 mg PO bid with food	
Mycobacterium tuberculosis disease	After collecting specimen for culture and molecular diagnostic tests, empirical TB treatment should be started in individuals with clinical and radiographic presentation suggestive of TB *Initial phase (2 mo, given daily, 5–7 times per week by DOT):* INH + [RIF or RFB] + PZA + EMB *Continuation phase:* INH + (RIF or RFB) daily (5–7 times per week) *Total duration of therapy (for drug-susceptible TB):* Pulmonary, drug-susceptible TB: 6 mo Pulmonary TB and culture-positive after 2 mo of TB treatment: 9 mo Extrapulmonary TB with CNS infection: 9–12 mo Extrapulmonary TB with bone or joint involvement: 6–9 mo Extrapulmonary TB in other sites: 6 mo Total duration of therapy should be based on number of doses received, not on calendar time	Treatment for drug-resistant TB *Resistant to INH:* (RIF or RFB) + EMB + PZA + (moxifloxacin or levofloxacin) for 2 mo; followed by (RIF or RFB) + EMB + (moxifloxacin or levofloxacin) for 7 mo *Resistant to rifamycins ± other drugs:* Regimen and duration of treatment should be individualized based on resistance pattern and clinical and microbiologic responses and in close consultation with experienced specialists	Adjunctive corticosteroids improve survival for TB meningitis and pericarditis. See text for drug, dose, and duration recommendations All rifamycins may have significant pharmacokinetic interactions with antiretroviral drugs Therapeutic drug monitoring should be considered in patients receiving rifamycin and interacting ART Paradoxical IRIS that is not severe can be treated with NSAIDs without a change in TB or HIV therapy For severe IRIS reaction, consider prednisone and taper over 4 wk based on clinical symptoms For example: *If receiving RIF:* prednisone 1.5 mg/kg/day for 2 wk, then 0.75 mg/kg/day for 2 wk *If receiving RFB:* prednisone 1.0 mg/kg/day for 2 wk, then 0.5 mg/kg/day for 2 wk A more gradual tapering schedule over a few mo may be necessary for some patients
Disseminated *Mycobacterium avium-intracellulare* complex (MAC) disease	At least 2 drugs as initial therapy with: Clarithromycin 500 mg PO bid + ethambutol 15 mg/kg PO daily, *or* (Azithromycin 500–600 mg + ethambutol 15 mg/kg) PO daily if drug interaction or intolerance precludes use of clarithromycin *Duration:* At least 12 mo of therapy, then can discontinue if no signs and symptoms of MAC disease and sustained (>6 mo) $CD4^+$ count >100 cells/mm^3 in response to ART	Addition of a third or fourth drug should be considered for patients with advanced immunosuppression ($CD4^+$ counts <50 cells/mm^3) or high mycobacterial loads (>2 log CFU/mL of blood) or in the absence of effective ART Third or fourth drug options may include: RFB 300 mg PO daily (dosage adjustment may be necessary based on drug interactions) Amikacin 10–15 mg/kg IV daily or streptomycin 1 g IV or IM daily, *or* Moxifloxacin 400 mg PO daily or levofloxacin 500 mg PO daily	Testing of susceptibility to clarithromycin and azithromycin is recommended NSAIDs can be used for patients who experience moderate-to-severe symptoms attributed to IRIS If IRIS symptoms persist, short-term (4–8 wk) systemic corticosteroids (equivalent to 20–40 mg prednisone) can be used

Continued

TABLE 129.2 Treatment of AIDS-Associated Opportunistic Infections—cont'd

OPPORTUNISTIC INFECTION	PREFERRED THERAPY	ALTERNATIVE THERAPY	OTHER COMMENTS
Bacterial respiratory diseases *(with focus on pneumonia)*	Empirical antibiotic therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed are suggested empirical therapy. The regimen should be modified as needed once microbiologic results are available. Empirical outpatient therapy: PO β-lactam + PO macrolide (azithromycin or clarithromycin) *Preferred β-lactams:* high-dose amoxicillin or amoxicillin/clavulanate *Alternative β-lactams:* cefpodoxime or cefuroxime, *or* *For penicillin-allergic patients:* Levofloxacin 750 mg PO once daily or moxifloxacin 400 mg PO once daily *Duration:* 7–10 days (minimum of 5 days). Patients should be afebrile for 48–72 hours and clinically stable before stopping antibiotics Empirical therapy for non-ICU hospitalized patients: IV β-lactam + macrolide (azithromycin or clarithromycin) *Preferred β-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam *For penicillin-allergic patients:* Levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily Empirical therapy for ICU patients: IV β-lactam + IV azithromycin, *or* IV β-lactam + (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) *Preferred β-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam Empirical therapy for patients at risk of *Pseudomonas* pneumonia: IV antipneumococcal, antipseudomonal β-lactam + (ciprofloxacin 400 mg IV q8–12h or levofloxacin 750 mg IV once daily) *Preferred β-lactams:* piperacillin-tazobactam, cefepime, imipenem, or meropenem Empirical therapy for patients at risk for methicillin-resistant *Staphylococcus aureus* pneumonia: Add vancomycin IV or linezolid (IV or PO) to baseline regimen Addition of clindamycin to vancomycin (but not to linezolid) can be considered for severe necrotizing pneumonia to minimize bacterial toxin production	Empirical outpatient therapy: PO β-lactam + PO doxycycline *Preferred β-lactams*: high-dose amoxicillin or amoxicillin/clavulanate *Alternative β-lactams*: cefpodoxime or cefuroxime Empirical therapy for non-ICU hospitalized patients: IV β-lactam + doxycycline Empirical therapy for ICU patients: *For penicillin-allergic patients*: Aztreonam IV + (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) Empirical therapy for patients at risk of *Pseudomonas* pneumonia: IV antipneumococcal, antipseudomonal β-lactam + aminoglycoside + azithromycin, *or* Above β-lactam + aminoglycoside + (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily), *or* *For penicillin-allergic patients:* Replace β-lactam with aztreonam	Fluoroquinolones should be used with caution in patients in whom TB is suspected but is not being treated Empirical therapy with a macrolide alone is not routinely recommended because of increasing pneumococcal resistance Patients receiving a macrolide for MAC prophylaxis should not receive macrolide monotherapy for empirical treatment of bacterial pneumonia For patients started on IV antibiotic therapy, switching to PO therapy should be considered when they are clinically improved and able to tolerate oral medications Chemoprophylaxis can be considered for patients with frequent recurrences of serious bacterial pneumonia Clinicians should be cautious about using antibiotics to prevent recurrences because of the potential for developing drug resistance and drug toxicities
Salmonellosis	All HIV-infected patients with salmonellosis should receive antimicrobial treatment due to an increase of bacteremia (by 20- to 100-fold) and mortality (by up to 7-fold) compared with HIV-negative individuals. Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h, if susceptible Duration of therapy: *For gastroenteritis without bacteremia*: If $CD4^+$ count ≥200 cells/mm^3: 7–14 days If $CD4^+$ count <200 cells/mm^3: 2–6 wk *For gastroenteritis with bacteremia*: If $CD4^+$ count ≥200/mm^3: 14 days or longer duration if bacteremia persists or if infection is complicated (e.g., if metastatic foci of infection are present) If $CD4^+$ count <200 cells/mm^3: 2–6 wk Secondary prophylaxis should be considered for: Patients with recurrent *Salmonella* gastroenteritis ± bacteremia, *or* Patients with $CD4^+$ <200 cells/mm^3 with severe diarrhea	Levofloxacin 750 mg (PO or IV) q24h, *or* Moxifloxacin 400 mg (PO or IV) q24h, *or* TMP-SMZ 160 mg/800 mg (PO or IV) q12h, *or* Ceftriaxone 1 g IV q24h, *or* Cefotaxime 1 g IV q8h	PO or IV rehydration if indicated Antimotility agents should be avoided Role of long-term secondary prophylaxis in patients with recurrent *Salmonella* bacteremia is not well established; must weigh benefit against risks of long-term antibiotic exposure Effective ART may reduce frequency, severity, and recurrence of *Salmonella* infections

TABLE 129.2 Treatment of AIDS-Associated Opportunistic Infections—cont'd

OPPORTUNISTIC INFECTION	PREFERRED THERAPY	ALTERNATIVE THERAPY	OTHER COMMENTS
Mucocutaneous candidiasis	For oropharyngeal candidiasis; initial episodes (for 7–14 days): *Oral therapy:* Fluconazole 100 mg PO daily	For oropharyngeal candidiasis; initial episodes (for 7–14 days): *Oral therapy:* Itraconazole oral solution 200 mg PO daily, *or* Posaconazole oral suspension 400 mg PO bid for 1 day, then 400 mg daily *Topical therapy:* Clotrimazole troches, 10 mg PO 5 times daily, *or* Miconazole mucoadhesive buccal 50-mg tablet—apply to mucosal surface over canine fossa once daily (do not swallow, chew, or crush), *or* Nystatin suspension 4–6 mL qid or 1–2 flavored pastilles 4–5 times daily	Long-term or prolonged use of azoles may promote development of resistance Higher relapse rate for esophageal candidiasis seen with echinocandins than with fluconazole use Suppressive therapy usually not recommended unless patients have frequent or severe recurrences If decision is to use suppressive therapy: *Oropharyngeal candidiasis:* Fluconazole 100 mg PO daily or thrice weekly, *or* Itraconazole oral solution 200 mg PO daily *Esophageal candidiasis:* Fluconazole 100–200 mg PO daily, *or* Posaconazole 400 mg PO bid *Vulvovaginal candidiasis:* Fluconazole 150 mg PO once weekly Isavuconazole not approved for treatment of esophageal candidiasis
	For esophageal candidiasis (for 14–21 days): Fluconazole 100 mg (up to 400 mg) PO or IV daily, *or* Itraconazole oral solution 200 mg PO daily	For esophageal candidiasis (for 14–21 days): Voriconazole 200 mg PO or IV bid, *or* Isavuconazole 200 mg PO as loading dose, followed by 50 mg PO daily, *or* Isavuconazole 400 mg PO as loading dose, followed by 100 mg PO daily, *or* Isavuconazole 400 mg PO once weekly, *or* Anidulafungin 100 mg IV 1 time, then 50 mg IV daily, *or* Caspofungin 50 mg IV daily, *or* Micafungin 150 mg IV daily, *or* Amphotericin B deoxycholate 0.6 mg/kg IV daily, *or* Lipid formulation of amphotericin B 3–4 mg/kg IV daily	
	For uncomplicated vulvovaginal candidiasis: Oral fluconazole 150 mg PO for 1 dose, *or* Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days For severe or recurrent vulvovaginal candidiasis: Fluconazole 100–200 mg PO daily for ≥7 days, *or* Topical antifungal ≥7 days	For uncomplicated vulvovaginal candidiasis: Itraconazole oral solution 200 mg PO daily for 3–7 days	
Cryptococcosis	Cryptococcal meningitis: *Induction therapy (for at least 2 wk, followed by consolidation therapy):* Liposomal amphotericin B 3–4 mg/kg IV daily + flucytosine 25 mg/kg PO qid *Note:* Flucytosine dose should be adjusted in patients with renal dysfunction	Cryptococcal meningitis: *Induction therapy (for at least 2 wk, followed by consolidation therapy):* Amphotericin B deoxycholate 0.7 mg/kg IV daily + flucytosine 25 mg/kg PO qid, *or* Amphotericin B lipid complex 5 mg/kg IV daily + flucytosine 25 mg/kg PO qid, *or* Liposomal amphotericin B 3–4 mg/kg IV daily + fluconazole 800 mg PO or IV daily, *or* Amphotericin B deoxycholate 0.7 mg/kg IV daily + fluconazole 800 mg PO or IV daily, *or* Fluconazole 400–800 mg PO or IV daily + flucytosine 25 mg/kg PO qid, *or* Fluconazole 1200 mg PO or IV daily	Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF and decreased risk for subsequent relapse Patients receiving flucytosine should have either blood levels monitored (peak level 2 h after dose should be 30–80 μg/mL) or close monitoring of blood counts for development of cytopenia Flucytosine dose should be adjusted in patients with renal insufficiency Opening pressure should always be measured when LP is performed; repeated LPs or CSF shunts are essential to effectively manage increased ICP Corticosteroids and mannitol are ineffective in reducing ICP and are *not* recommended Corticosteroids should not be routinely used during induction therapy except for management of IRIS
	Consolidation therapy (for at least 8 wk, followed by maintenance therapy): Fluconazole 400 mg PO (or IV) daily *Maintenance therapy:* Fluconazole 200 mg PO daily for at least 12 mo	*Consolidation therapy (for at least 8 wk, followed by maintenance therapy):* Itraconazole 200 mg PO bid for 8 wk—less effective than fluconazole *Consolidation therapy (for at least 8 wk, followed by maintenance therapy):* Itraconazole 200 mg PO bid for 8 wk—less effective than fluconazole	
	For non-CNS, extrapulmonary cryptococcosis and diffuse pulmonary disease: Treatment same as for cryptococcal meningitis Non-CNS cryptococcosis with mild-to-moderate symptoms and focal pulmonary infiltrates: Fluconazole, 400 mg PO daily for 12 mo		

Continued

TABLE 129.2 Treatment of AIDS-Associated Opportunistic Infections—cont'd

OPPORTUNISTIC INFECTION	PREFERRED THERAPY	ALTERNATIVE THERAPY	OTHER COMMENTS
Histoplasmosis	Moderately severe to severe disseminated disease: *Induction therapy (for at least 2 wk or until clinically improved):* Liposomal amphotericin B 3 mg/kg IV daily *Maintenance therapy* Itraconazole 200 mg PO tid for 3 days, then 200 mg PO bid Less severe disseminated disease: *Induction and maintenance therapy:* Itraconazole 200 mg PO tid for 3 days, then 200 mg PO bid *Duration of therapy:* At least 12 mo Meningitis: *Induction therapy (4–6 wk):* Liposomal amphotericin B 5 mg/kg/day *Maintenance therapy:* Itraconazole 200 mg PO bid to tid for ≥1 yr and until resolution of abnormal CSF findings Long-term suppression therapy: *For patients with severe disseminated or CNS infection after completion of at least 12 mo of therapy and patients who relapse despite appropriate therapy:* Itraconazole 200 mg PO daily	Moderately severe to severe disseminated disease: *Induction therapy (for at least 2 wk or until clinically improved):* Amphotericin B lipid complex 3 mg/kg IV daily, *or* Amphotericin B cholesteryl sulfate complex 3 mg/kg IV daily (not sold in US) Alternatives to itraconazole for maintenance therapy or treatment of less severe disease: Voriconazole 400 mg PO bid for 1 day, then 200 mg bid, *or* Posaconazole 400 mg PO bid Fluconazole 800 mg PO daily Meningitis: No alternative therapy recommendation Long-term suppression therapy: Fluconazole 400 mg PO daily	Itraconazole, posaconazole, and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bidirectional Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and ARV efficacy and reduce concentration-related toxicities Random serum concentration of itraconazole + hydroitraconazole should be >1 μg/mL Clinical experience with voriconazole or posaconazole in treatment of histoplasmosis is limited Acute pulmonary histoplasmosis in HIV-infected patients with $CD4^+$ counts >300 cells/mm^3 should be managed as nonimmunocompromised host
Coccidioidomycosis	Clinically mild infections (e.g., focal pneumonia): Fluconazole 400 mg[b] PO daily, *or* Itraconazole 200 mg[b] PO bid Bone or joint infections: Itraconazole 200 mg[b] PO bid Severe, nonmeningeal infection (diffuse pulmonary infection or severely ill patients with extrathoracic, disseminated disease): Lipid formulation amphotericin B 3–5 mg/kg IV daily, *or* Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily *Duration of therapy:* continue until clinical improvement, then switch to a triazole Meningeal infections: Fluconazole 400–800 mg[b] IV or PO daily	Mild infections (focal pneumonia): *For patients who failed to respond to fluconazole or itraconazole:* Posaconazole 300 mg delayed-release tablet[b] PO bid × 1 day, then once daily, *or* Posaconazole 400 mg PO suspension[b] PO bid, *or* Voriconazole 200 mg[b] PO bid Bone or joint infection: Fluconazole 400 mg[b] PO daily Severe, nonmeningeal infection (diffuse pulmonary infection or severely ill patients with extrathoracic, disseminated disease): Some specialists add a triazole (fluconazole[b] or itraconazole[b]) 400 mg per day to amphotericin B therapy and continue triazole once amphotericin B is stopped Meningeal infections: Itraconazole 200 mg[b] PO tid for 3 days, then 200 mg PO bid, *or* Voriconazole 200–400 mg[b] PO bid, *or* Posaconazole 300 mg delayed-release tablet[b] PO bid × 1 day, then once daily, *or* Posaconazole 400 mg oral suspension[b] PO bid, *or* Intrathecal amphotericin B deoxycholate when triazole antifungals are ineffective	Relapse can occur in 25%–33% of HIV-negative patients with diffuse pulmonary or disseminated diseases. Therapy should be given for at least 12 mo and usually much longer; discontinuation depends on clinical and serologic response and should be done in consultation with experts Therapy should be lifelong in patients with meningeal infections because relapse occurs in 80% of HIV-infected patients after discontinuation of triazole therapy Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and antiretroviral efficacy and reduce concentration-related toxicities Intrathecal amphotericin B should be given only in consultation with a specialist and administered by an individual with experience with the technique
Cytomegalovirus (CMV) disease	CMV retinitis: *Induction therapy (followed by long-term maintenance therapy)* *For immediate sight-threatening lesions (within 1500 μm of the fovea):* Intravitreal injections of ganciclovir (2 mg) or foscarnet (2.4 mg) for 1–4 doses over 7–10 days to achieve high intraocular concentration faster, *plus* Valganciclovir 900 mg PO bid for 14–21 days, then 900 mg once daily *For peripheral lesions:* Valganciclovir 900 mg PO bid for 14–21 days, then 900 mg once daily	CMV retinitis: *For immediate sight-threatening lesions (within 1500 μm of the fovea):* Intravitreal therapy as listed in Preferred Therapy, plus one of the following: *Alternative systemic induction therapy (followed by long-term maintenance therapy):* Ganciclovir 5 mg/kg IV q12h for 14–21 days, *or* Foscarnet 90 mg/kg IV q12h or 60 mg/kg q8h for 14–21 days, *or* Cidofovir 5 mg/kg/wk IV for 2 wk; saline hydration before and after therapy and probenecid 2 g PO 3 hours before dose, followed by 1 g PO 2 hours and 8 hours after dose (total 4 g). *Note:* This regimen should be avoided in patients with sulfa allergy because of cross-hypersensitivity with probenecid	Choice of therapy for CMV retinitis should be individualized, based on location and severity of lesions, level of immunosuppression, and other factors (e.g., concomitant medications and ability to adhere to treatment) Given the evident benefits of systemic therapy in preventing contralateral eye involvement, reducing CMV visceral disease, and improving survival, whenever feasible, treatment should include systemic therapy The ganciclovir ocular implant, which is effective for treatment of CMV retinitis, is no longer available. For sight-threatening retinitis, intravitreal injections of ganciclovir or foscarnet can be given to achieve higher ocular concentration faster Routine (i.e., every 3 mo) ophthalmologic follow-up is recommended after stopping long-term maintenance therapy for early detection of relapse or IRU, and then periodically after sustained immune reconstitution

TABLE 129.2 Treatment of AIDS-Associated Opportunistic Infections—cont'd

OPPORTUNISTIC INFECTION	PREFERRED THERAPY	ALTERNATIVE THERAPY	OTHER COMMENTS
	Long-term maintenance: Valganciclovir 900 mg PO daily for 3–6 mo until ART-induced immune recovery	Long-term maintenance (for 3–6 mo until ART-induced immune recovery: Ganciclovir 5 mg/kg IV 5–7 times weekly, *or* Foscarnet 90–120 mg/kg IV once daily, *or* Cidofovir 5 mg/kg IV every other week with saline hydration and probenecid as above	IRU may develop in the setting of immune reconstitution Treatment of IRU: Periocular corticosteroid or short courses of systemic steroid Initial therapy in patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include initiation or optimization of ART
	CMV esophagitis or colitis: Ganciclovir 5 mg/kg IV q12h; may switch to valganciclovir 900 mg PO q12h once patient can tolerate oral therapy *Duration:* 21–42 days or until symptoms have resolved Maintenance therapy is usually not necessary but should be considered after relapses	CMV esophagitis or colitis: Foscarnet 90 mg/kg IV q12h or 60 mg/kg q8h for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance, *or* Valganciclovir 900 mg PO q12h in milder disease and if able to tolerate PO therapy, *or* *Duration:* 21–42 days or until symptoms have resolved For mild disease, if ART can be initiated without delay, consider withholding CMV therapy	
	Well-documented, histologically confirmed CMV pneumonia: Experience treating CMV pneumonitis in patients with HIV infection is limited. Use of IV ganciclovir or IV foscarnet is reasonable (doses same as for CMV retinitis) Optimal duration of therapy and role of oral valganciclovir have not been established. CMV neurologic disease: *Note:* Treatment should be initiated promptly Ganciclovir 5 mg/kg IV q12h + (foscarnet 90 mg/kg IV q12h or 60 mg/kg IV q8h) to stabilize disease and maximize response; continue until symptomatic improvement and resolution of neurologic symptoms Optimal duration of therapy and role of oral valganciclovir have not been established Optimize ART to achieve viral suppression and immune reconstitution		
Herpes simplex virus (HSV) disease	Orolabial lesions (for 5–10 days): Valacyclovir 1 g PO bid, *or* Famciclovir 500 mg PO bid, *or* Acyclovir 400 mg PO tid Initial or recurrent genital HSV (for 5–14 days): Valacyclovir 1 g PO bid, *or* Famciclovir 500 mg PO bid, *or* Acyclovir 400 mg PO tid Severe mucocutaneous HSV: Initial therapy acyclovir 5 mg/kg IV q8h After lesions begin to regress, change to PO therapy as above; continue until lesions are completely healed Long-term suppressive therapy *For patients with severe recurrences of genital herpes or patients who want to minimize frequency of recurrences:* Valacyclovir 500 mg PO bid Famciclovir 500 mg PO bid Acyclovir 400 mg PO bid Continue indefinitely regardless of $CD4^+$ cell count.	For acyclovir-resistant HSV: *Preferred therapy:* Foscarnet 80–120 mg/kg/day IV in 2–3 divided doses until clinical response *Alternative therapy:* IV cidofovir (dose as in CMV retinitis), *or* Topical trifluridine, *or* Topical cidofovir, *or* Topical imiquimod Duration of therapy: 21–28 days or longer	Patients with HSV infections can be treated with episodic therapy when symptomatic lesions occur or with daily suppressive therapy to prevent recurrences Topical formulations of trifluridine and cidofovir are not commercially available Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and IV formulation of cidofovir

Continued

TABLE 129.2 Treatment of AIDS-Associated Opportunistic Infections—cont'd

OPPORTUNISTIC INFECTION	PREFERRED THERAPY	ALTERNATIVE THERAPY	OTHER COMMENTS
Varicella-zoster virus (VZV) disease	Primary varicella infection (chickenpox): *Uncomplicated cases (for 5–7 days):* Valacyclovir 1 g PO tid, *or* Famciclovir 500 mg PO tid *Severe or complicated cases:* Acyclovir 10–15 mg/kg IV q8h for 7–10 days May switch to oral valacyclovir, famciclovir, or acyclovir after defervescence if no evidence of visceral involvement Herpes zoster (shingles): *Acute localized dermatomal:* For 7–10 days; consider longer duration if lesions are slow to resolve Valacyclovir 1 g PO tid, *or* Famciclovir 500 mg tid *Extensive cutaneous lesion or visceral involvement:* Acyclovir 10–15 mg/kg IV q8h until clinical improvement is evident May switch to PO therapy (valacyclovir, famciclovir, or acyclovir) after clinical improvement (i.e., when no new vesicle formation or improvement of signs and symptoms of visceral VZV), to complete 10- to 14-day course Progressive outer retinal necrosis: (Ganciclovir 5 mg/kg ± foscarnet 90 mg/kg) IV q12h + (ganciclovir 2 mg/0.05 mL ± foscarnet 1.2 mg/0.05 mL) intravitreal injection biw Initiate or optimize ART Acute retinal necrosis (ARN): (Acyclovir 10–15 mg/kg IV q8h) + (ganciclovir 2 mg/0.05 mL intravitreal injection biw × 1–2 doses) for 10–14 days, followed by valacyclovir 1 g PO tid for 6 wk	Primary varicella infection (chickenpox): *Uncomplicated cases (for 5–7 days):* Acyclovir 800 mg PO 5 times/day Herpes zoster (shingles): *Acute localized dermatomal:* For 7–10 days; consider longer duration if lesions are slow to resolve Acyclovir 800 mg PO 5 times/day	In managing VZV retinitis, consultation with an ophthalmologist experienced in management of VZV retinitis is strongly recommended Duration of therapy for VZV retinitis is not well defined and should be determined based on clinical, virologic, immunologic, and ophthalmologic responses Optimization of ART is recommended for serious and difficult-to-treat VZV infections (e.g., retinitis, encephalitis)
Progressive multifocal leukoencephalopathy (PML) (JC virus infections)	There is no specific antiviral therapy for JC virus infection. The main treatment approach is to reverse immunosuppression caused by HIV Initiate ART immediately in ART-naïve patients Optimize ART in patients who develop PML in phase of HIV viremia on ART	None	Corticosteroids may be used for PML-IRIS characterized by contrast enhancement, edema, or mass effect and with clinical deterioration

[a]Pyrimethamine and leucovorin doses are the same as for preferred therapy.
[b]Fluconazole, itraconazole, posaconazole, and voriconazole may have significant interactions with other medications including ARV drugs. These interactions are complex and can be bidirectional.
AIDS, Acquired immunodeficiency syndrome; *ART,* antiretroviral therapy; *ARV,* antiretroviral; *bid,* twice daily; *biw,* biweekly; *CFU,* colony-forming unit; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *CYP3A4,* cytochrome P-450 3A4; *DOT,* directly observed therapy; *DS,* double-strength; *EMB,* ethambutol; *G6PD,* glucose-6-phosphate dehydrogenase; *HIV,* human immunodeficiency virus; *ICP,* intracranial pressure; *ICU,* intensive care unit; *IM,* intramuscular; *INH,* isoniazid; *IRIS,* immune reconstitution inflammatory syndrome; *IRU,* immune recovery uveitis; *IV,* intravenous; *LP,* lumbar puncture; *mo,* month(s); *NSAIDs,* nonsteroidal antiinflammatory drugs; *PI,* protease inhibitor; *PO,* per os (oral); PZA, pyrazinamide; *q,* every; *RFB,* rifabutin; *RIF,* rifampin; *SS,* single-strength; *TB,* tuberculosis; *tid,* thrice daily; *TMP-SMZ,* trimethoprim-sulfamethoxazole; *TVR,* telaprevir; *wk,* week(s); *yr,* year(s); *ZDV,* zidovudine.
From Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/guidelines. Accessed March 1, 2019.

TABLE 129.3 Indications for Discontinuing and Restarting Opportunistic Infection Prophylaxis in HIV-Infected Adults and Adolescents

OPPORTUNISTIC INFECTION	INDICATION FOR DISCONTINUING PRIMARY PROPHYLAXIS	INDICATION FOR RESTARTING PRIMARY PROPHYLAXIS	INDICATION FOR DISCONTINUING SECONDARY PROPHYLAXIS/LONG-TERM MAINTENANCE THERAPY	INDICATION FOR RESTARTING SECONDARY PROPHYLAXIS/LONG-TERM MAINTENANCE
Pneumocystis pneumonia (PCP)	$CD4^+$ count increased from <200 to >200 cells/mm^3 for >3 mo in response to ART Can consider when $CD4^+$ count 100–200 cells/mm^3 if HIV RNA remains below limits of detection for at least 3–6 mo	$CD4^+$ count <100 cells/mm^3 $CD4^+$ count 100–200 cells/mm^3 and with HIV RNA above detection limit of assay	$CD4^+$ count increased from <200 cells/mm^3 to >200 cells/mm^3 for >3 mo in response to ART Can consider when $CD4^+$ count 100–200 cells/mm^3 if HIV RNAs remain below limits of detection for at least 3–6 mo If PCP occurs at $CD4^+$ count >200 cells/mm^3 while not on ART, discontinuation of prophylaxis can be considered once HIV RNA levels are suppressed to below limits of detection for at least 3–6 mo *Note:* If PCP occurs at $CD4^+$ count >200 cells/mm^3 while on ART, continue PCP prophylaxis for life, regardless of how high $CD4^+$ cell count rises as a consequence of ART	$CD4^+$ count <100 cells/mm^3 $CD4^+$ count 100–200 cells/mm^3 and with HIV RNA above detection limit of assay

TABLE 129.3 Indications for Discontinuing and Restarting Opportunistic Infection Prophylaxis in HIV-Infected Adults and Adolescents—cont'd

OPPORTUNISTIC INFECTION	INDICATION FOR DISCONTINUING PRIMARY PROPHYLAXIS	INDICATION FOR RESTARTING PRIMARY PROPHYLAXIS	INDICATION FOR DISCONTINUING SECONDARY PROPHYLAXIS/LONG-TERM MAINTENANCE THERAPY	INDICATION FOR RESTARTING SECONDARY PROPHYLAXIS/LONG-TERM MAINTENANCE
Toxoplasma gondii encephalitis (TE)	$CD4^+$ count increased to >200 cells/mm^3 for >3 mo in response to ART Can consider when $CD4^+$ count 100–200 cells/mm^3 if HIV RNA remains below limits of detection for at least 3–6 mo	$CD4^+$ count <100 cells/mm^3 $CD4^+$ count 100–200 cells/mm^3 and with HIV RNA above detection limit of assay	Successfully completed initial therapy, receiving maintenance therapy and free of signs and symptoms of TE, and $CD4^+$ count >200 cells/mm^3 for >6 mo in response to ART	$CD4^+$ count <200 cells/mm^3
Microsporidiosis	NA	NA	No signs and symptoms of nonocular or ocular microsporidiosis and $CD4^+$ count >200 cells/mm^3 for >6 mo in response to ART	No recommendation
Salmonellosis	NA	NA	Resolution of *Salmonella* infection and after response to ART with sustained viral suppression and $CD4^+$ counts >200 cells/mm^3	No recommendation
Cryptococcal meningitis	NA	NA	<u>If following criteria are fulfilled:</u> Completed initial (induction and consolidation) therapy, and Received at least 1 yr of maintenance therapy, and Remain free of symptoms of cryptococcal infection, and $CD4^+$ count ≥100 cells/mm^3 for >3 mo, and with suppressed plasma HIV RNA in response to ART	$CD4^+$ count <100 cells/mm^3
Histoplasma capsulatum infection	$CD4^+$ count >150 cells/mm^3 for 6 mo while on ART	For patients at high risk of acquiring histoplasmosis, restart at $CD4^+$ count <150 cells/mm^3	<u>If following criteria are fulfilled:</u> Received itraconazole for >1 yr, and Negative fungal blood cultures, and $CD4^+$ count ≥150 cells/mm^3 for ≥6 mo in response to ART, and Serum *Histoplasma* antigen <2 ng/mL	$CD4^+$ count <150 cells/mm^3
Coccidioidomycosis	$CD4^+$ count ≥250 cells/mm^3 and with viral suppression while on ART	Restart at $CD4^+$ count <250 cells/mm^3	<u>Only for patients with focal coccidioidal pneumonia:</u> Clinically responded to ≥6 mo antifungal therapy, with $CD4^+$ count ≥250 cells/mm^3, and with viral suppression while on ART Should continue monitoring for recurrence with serial chest radiographs and coccidioidal serology every 6–12 mo <u>For patients with diffuse pulmonary or disseminated nonmeningeal diseases:</u> Therapy is at least 12 mo and usually much longer; discontinuation depends on clinical and serologic response and should be done in consultation with experts <u>For meningeal diseases</u>: Suppressive therapy should be continued indefinitely even with increase in $CD4^+$ count on ART	No recommendation
Cytomegalovirus (CMV) retinitis	NA	NA	CMV treatment for at least 3–6 mo and with $CD4^+$ count >100 cells/mm^3 for >3–6 mo in response to ART Therapy should be discontinued only after consultation with an ophthalmologist, taking into account anatomic location of lesions, vision in contralateral eye, and feasibility of regular ophthalmologic monitoring Routine (i.e., every 3 mo) ophthalmologic follow-up is recommended after stopping therapy for early detection of relapse or immune restoration uveitis and then periodically after sustained immune reconstitution	$CD4^+$ count <100 cells/mm^3

ART, Antiretroviral therapy; *HIV,* human immunodeficiency virus; *NA,* not applicable.
From Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/guidelines. Accessed March 1, 2019.

not adhere to prescribed chemoprophylaxis or ART. Therefore PCP continues to be a substantial cause of morbidity and mortality despite the availability of approaches that can markedly reduce its incidence.

Pneumocystis causes disease almost exclusively in the lungs. Extrapulmonary disease occurs but is uncommon. Patients characteristically have chest tightness or exercise intolerance as very early symptoms, before routine chest radiographs demonstrate infiltrates or before arterial blood gases reveal hypoxemia. If therapy is to have the greatest chance to succeed, patients and clinicians must be trained to initiate diagnostic evaluation at this stage, before pulmonary dysfunction is severe.[89,91]

Even with very mild manifestations of disease, organisms can be detected readily from sputum or bronchoalveolar lavage,[92–95] allowing initiation of therapy on an outpatient basis at a stage when prognosis is excellent. These secretions can also be analyzed for other pathogens, thus leading to diagnoses other than PCP. In many cases, PCP can be distinguished on a clinical basis with a high (but not complete) degree of certainty from bacterial pneumonia or viral pneumonia by the duration of symptoms, characteristics of the sputum, and radiologic manifestations. PCP can be especially difficult to reliably distinguish from certain other infectious and noninfectious processes that can manifest subacutely as symmetrical interstitial infiltrates including TB, histoplasmosis, and nonspecific interstitial pneumonitis.[96–99] Therefore, it is important to establish a specific diagnosis to ascertain that the correct pathogen is being treated and to avoid the toxicities, cost, and inconvenience of unnecessary drugs.

Establishing a specific diagnosis also has epidemiologic implications in terms of ascertaining the isolation precautions and contact tracing that are needed (e.g., such considerations are very different for TB as opposed to PCP). However, given the cost of a diagnostic evaluation, in some settings it may be necessary to treat cases of presumptive PCP empirically. If patients do not improve, the yield of a diagnostic evaluation of *Pneumocystis* infection should not be diminished substantially within the first several days or even 2 weeks after initiation of therapy, which is quite different from the experience with PCP in other patient populations. Empirical diagnoses by definition preclude the possibility of testing for active TB, eliminating the potential for early identification of TB and reduction of transmission. The availability of induced sputum examination provides a very sensitive, relatively low-cost method for diagnosis of PCP.[95] The visualization of *Pneumocystis* by colorimetric or immunofluorescent stain in sputum, bronchoalveolar lavage, or tissue is definitive for diagnosis of PCP.

Nucleic acid amplification systems for PCP that use oral washes, gargles, sputum, or bronchoalveolar lavage have not yet been standardized and validated for clinical use.[100,101] More and more laboratories are using nucleic acid amplification, however, so the clinician must be cognizant of how to interpret the results.

A negative nucleic acid amplification test on a bronchoalveolar lavage is very strong evidence that the cause of the pulmonary dysfunction is something other than *Pneumocystis,* assuming the laboratory has validated its assay. A negative result on an induced sputum is less useful. A positive result in a bronchoalveolar lavage or sputum is consistent with either colonization of the airways or acute disease. In theory the copy number of sequences in the specimen is helpful: a high copy number is suggestive of active disease, and a low copy number is more suggestive of colonization. However, given the variability in specimen acquisition, such suggestions are far from definitive. In contrast, detection of organisms by direct visualization is definitive evidence that the pneumonia is due to *Pneumocystis,* presumably because direct visualization is less sensitive and thus a positive result indicates a substantial number of organisms, indicating disease rather than colonization.

β_1-Glucan detection in serum or bronchoalveolar lavage is not sufficiently sensitive or specific to be diagnostically useful.[102–106] Some experts use this test as supportive of a diagnosis of PCP, but it is clearly not definitive. Some experts also follow results serially to document decreasing organism burden, which is logical but not proven to be useful.

The likelihood that a patient with AIDS will survive an episode of PCP depends on the severity of pulmonary dysfunction at the time of initiation of therapy, the patient's ability to tolerate available regimens, the presence of comorbidities, and the severity of the patient's immunologic dysfunction. An alveolar-arterial gradient greater than 30 mm Hg, a severely abnormal chest radiograph, a large number of organisms detected on lavage or biopsy, and comorbid conditions are strongly correlated with a poor prognosis.[89] Any drug therapy is more likely to be successful if it is started at a time when pulmonary dysfunction is mild and if other severe opportunistic infections or neoplasms are absent. Second, third, and subsequent episodes of PCP do not necessarily carry a worse prognosis than the first episode.[107,108] More relevant to prognosis is the severity of the acute disease, the presence of comorbidities, and the patient's current $CD4^+$ T-lymphocyte count, and HIV viral load.

TMP-SMZ is the treatment of choice for acute PCP because of its convenience of administration, high degree of efficacy, and manageability of associated toxicities (see Table 129.2).[8,109,110] No agent has been shown to have a higher efficacy for PCP than TMP-SMZ. There is no clear reason to prefer intravenous over oral TMP-SMZ in patients with mild disease who adhere to the treatment and who are without potential gastrointestinal dysfunction. Patients usually improve clinically within 4 to 8 days in terms of fever, respiratory rate, arterial-alveolar gradient, and dyspnea, although there may be an initial worsening during the first 8 to 72 hours of therapy if adjunctive corticosteroid therapy is not given.[87,111–114]

Survival for mild episodes treated with TMP-SMZ has improved steadily during the past 3 decades.[109–114] For patients with an initial room-air partial pressure of oxygen (Po_2) greater than 70 mm Hg, survival has improved from 85%–90% to 95%–99% in optimal circumstances.[109–114] Patients with significant concomitant disorders do not have such good results. This improvement in patient outcome for patients with moderate-to-severe disease presumably reflects better supportive treatment in critical care units and the better understanding that TMP-SMZ can be continued despite non–life-threatening toxicities. In addition, better alternative agents have been available since the early 1990s for patients who truly have treatment failure with TMP-SMZ or who are unable to tolerate the drug.[8,115–117]

In vitro resistance of *Pneumocystis* to TMP-SMZ was not described until the 1990s. Some human isolates contain mutations in the dihydropteroate synthase enzyme, the target for sulfonamides. When these same mutations occur in other organisms (e.g., *S. pneumoniae* or *Plasmodium* spp.), they produce microbiologic and clinical resistance. Further information is needed to determine whether these mutations in fact confer sulfonamide resistance to *Pneumocystis* that is clinically significant and whether the frequency of such resistance will become sufficient to warrant new therapeutic and prophylactic strategies.[118–122] The recent cloning of the human species of *Pneumocystis* will likely provide insights into resistance mechanisms and new targets for therapy.[123]

Common adverse reactions to TMP-SMZ include rash, nausea, vomiting, granulocytopenia, transaminase elevations, nephritis, and hyperkalemia.[87,124] These reactions do not invariably require discontinuation of TMP-SMZ therapy. The rashes, which commonly occur between days 8 and 12 of therapy, may be limited in extent and associated with a degree of pruritus that the patient can tolerate for 21 days. They are more frequent in patients with higher $CD4^+$ T-cell counts. Life-threatening desquamating processes (e.g., Stevens-Johnson syndrome) are rare in HIV-infected patients, although a few fatal cases have been described. Severe febrile, hypotensive episodes that resemble septic shock in terms of hemodynamics have also been reported. Granulocytopenia is most often a dose-related phenomenon that may resolve partially or completely if the dose of TMP-SMZ is reduced by 25%. Granulocytopenia responds to leucovorin administration only rarely. A report that leucovorin administration can diminish the likelihood of therapeutic response to TMP-SMZ was intriguing but not conclusive and has not been replicated.[125] Nausea and vomiting can be troublesome complications of TMP-SMZ therapy. Severe nausea may result from very high sulfonamide levels and may resolve if the dose is reduced such that sulfonamide levels 2 hours after dosing are 100 to 150 μg/mL.[126] Transaminase levels may fluctuate to three to five times normal until therapy is stopped; they usually return promptly to baseline values if they were caused by TMP-SMZ rather than another drug or a coexisting process such as hepatitis A virus, HBV, or HCV.

Overall, adverse reactions have required discontinuation of TMP-SMZ therapy in about 25% of cases.[8,89,124] Although it has not been proved

by a prospective study, adverse reactions can probably be reduced without sacrificing efficacy by lowering the recommended dose of TMP-SMZ from TMP 20 mg/kg/day (with SMZ 100 mg/kg/day) to TMP 15 mg/kg/day (with SMZ 75 mg/kg/day).[109] Gradual dose escalation of TMP-SMZ can reduce the impact of adverse effects, but this approach is appropriate in selected patients when trying to institute prophylaxis, not when instituting therapy in patients with acute illness.[127,128]

Parenteral pentamidine is effective therapy for PCP.[8,109] The intravenous regimen is inconvenient to administer, however, and the adverse reactions associated with it can be life threatening. Renal dysfunction, hypoglycemia, hyperglycemia, granulocytopenia, and hypotension are reported in 10% to 50% of patients.[8,109,129–132] If pentamidine is administered over a period of at least 60 minutes in 100 to 150 mL of dextrose in water, clinically important hypotension is unusual.[131] The renal dysfunction associated with pentamidine can be severe. If the serum creatinine level rises by more than 1 to 2 mg/dL, strong consideration should be given to withholding therapy for a few days or changing to an alternative agent. Pentamidine prolongs the QT interval, and this has led to torsades de pointes in a few patients with fatal outcomes, especially if patients had a preexisting QT prolongation or were receiving other drugs that prolong the QT interval. Hypoglycemia can be a life-threatening complication of pentamidine therapy; it can occur at any juncture during therapy or for many weeks after therapy has been completed.[132] Hypoglycemia occurs more frequently in patients who have pentamidine-induced renal dysfunction. The unpredictability of the hypoglycemia adds an element of risk to inpatient or outpatient use of this drug. Life-threatening hypoglycemia is sufficiently uncommon, however, that this effective agent is still recommended for patients with severe disease who cannot tolerate TMP-SMZ. Lowering the dose of parenteral pentamidine from 4 to 3 mg/kg/day has been advocated to reduce toxicity; whether this also reduces efficacy is unknown. Aerosol pentamidine is not sufficiently effective for use to treat PCP.[133]

Dapsone is rarely used in this era for therapy or prophylaxis of PCP, but this drug does have clinical activity against *Pneumocystis*.[109,134–136] Dapsone (100 mg orally every day) plus TMP (5 mg/kg orally every 8 hours or 300 mg orally every 8 hours) appears to be as effective as TMP-SMZ but less toxic.[8,111,134–136] This regimen is not frequently used because it is less convenient to administer than TMP-SMZ (there is no tablet that combines dapsone and TMP). Dapsone-based regimens have no major advantages in terms of efficacy or safety. Rashes are common among HIV-infected patients treated with dapsone, but a 21-day course of therapy can usually be completed without interruption. Methemoglobinemia can occur and can be life threatening. Oral dapsone alone has some efficacy when 100 mg is administered every day for 21 days, but there is probably not enough activity to warrant use of this agent as single-drug therapy. Higher doses are not well tolerated. Dapsone should not be administered to patients who have had immediate hypersensitivity reactions to sulfonamides.[134]

Atovaquone is a hydroxynaphthoquinone that affects mitochondrial electron transport in microorganisms and therefore has a mechanism of action distinct from that of TMP-SMZ or pentamidine.[115,137] Atovaquone is available as an oral suspension but is not available in a parenteral form. For patients with mild or moderate PCP, it has a high degree of efficacy and is extremely well tolerated. A large, prospective, double-blind study demonstrated that atovaquone, although very effective and much better tolerated than TMP-SMZ, is associated with more treatment failures.[115] Because atovaquone, in contrast to TMP-SMZ, has no antibacterial activity, it is possible that patients in the atovaquone-treated groups were more likely to experience a deterioration of their condition owing to unrecognized, concurrent bacterial processes. Atovaquone is better tolerated than intravenous pentamidine.[137] The absorption of atovaquone suspension can be erratic, especially in patients who cannot consume fatty foods with this medication. Atovaquone takes several days to reach steady-state levels. It should not be given to patients with significant gastrointestinal dysfunction and should not be initiated as primary therapy in patients with severe disease. Mutations that could confer atovaquone resistance have been identified in human isolates, but their clinical relevance remains to be determined.[138] The primary toxicities associated with atovaquone are nausea, abdominal pain, low-level transaminase elevations, and rash. Atovaquone is a reasonable treatment option for patients with mild or moderate PCP who cannot tolerate TMP-SMZ and who are good candidates for oral therapy.

Clindamycin plus primaquine is also effective therapy for PCP.[8,110,117] Despite the fact that primaquine can be given only orally, this regimen has been used successfully in patients with mild, moderate, and severe disease. Clindamycin plus primaquine is associated with toxicity including rash, serum aminotransferase elevation, diarrhea, and hemolysis. It is a reasonable regimen for patients who are unable to tolerate other regimens. Clindamycin-primaquine is also a reasonable option for patients with definitively established PCP who are unequivocally failing therapy with TMP-SMZ.

Regardless of which specific agent is chosen as the initial therapy for PCP, adjunctive corticosteroid therapy is indicated for any patient whose initial room-air Po_2 is less than 70 mm Hg.[8,111–115] Three prospective trials demonstrated that the frequencies of ventilatory failure and mortality can be reduced substantially by the prompt use of corticosteroids.[111–115] Physiologically, adjunctive corticosteroids appear to prevent much of the decline in oxygenation that characteristically occurs during the first 3 days of treatment.[114] This decline may be caused by the inflammatory response elicited by dying organisms. Adjunctive corticosteroids may also provide benefit for patients with an initial room-air Po_2 greater than 70 mm Hg. Physiologic evidence indicates improved lung function in such patients, but so few patients with mild PCP develop respiratory failure or die that it is difficult to substantiate a survival benefit. The safety of the 21-day regimen is well substantiated. Reactivation of TB, CMV, or Kaposi sarcoma is unusual. It is unclear whether such short courses of corticosteroids could predispose patients to osteonecrosis.[139,140] The frequency of TMP-SMZ–related rash is not diminished by corticosteroids.[141]

If an HIV-infected patient with PCP fails to improve while receiving conventional therapy, there are no controlled data to indicate which modifications in therapy are optimal.[8,142–146] The mean time to improvement for HIV-infected patients treated with conventional therapy is 4 to 8 days,[87,109] so therapeutic failure probably should not be diagnosed until patients have received 4 to 8 days of therapy. Clinicians often feel compelled to alter therapy earlier, however, especially if the patient's condition is deteriorating rapidly as opposed to failing to improve. If a patient has not improved after 5 to 10 days of therapy, repeat diagnostic procedures should be considered to determine whether another treatable (infectious or noninfectious) condition is present. Bronchoalveolar lavage is the procedure of choice. *Pneumocystis* is often present in lavage or tissue for at least 3 to 4 weeks after initiation of therapy, even in patients who respond promptly, so its presence after 7 to 10 days of therapy does not necessarily imply that therapy is ineffective. A decision regarding treatment effectiveness should be based on clinical and laboratory parameters such as oxygenation, ventilation, and fever. The presence of extensive intraalveolar exudate or extensive fibrosis after 7 to 10 days of therapy is a more ominous sign. Open lung biopsy is rarely necessary to establish a diagnosis of PCP, but it can occasionally be useful for identifying other processes. Kaposi sarcoma of the lung is usually apparent on bronchoscopy because of endobronchial lesions that are obvious to the bronchoscopist.[147] However, if such lesions are not seen on bronchoscopy, Kaposi sarcoma of the lung is one treatable process that is difficult or impossible to diagnose reliably from cytology or from transbronchial biopsy specimens. Nodular lesions on chest computed tomography, extensive intrabronchial lesions, and the presence of a bloody pleural effusion may be helpful clues that Kaposi sarcoma is the cause of pulmonary dysfunction. CMV and lymphoma are other processes that may be identified by cytology or by some form of biopsy more readily than by sputum assessment.

If *Pneumocystis* infection is the only identifiable cause of the pulmonary dysfunction after 7 to 10 days of therapy and no improvement has been observed, there are several therapeutic interventions to consider: (1) switch from TMP-SMZ to parenteral pentamidine or clindamycin-primaquine; (2) add corticosteroids to conventional therapy if they have not already been added; (3) use two specific therapies concurrently (e.g., TMP-SMZ plus pentamidine); and (4) add ART. Each of these approaches has been associated with a successful outcome in some cases.[142–144] A controlled trial is needed to determine the best approach, but such trials are difficult to perform because of the large size, complexity,

and cost of a valid study. Whether patients with AIDS with PCP should be supported aggressively with intensive care, mechanical ventilation, or other interventions depends on issues specific to each individual patient, as would be the case for any patient who is critically ill. The most reasonable approach would be to individualize each management plan in terms of the days of therapy that have been completed, the therapeutic alternatives that are available, and the concomitant processes that are present. The patient's wishes and the availability of resources need to be taken into account. Published data indicate that some patients with AIDS with PCP can survive intubation and mechanical ventilation and lead independent lives for years after hospital discharge. The best candidates for intensive care and mechanical ventilation are patients who had a good functional status before PCP, patients who have presented with no other serious opportunistic processes, patients who have received fewer than 7 days of specific therapy, and patients who have clearly articulated a desire for aggressive support.

As mentioned previously, for patients who were not receiving ART when PCP was diagnosed, ART is generally not initiated immediately, but is started within 2 weeks of the PCP episode.[71] An important study demonstrated that patients who started ART within 2 weeks had better survival than patients who started after 2 weeks, presumably because additional HIV-associated complications were prevented by the earlier introduction of therapy.[71] There are multiple reasons not to initiate ART immediately after the diagnosis of PCP: inability to take oral drugs, drug interactions with agents used during the acute disease, adverse effects of ART being confused with adverse effects of other recently added drugs, and IRIS against *Pneumocystis* or another pathogen are among the issues that influence this decision.[8] However, in challenging cases early initiation of ART may be a desirable strategy.

For the rare patients receiving ART at the time that PCP is diagnosed (an unusual occurrence most often related either to very recent initiation of ART or nonadherence to ART), ART is usually continued if the patient can tolerate it. Such decisions are complex, related to the patient's ability to reliably absorb oral ART during an acute illness as well as to potential drug interactions.

Prevention of PCP is a major priority in the management of HIV infection.[8] Prevention of PCP is logical because episodes are frequent (at least 80%–90% of HIV-infected patients in North America develop an episode at some point if they have received neither anti-*Pneumocystis* prophylaxis nor ART), morbidity and mortality due to PCP can be substantial, low-cost drugs are available that are effective, and the period of high susceptibility can be defined.[8,49] Prospective and retrospective studies have shown that most primary episodes of PCP occur in patients with $CD4^+$ T-cell counts less than 200 cells/mm^3.[8,33,49] Other documented predictors of the occurrence of PCP, independent of the $CD4^+$ T-cell count, are otherwise unexplained oropharyngeal candidiasis (e.g., no concurrent corticosteroids or antibacterials), high HIV viral load, wasting syndrome, previous AIDS-defining event, and prior pneumonia of any type.[8] These parameters should be added to the list of factors encouraging primary prophylaxis.

When ART is initiated and is effective, the HIV viral load declines rapidly, and the patient's risk of PCP decreases quickly regardless of the measured $CD4^+$ T-cell count. As the $CD4^+$ T-cell increases with a viral load below the level of assay detection, management strategies have been proposed suggesting that PCP prophylaxis is not necessary. However, if the patient's $CD4^+$ T-cell count was very low (e.g., less than 100 cells/mm^3) when ART was started, the $CD4^+$ count may not rise above 200 cells/mm^3 for many months. In such cases, PCP may be rare, yet PCP does occur, and thus most clinicians would continue PCP prophylaxis until the $CD4^+$ T-cell count is above 200 cells/mm^3.[148,149]

Before the era of ART, secondary prophylaxis (prevention of second or subsequent episodes of PCP) was indicated for everyone who had a documented PCP episode because the 1-year recurrence rate is about 65% for patients who receive no prophylaxis.[8,49] As mentioned earlier, there is considerable evidence suggesting that discontinuation of primary or secondary prophylaxis is appropriate for patients who respond to ART and who manifest $CD4^+$ T-cell counts that are persistently approximately 200 cells/mm^3 (see Table 129.3).[150]

TMP-SMZ is the preferred prophylactic regimen for any HIV-infected patient who can tolerate it (see Tables 129.1 and 129.2).[8,150–157] If administered at a dose of 160 mg TMP plus 800 mg SMZ (i.e., one double-strength tablet once daily), episodes of PCP are extremely uncommon among patients who adhere to the regimen. Trials have demonstrated that TMP-SMZ is much more effective for either primary or secondary prophylaxis than aerosolized pentamidine or dapsone-containing regimens.[151–156] TMP-SMZ also has the benefit, based on retrospective analyses, of reducing the frequency of toxoplasmosis,[157] and it probably has a beneficial effect on reducing the frequency of pneumococcal, staphylococcal (methicillin-sensitive *S. aureus* and MRSA), and *Haemophilus* spp. infections.[150,151]

There is not convincing evidence that clindamycin-primaquine or intravenous pentamidine should be used for PCP prophylaxis for patients with HIV infection. However, there are some small studies suggesting that intravenous pentamidine is effective in pediatric hematopoietic stem cell recipients.[158,159]

Comparative trials have confirmed that TMP-SMZ is not nearly as well tolerated as aerosolized pentamidine. Due to side effects of rash, pruritus, fever, granulocytopenia, thrombocytopenia, anemia, hepatitis, nephritis, nausea, or vomiting, 20% to 40% of patients cannot tolerate TMP-SMZ. Reducing the dose of TMP-SMZ by 50% (i.e., a single-strength tablet daily) or reducing the frequency to two or three times weekly lowers the toxicity.[152,156] In a study comparing TMP-SMZ at a dose of one double-strength tablet daily with TMP-SMZ at a dose of one double-strength tablet three times weekly, there was no difference in efficacy when the data were evaluated based on an intent-to-treat analysis.[156] However, there were more failures on the intermittent regimen when occurrences of PCP were analyzed based on the regimen patients were actually taking at the time that PCP was diagnosed. This finding has suggested to some investigators that the intermittent regimen is less effective.

Because TMP-SMZ is the preferred regimen, strategies to increase patient tolerance of this regimen are important. In two controlled studies, gradual dose escalation of TMP-SMZ at the time at which prophylaxis is restarted was shown to increase tolerability.[127,128]

There are several alternatives for patients who cannot tolerate TMP-SMZ. Dapsone is rarely used anymore. However, there are trials that show that daily dapsone or weekly dapsone-pyrimethamine has an efficacy comparable to that of aerosolized pentamidine (i.e., not as effective as daily TMP-SMZ when used as prophylaxis for PCP). Dapsone-containing regimens, especially dapsone-pyrimethamine regimens, are effective as prophylaxis against toxoplasmosis.[135,136,153] Similar to TMP-SMZ, dapsone or dapsone-pyrimethamine is poorly tolerated by a substantial number of patients; fever, rash, pruritus, and hemolysis occur. About 20% of patients who cannot tolerate TMP-SMZ also cannot tolerate dapsone-containing regimens.[134] Aerosolized pentamidine, although not as effective as TMP-SMZ, has a definite ability to reduce the frequency of PCP when used for primary or secondary prophylaxis. The manner in which aerosolized pentamidine is delivered to the patient is a major determinant of efficacy and safety.[160] Because different nebulizers deliver different spectra and different densities of particle sizes, they deliver different amounts of drug to the lung. Only the Respirgard II jet nebulizer and the Fisons ultrasonic nebulizer have been studied in large, well-controlled trials with clinical end points. Aerosolized pentamidine is well tolerated by most patients. Coughing and wheezing can be ameliorated or prevented by nebulized albuterol. A bitter taste is often reported. Cases of pancreatitis and renal dysfunction have been attributed to aerosolized pentamidine, but it is not always certain that aerosolized pentamidine was the cause.

A major concern related to the use of aerosolized pentamidine is environmental contamination with drug and respiratory aerosols, which is created when patients cough or become disconnected from the nebulizer. Health care workers and patients may inhale enough pentamidine to develop detectable urine levels of the drug.[161] The clinical importance of this is unknown. More important, if the patient has pulmonary TB, the environmental contamination produced by dispersed respiratory particles has considerable potential to spread TB.[162] Patients need to be carefully screened for pulmonary TB before aerosolized pentamidine prophylaxis is initiated.

Atovaquone has been assessed as prophylaxis in trials comparing it with either dapsone alone or aerosolized pentamidine.[163,164] In both

situations, atovaquone was equally effective as the alternative, and it was better tolerated than dapsone. As indicated earlier, optimal atovaquone absorption is dependent on ingestion of high-fat meals concurrent with drug administration.

If patients cannot tolerate TMP-SMZ, aerosolized pentamidine, or atovaquone, there are several poorly studied options. The best option for patients intolerant of the normally used therapies is to try to maximize the patient's ability to tolerate TMP-SMZ by using a dose-escalation strategy or an intermittent (three times weekly) regimen. Aerosolized pentamidine can be administered by employing doses greater than the approved regimen (300 mg twice monthly or 600 mg once monthly, rather than the approved dose of 300 mg monthly),[165] although experience documenting the superiority of twice-monthly pentamidine is limited. Results with clindamycin-primaquine have been disappointing. Whether the need for alternative regimens will grow substantially depends on the clinical relevance of sulfonamide resistance.

Before effective ART was available, there were analyses of why patients experienced breakthrough PCP while receiving prophylactic therapy. These analyses demonstrated that breakthroughs usually occurred in patients who were not receiving TMP-SMZ (i.e., they were receiving other regimens for prophylaxis), patients who were not adherent to prophylaxis, or patients who had very low $CD4^+$ T-cell counts with high viral loads.[166,167] These factors are undoubtedly relevant, but the major focus for PCP prevention in this era should be institution of effective ART.

Toxoplasma gondii

Toxoplasma gondii (see Chapter 278) causes disease in patients with HIV infection primarily by reactivation of latent disease rather than by primary infection.[168–173] Patients almost always have IgG antibodies against *Toxoplasma* (although insensitive enzyme-linked immunosorbent assays may fail to detect such antibodies), have fairly advanced immunosuppression ($CD4^+$ T-cell counts <50 cells/mm^3), and have not been receiving TMP-SMZ prophylaxis. Because the seroprevalence of toxoplasmosis is much higher in some areas such as Western Europe (50%–80%) and South America than in the United States (11%) (i.e., there is a higher incidence of latent infection), those areas have much higher frequencies of AIDS-associated toxoplasmosis because the latent disease has the potential to reactivate when patients are severely immunosuppressed.[174,175]

In patients with HIV infection, toxoplasmosis manifests most often as focal cerebral disease with fever, headache, confusion, motor defects, and seizures. Retinochoroiditis, pneumonitis, disseminated disease, diffuse and nonfocal cerebral disease, and a sepsis-like syndrome all have been reported, but these are not as frequent as focal lesions of the central nervous system (CNS).

If an HIV-infected patient with a $CD4^+$ T-cell count less than 100 cells/mm^3 presents with a space-occupying cerebral lesion that involves gray matter, the differential diagnosis in North America should focus on two entities: toxoplasmosis and lymphoma. Fungal, mycobacterial, viral, and nonlymphoma neoplastic processes also manifest as space-occupying lesions, but these entities are causative processes seen less commonly in the United States and Western Europe than *Toxoplasma* and lymphoma. Progressive multifocal leukoencephalopathy (PML) should manifest differently because it affects primarily white matter. The incidence of malignant neoplasms that are not included as AIDS-defining conditions is increasing; thus clinicians must also be alert to the possibility that CNS masses represent metastatic tumor.[27,28,176,177] Also, in the era of ART, CNS lymphoma appears to be increasing in frequency compared with CNS toxoplasmosis.

Clinical or imaging characteristics help to distinguish lymphoma from toxoplasmosis but are not definitive.[178–183] Magnetic resonance imaging is more sensitive than computed tomography for radiologic diagnosis of *Toxoplasma* encephalitis. Positron emission tomography or single-photon emission computed tomography may also be helpful in distinguishing *Toxoplasma* encephalitis from primary CNS lymphoma.[179,178] However, no imaging technique is completely specific.

If safe and feasible, a lumbar puncture should be performed for *T. gondii* PCR assay.[180–186] A positive CSF PCR assay for Epstein-Barr virus (EBV) is moderately specific for primary CNS lymphoma.[187] Some positive EBV PCR results have been documented in patients with proven cerebral toxoplasmosis—that is, the CSF is EBV PCR positive, but the lesion is caused by *Toxoplasma*. For toxoplasmosis, detection of the *Toxoplasma* organism by CSF PCR should be virtually diagnostic that *Toxoplasma* is the causative agent; however, the test is not standardized across laboratories. Published results have shown that some laboratories can achieve high specificity but low sensitivity. Sensitivity may be low after specific therapy has been started.

Although most cases of *Toxoplasma* encephalitis are clinically diagnosed by response to empirical therapy or by PCR assay of the CSF, an unequivocal diagnosis of *Toxoplasma* encephalitis requires a brain biopsy, which is most commonly performed by a stereotactic CT-guided needle biopsy. Hematoxylin and eosin stains can be used for detection of *T. gondii,* but sensitivity is significantly increased if immunoperoxidase or immunofluorescent staining is used. The detection of *Toxoplasma* in tissue samples by PCR is not a standardized approach and can be difficult to interpret because *Toxoplasma* can be present in brain tissue as a latent organism unrelated to the process that is causing the space-occupying lesion.

If an HIV-infected patient with a circulating $CD4^+$ T-cell count less than 50 cells/mm^3 and positive serum anti-*Toxoplasma* antibody presents with a CNS mass lesion involving gray matter, most clinicians would treat the patient empirically for toxoplasmosis.[188–192] A definitive diagnostic study (i.e., brain biopsy) has morbidity associated with it, and the diagnostic yield may be only 50% if toxoplasmosis is the cause depending on the size of the biopsy specimen and skill of the pathologist. The cysts and tachyzoites of *T. gondii* can be difficult to recognize in fragments of necrotic brain tissue, and even several small needle biopsy samples may miss the area that has abundant organisms. When patients are treated with either sulfadiazine-pyrimethamine or clindamycin-pyrimethamine, unequivocal improvement clinically and radiologically should occur within 10 to 21 days. If such improvement does not occur, a biopsy should be performed to establish whether the cause is an infectious or a neoplastic process other than toxoplasmosis.[188–192] Pyrimethamine and sulfadiazine are becoming more difficult to find in some regions. TMP-SMZ has not been as extensively evaluated in published literature as pyrimethamine and sulfadiazine, but several small trials or observational cohorts suggest that TMP-SMZ has comparable efficacy and safety to sulfadiazine plus pyrimethamine.[191–194] TMP-SMZ has the advantage of being available as an oral or an intravenous preparation.

Corticosteroids to reduce inflammation may be necessary in patients with signs of increased ICP. As there are no well-defined parameters to determine when corticosteroid therapy is indicated, clinical judgment must be used. The administration of corticosteroids can make early evaluation of the clinical and radiologic response to specific therapy difficult because the observed improvement may be solely the result of corticosteroid therapy and unrelated to the anti-*Toxoplasma* regimen employed. Doses of corticosteroids should be tapered as soon as feasible.

Although some clinicians institute antiseizure drugs prophylactically, most experts would initiate such therapy only if a seizure occurs.

For patients who have a clinical and radiologic response, anti-*Toxoplasma* therapy should be continued lifelong, in the absence of an ART-induced increase in the $CD4^+$ T-cell count, because relapses occur in the same sites manifesting initially if therapy is discontinued, even after 8 to 12 months of treatment. If the $CD4^+$ T-cell count rises substantially (e.g., to levels >200 cells/mm^3) due to ART and the patient has received at least 6 months of anti-*Toxoplasma* therapy, the anti-*Toxoplasma* therapy can be safely discontinued, provided that the lesion has largely resolved on cerebral imaging and the patient is neurologically stable (see Table 129.3).[8,195,196]

Treatment failures are unusual for patients with toxoplasmosis who are able to tolerate both pyrimethamine and sulfadiazine or TMP-SMZ. Radiologically proven failures in patients who are adhering to their drug regimen should raise the possibility that toxoplasmosis is not the correct or the only diagnosis.

Adverse reactions to sulfadiazine (leukopenia, rash, elevated levels of aminotransferases, nausea, nephritis) and to pyrimethamine (leukopenia, thrombocytopenia) are common. TMP-induced or pyrimethamine-induced leukopenia often does not respond to leucovorin therapy,

although a short course of leucovorin (10–20 mg orally or intravenously every 6 hours) should be administered. For patients unable to tolerate sulfadiazine, clindamycin plus pyrimethamine is also effective (see Table 129.2).[188,190]

Immune reconstitution syndromes associated with toxoplasmosis have only rarely been reported.[197,198] The potential for such syndromes to occur should be considered before initiating ART, especially in patients who have elevated ICP.

TMP-SMZ offers considerable protection as primary prophylaxis for *Toxoplasma*-seropositive patients with $CD4^+$ T-cell counts less than 100 cells/mm^3.[8,157] Dapsone-pyrimethamine and atovaquone also have substantial efficacy. However, prevention should focus primarily on improving immune function by instituting ART. As with other opportunistic infections, susceptibility to toxoplasmosis is reduced substantially as soon as the viral load is suppressed.

Herpes Simplex Virus and Varicella-Zoster Virus

In the United States, 60% of the general adult population is seropositive for HSV-1, and 17% is seropositive for HSV-2. For HIV-positive individuals, 95% are seropositive for HSV-1 or HSV-2.[199–201] HSV (see Chapter 135) is a frequent cause of oral, genital, and perirectal ulcerations in patients with HIV infection who have low $CD4^+$ T-cell counts and who are not receiving effective ART. Ulcers in such patients can be several centimeters in diameter.

The response of acyclovir-sensitive HSV lesions is usually prompt and occurs within 3 to 10 days.[202,203] Therapy should continue until the lesions are crusted over or epithelialized. Relapses occur with high frequency. If relapses occur quickly or often, long-term suppressive therapy may be necessary. Acyclovir-resistant isolates occur primarily in patients who have low $CD4^+$ T-cell counts and who have received long-term suppressive therapy. Foscarnet and cidofovir are active against herpes simplex and have been used successfully against acyclovir-resistant strains.[204–207] Cases of foscarnet-resistant and cidofovir-resistant HSV have also been reported. Favorable experience has been reported with topical preparations of trifluridine, foscarnet, imiquimod, or cidofovir.[208,209] If lesions recur, the causative virus may be a drug-susceptible strain even if the prior episode was caused by a drug-resistant strain.

Chemoprophylaxis is not routinely recommended to prevent occurrences of HSV-1 or HSV-2 disease. If recurrences are severe or frequent, such suppression could be considered using valacyclovir or famciclovir.

Esophagitis due to HSV occurs but is not as common as *Candida* esophagitis. Disseminated herpes simplex viral infections and focal visceral manifestations, including encephalitis, are unusual in HIV-infected patients, even in patients with very low $CD4^+$ T-cell counts.

The incidence of herpes zoster is 15-fold higher in HIV-infected individuals than in age-matched control subjects.[210,211] ART does not diminish the incidence of herpes zoster substantially.[210,211] In fact, zoster occurs with increased frequency in the initial 6 months after starting ART, which may represent a form of either "unmasking" or IRIS. Dermatomal herpes zoster lesions are usually similar in extent and distribution to lesions seen in immunocompetent patients (see Chapter 136). Dissemination of varicella-zoster virus (VZV) is an unusual event.[212] If dissemination does occur, visceral disease is unusual, and cutaneous manifestations can be quite variable in presentation. A high index of suspicion should be maintained that hyperkeratotic, verrucous, or ecthymatous lesions in patients with low $CD4^+$ T-cell counts could be caused by VZV infection.

Neurologic disease due to VZV is well described in association with HIV infection. Manifestations include CNS vasculitis, multifocal leukoencephalopathy, ventriculitis, myelitis, cranial nerve palsies, aseptic meningitis, progressive outer retinal necrosis, and acute retinal necrosis.

For dermatomal disease, acyclovir, valacyclovir, or famciclovir therapy hastens the crusting of lesions and aids in preventing postherpetic neuralgia and preventing recurrences in HIV-infected patients (see Table 129.2).[8] Therapy is indicated within the first week of rash onset or if lesions have not fully crusted. Treatment should probably continue until all lesions are scabbed or crusted, even if this requires more than 7 to 10 days. Patients with zoster ophthalmicus and neurologic complications would be logical candidates for high-dose intravenous acyclovir, probably with adjunctive corticosteroids. Many clinicians are reluctant to use corticosteroids to treat dermatomal disease in patients with HIV infection despite evidence regarding a beneficial effect in patients without HIV infection.[213,214] Acyclovir-resistant isolates rarely occur,[215] and some of these cases have been treated successfully with parenteral foscarnet or cidofovir.

About 5% of patients with HIV infection do not have detectable antibodies to VZV, although routine serologic testing is not recommended. Seronegative patients may benefit from ensuring that all household contacts have been immunized, thus avoiding exposure of the patient to a family member with varicella. If seronegative patients are exposed to this virus, primary varicella may result and can be severe.[216] The live-attenuated varicella vaccine can be considered for HIV-infected adults with $CD4^+$ T-cell counts greater than 200 cells/mm^3.[8] Seronegative HIV-infected patients who are exposed to varicella probably benefit from VariZIG (administered immediately after exposure, but within 10 days of exposure) or acyclovir (initiate 7–10 days after exposure) (see Chapter 136).

Two vaccines now are available for non–HIV-infected individuals to prevent herpes zoster and postherpetic neuralgia in people ≥50 years of age: RZV (a recombinant glycoprotein E vaccine) and ZVL (a live-attenuated vaccine). The live-attenuated vaccine to prevent herpes zoster (Zostavax) can be considered for HIV-infected patients with $CD4^+$ T-cell counts greater than 200 cells/mm^3.[8,208,217] For preventing zoster in HIV-infected individuals, there are not enough data currently available to make recommendations regarding the inactivated recombinant vaccine.[218,219]

Cytomegalovirus

CMV retinitis was one of the earliest manifestations that clinicians recognized as characteristic of AIDS. During the first decade of the AIDS epidemic, CMV retinitis was a devastating and common occurrence in patients with this new syndrome. In that era, CMV retinitis caused severe visual impairment because no specific therapy was available for CMV, and no durably effective therapy was available for HIV.

CMV infection, as assessed by serology, is almost universal among HIV-infected patients who have acquired HIV infection through homosexual contact (see Chapter 137). In contrast, only about 75% of HIV-infected patients who are heterosexual are seropositive for CMV.[220,221]

Historically, before either specific anti-CMV prophylaxis or ART was available, 21% to 44% of patients developed CMV-associated disease at some point during their illness.[7,222–224] HIV-infected patients with circulating $CD4^+$ T-cell counts less than 50 cells/mm^3 are often viremic and viruric with CMV, which does not imply that they have disease due to CMV.[225,226] The likelihood of development of CMV-associated disease is related to both the degree of immunosuppression and the quantity of circulating CMV. The latter can be assessed by a variety of quantitative systems that detect antigen or nucleic acid in circulating blood, although this is not done routinely. A strategy to intervene in high-risk patients (i.e., patients with low $CD4^+$ T-cell counts and detectable CMV above some defined threshold) may be plausible because oral agents are available, but such an approach does not seem necessary in the era of effective ART.

Retinitis is the most commonly recognized disease caused by CMV.[7,221–224,227–229] Most cases occur at $CD4^+$ T-cell counts less than 50 cells/mm^3. CMV retinitis has the potential to involve and rapidly damage the macula and optic disk, to cause retinal detachments, and to result in irreversible visual impairment and ultimately in blindness. Disease is usually recognized unilaterally at first but may present or become bilateral.[229–231]

The diagnosis of CMV retinitis is usually made clinically. Obtaining retinal or vitreous material for examination is risky (detached retina or secondary infection can result). The appearance of CMV retinitis is characteristic to an experienced ophthalmologist, and CMV causes most cases of retinitis that occur in HIV-infected patients whose HIV viremia is not durably suppressed and who have $CD4^+$ T-cell counts less than 100/mm^3.

If effective treatment is not initiated, bilateral disease occurs in most cases, and blindness can occur.[231,232] Therefore therapy is urgent when

disease is recognized unless the lesions are small and peripheral in patients not receiving ART, in which case anti-CMV therapy could possibly be withheld while ART is initiated if the patient is closely monitored.

A variety of therapeutic approaches have been used employing intravenous ganciclovir, intravenous foscarnet, intravenous cidofovir, oral valganciclovir, local injections of antiviral drugs, and sustained-release ganciclovir implants (see Table 129.2).[8,233–241] Many strategies have relied on sustained-release ganciclovir implants, but these are no longer marketed. Unless these implants again become available, alternative therapeutic strategies are necessary, although published studies of such alternative approaches are sparse.

For extensive retinitis or vision-threatening retinitis, many ophthalmologists use a strategy of immediate intraocular ganciclovir injections followed promptly by intravenous ganciclovir, followed by oral valganciclovir. For small peripheral lesions, oral valganciclovir alone is a reasonable option, especially if ART is being initiated. These patients must be followed closely by an ophthalmologist.

Intravenous ganciclovir and intravenous foscarnet are equally effective in terms of inducing remission of retinitis. Intravenous cidofovir is also effective.[8,237–239] Ganciclovir is usually the intravenous drug of choice because of its more favorable toxicity profile compared with foscarnet or cidofovir. New lesions or progressive disease may be identified during the first 7 days of therapy: These do not necessarily imply a poor response. Considerable improvement in inflammation, edema, and hemorrhage will be recognized in responders before the end of 21 days of therapy. Serial PCR monitoring of CMV viremia may be a plausible method to monitor therapy but is not usually recommended, and it has not been shown to be useful (see Chapter 137).

Maintenance regimens using intravenous ganciclovir or intravenous foscarnet were more commonly administered in an earlier era before effective ART, but without ART these regimens only prolonged the interval until relapse by several weeks. The mean time to progression for patients receiving ganciclovir or foscarnet maintenance regimens without effective ART is 50 to 59 days.[242]

Oral valganciclovir is an attractive alternative to intravenous therapy for maintenance regimens and for initial regimens in some patients. Oral valganciclovir has pharmacokinetics similar, but not identical, to intravenous ganciclovir. Its oral bioavailability is predictable for patients with normal gastrointestinal function, but the oral route is not preferred as the sole initial therapy for patients with severe or vision-threatening disease. Since the advent of oral valganciclovir, oral ganciclovir is no longer available. Other drugs including letermovir are being developed that could have a role in prophylaxis in the near future.[243]

The major toxicity of ganciclovir and valganciclovir is bone marrow suppression with neutropenia and thrombocytopenia. Confusion, nausea, vomiting, aminotransferase elevation, and inhibition of spermatogenesis also occur. Granulocyte colony-stimulating factor may be useful to permit continued ganciclovir or valganciclovir therapy. Foscarnet is nephrotoxic and can cause nausea, vomiting, anorexia, seizures, hypocalcemia, and hypomagnesemia. Foscarnet generally must be infused over 60 minutes, after salt loading with a 60-minute infusion of normal saline, and therefore requires more infusion time than ganciclovir therapy. Cidofovir is not used often but has the advantage that it can be given once every 2 weeks after two consecutive weekly doses, obviating the need for permanent intravenous access. Cidofovir is nephrotoxic and should not be given to patients with serum creatinine >1.5 mg/dL, and each dose should be administered with probenecid after hydration with 1 L of normal saline. The long half-life can be a disadvantage if toxicity occurs.

Esophagitis, colitis, pneumonitis, and encephalitis are life-threatening syndromes caused by CMV that have been documented to respond to therapy.[244–249] A specific diagnosis for these syndromes should be established by histology or cytology because they are indistinguishable from syndromes caused by other pathogens on the basis of clinical criteria alone. Culture of CMV or CMV PCR from tissue, secretions, or excretions is insufficiently specific for CMV-caused disease to be used as a basis for therapy except in the case of neurologic disease. Detection of CMV by culture or, more often, by PCR in CSF is highly suggestive that CMV is the cause of a compatible neurologic syndrome.[250]

For patients with esophagitis, colitis, or rectal ulcers, improvement in clinical symptoms is usually noted during the first week of therapy with valganciclovir, ganciclovir, or foscarnet. Improved performance status and increased weight are often noted, especially if therapy results in reduced dysphagia or reduced diarrhea.

There is considerably less knowledge about ganciclovir therapy for CMV pneumonia because there are so few well-documented cases. No consensus exists regarding the specific criteria for establishing this diagnosis short of lung biopsy, and many patients with no response to ganciclovir therapy had severe and advanced lung damage before ganciclovir treatment was started. Ganciclovir therapy for bone marrow or stem cell transplant recipients is usually given concurrently with immune serum globulin or hyperimmune globulin. However, even though there are no convincing data that immune or hyperimmune globulin enhances efficacy in transplant populations, this strategy is often employed for patients with HIV infection and CMV disease.

Recurrence of CMV retinitis after effective therapy is extremely unusual if the $CD4^+$ T-cell count rises to more than 50 to 100 cells/mm^3 after institution of ART.[8] It is reasonable to stop maintenance therapy if the $CD4^+$ T-cell count has been greater than 50 to 100 cells/mm^3, the lesion is inactive, and regular ophthalmologic follow-up is possible.[8] Clinicians need to distinguish between the recurrence of CMV retinitis and immune reconstitution vitritis because management of immune reconstitution syndromes is quite different from management of CMV retinitis.[251–254]

Drug-resistant CMV isolates are not as common in the era of ART as they were previously.[255–261] Isolates that are resistant to ganciclovir may be susceptible to foscarnet depending on the mutation that occurred.

Because CMV frequently causes specific organ damage in patients with HIV infection and may contribute to the febrile wasting syndromes associated with untreated HIV disease, specific prevention of CMV disease was a logical goal in the era when ART was not highly effective. Strategies based on intervention with intravenous or oral regimens when CMV is detected by a nucleic acid or antigen assay of serum or peripheral white blood cells are logical, but benefit has not been demonstrated over and above what can be achieved with ART. Patients who will not take ART are unlikely to take an anti-CMV agent.

Patients could consider methods to reduce infection or reinfection by practicing safe sex, avoiding infected needles, and receiving only blood products that have been determined to be free of CMV or have been filtered. Child care providers in child care facilities are also at increased risk due to contact with infected secretions. However, ART is the clearly effective intervention.

When oral ganciclovir was the only oral drug available, it was used to prevent primary CMV disease; studies suggested that this drug was effective in the era before effective ART.[262,263] Even then, few clinicians used oral ganciclovir as primary prophylaxis because of the cost, toxicity, and inconvenience of this drug. Valganciclovir has replaced oral ganciclovir as a marketed product because it is more potent. Oral valganciclovir has not been studied extensively for primary prophylaxis. However, there is little role for specific CMV prophylaxis in this era when ART is so effective.

When ART is initiated, CMV IRIS can occur either at a site of CMV disease that had been recognized and treated or at a site that was not clinically recognized to be infected with CMV.[251–254] IRIS associated with CMV is most commonly recognized in the retina and typically occurs in patients with $CD4^+$ counts less than 50 cells/mm^3 at the time ART was started. IRIS may manifest in patients who start ART after CMV was diagnosed, or CMV IRIS may manifest in patients starting ART who never had prior retinal disease, even if screened by careful ophthalmologic examination before ART. Immune reactivation syndromes typically have more inflammation in the anterior or posterior chambers than CMV disease and typically occur in the first 4 to 12 weeks after ART is started. These lesions can be difficult to distinguish from active CMV retinitis. Therapy has not been studied in large clinical trials but usually includes periocular corticosteroids or short courses of systemic corticosteroids. Some clinicians use oral valganciclovir in conjunction with corticosteroid therapy to treat presumed CMV IRIS on the presumption that replicating virus rather than residual antigen alone is present.

Epstein-Barr Virus and Human Herpesvirus 6 and 7

EBV (see Chapter 138) has been implicated in the pathogenesis of oral hairy leukoplakia and primary CNS lymphoma and may have a role in the pathogenesis of some cases of nonspecific pneumonitis, lymphadenopathy, systemic lymphoma, fever, or wasting. There is currently insufficient evidence to warrant specific testing for EBV except for diagnostic CSF testing when CNS lymphoma is being considered. Detection of EBV by qualitative CSF PCR assay in a patient with a CNS mass lesion is suggestive of primary CNS lymphoma but is not unequivocally specific.[187]

Human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7) (see Chapter 139) can be isolated from some patients with HIV infection. It is unclear how often these viruses cause clinically important syndromes such as fever, rash, pneumonitis, or cerebritis in this patient population. Encephalitis due to HHV-6 is the best described disease entity in this population. If there is a strong suspicion that HHV-6 could be the cause of a clinical syndrome, ganciclovir or foscarnet therapy (or both) is the preferred choice for therapy based on in vitro studies. Cidofovir also has activity against HHV-6 and HHV-7.

JC Virus Encephalitis (Progressive Multifocal Leukoencephalopathy)

JC virus encephalitis (PML) is a unifocal or multifocal demyelinating process caused by JC virus (see Chapter 144). This disorder produces characteristic white matter lesions and manifests subacutely as cognitive impairment, focal motor deficits, and seizures.[264] Clinically, PML must be distinguished from AIDS dementia complex, CMV encephalitis, and cerebral infarction. Imaging is helpful in identifying these disorders. Detection of JC virus in the CSF by nucleic acid amplification is helpful diagnostically, but some patients with positive JC virus in the CSF have neurologic disease due to some other process.[265–267] Detection of JC virus or antibody outside the CNS is not helpful for clinical management.

Examples of dramatic clinical and radiologic improvement after institution of ART have been reported, although some patients worsen after institution of ART owing to an immune reconstitution syndrome.[268–272] No specific antiviral therapy has been effective.

Candida Species

Mucosal candidiasis is a hallmark of HIV infection. One of the earliest clinical observations in the era before there was a serologic test for HIV infection was that the presence of oral candidiasis was almost diagnostic of AIDS in patients who did not have some other obvious risk factor such as high-dose corticosteroid therapy, pregnancy, recent antibacterial therapy, or diabetes mellitus. Vaginal candidiasis was not so specifically suggestive of HIV infection because there are many reasons for women to develop vaginal candidiasis other than HIV/AIDS (i.e., pregnancy, concurrent antibacterial therapy, corticosteroid therapy).

Stomatitis, esophagitis, vaginitis, and proctitis caused by *Candida albicans* infection are common and often respond to topical therapy (nystatin or clotrimazole), oral therapy (itraconazole, fluconazole, voriconazole, posaconazole), or intravenous therapy (fluconazole, voriconazole, posaconazole, isavuconazole, caspofungin, micafungin, anidulafungin, or amphotericin B). Oral fluconazole is convenient and relatively inexpensive and therefore is preferred unless there is a strong suspicion that the pathogen is resistant to fluconazole. Fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole all inhibit specific hepatic enzymes of the cytochrome P-450 class, resulting in elevated levels of drugs metabolized by those enzymes such as protease inhibitors and NNRTIs.[8]

There is usually no urgent reason to institute antifungal therapy for any of these candidal mucosal disorders other than patient discomfort. Esophagitis in this patient population is rarely associated with bleeding, perforation, fungemia, or disseminated fungal disease, in contrast to the experience with neutropenic patients after antineoplastic chemotherapy.

Stomatitis, esophagitis, and proctitis often recur after specific therapy is discontinued if $CD4^+$ T-cell counts remain low. Chemoprophylaxis is not routinely recommended. However, fluconazole administration may have to be continued for long durations if recurrences are frequent or severe and the $CD4^+$ T-cell counts remain low (see Table 129.2). Patients with no response to oral azole therapy after 1 to 2 weeks usually have $CD4^+$ T-cell counts less than 50 cells/mm^3 or extensive prior exposure to fluconazole that has led to fluconazole resistance (or both). *Candida* isolates that are clinically and microbiologically resistant to fluconazole have been described in patients on long-term azole therapy.[272,273] Resistance to echinocandins has also been described.[274]

If there is no response to a 7-day course of oral fluconazole (200 mg or more every day), higher doses of fluconazole are rarely effective. Other options include itraconazole-cyclodextrin solution, voriconazole, posaconazole, isovuconazole, an echinocandin, or a short course of intravenous liposomal amphotericin B.

Disseminated candidiasis is not characteristic of AIDS. If candidemia occurs, it is usually associated with an intravenous catheter or intravenous substance abuse. Treatment is similar to that in other patient populations, with particular attention directed at removing infected intravenous lines.

Cryptococcus neoformans, Histoplasma capsulatum, and *Coccidioides immitis/Coccidioides posadii*

Meningitis is the most frequent manifestation of cryptococcosis in HIV-infected patients.[275–285] Patients with cryptococcal meningitis usually present with fever, headache, neck stiffness, or photophobia. Most, but not all, have $CD4^+$ T-cell counts less than 50 cells/mm^3. Extraneurologic manifestations such as pneumonia or skin lesions with or without apparent neurologic disease also occur.

In patients with cryptococcal meningitis, CSF typically demonstrates elevated protein levels and elevated numbers of mononuclear cells and decreased glucose concentration. In some patients, one or all of these CSF parameters may be normal. The cryptococcal antigen tests in serum and CSF are almost always positive, and 75% of patients have an elevated opening pressure when a lumbar puncture is performed. Baseline factors predicting a poor therapeutic response in patients with meningitis include altered mental status (e.g., confusion, lethargy, obtundation), CSF antigen titer >1:32, decreased CSF leukocyte count (<20 cells/mm^3), age <35 years, positive blood cultures for *Cryptococcus,* hyponatremia, and positive CNS culture for *Cryptococcus.*

As with other opportunistic infections, early recognition and institution of therapy are important for maximizing the likelihood of a favorable response. Diagnosis is readily established by culture or cryptococcal antigen testing of blood or CSF. Long-term outcomes improve if effective ART is initiated.[286]

The best-studied therapy for cryptococcal meningitis is amphotericin B administered intravenously plus flucytosine given orally until clinical improvement has occurred and at least for 2 weeks; this is followed by fluconazole, 400 mg orally every day for 8 weeks, followed by fluconazole, 200 mg orally every day for life unless $CD4^+$ T-cell counts rise above 100 to 200/mm^3 (see Table 129.2).[8,277–285] Both amphotericin B deoxycholate and liposomal amphotericin have been used (see Table 129.2). Liposomal amphotericin B, in a dose of 3 to 4 mg/kg/daily, is recommended as the preferred amphotericin B formulation for primary induction therapy, based on clinical experience and reduced renal toxicity compared with amphotericin B deoxycholate. Flucytosine, when combined with amphotericin B, accelerates fungal clearance from the CSF and reduces the rate of relapse.[279,281,287] Flucytosine is associated with potential bone marrow suppression and hepatotoxicity. Patients receiving flucytosine should have either blood levels monitored (peak level 2 hours after dose should be between 25 and 100 μg/mL) or close monitoring of complete blood cell counts to identify developing cytopenias.

Fluconazole therapy is used as initial therapy to treat cryptococcal meningitis with a high degree of success in many parts of the world outside the United States, but fluconazole even at doses of 2000 mg/day is not as effective as amphotericin B.[8,281–283] There is no specific reason to use voriconazole, posaconazole, isavuconazole, or itraconazole to treat cryptococcal disease.[284] *Cryptococcus* rarely becomes clinically resistant to amphotericin B or fluconazole. Susceptibility testing is available only as a research procedure.

The clinical status of patients with cryptococcal disease may deteriorate because of the consequences of increased ICP that result from cryptococcal disease independent of any effects of ART or IRIS.[288,289] Clinical signs of increased ICP need to be sought, especially at presentation and during acute induction therapy. The baseline opening pressure

should be measured at the time of the initial lumbar puncture in patients with focal neurologic findings or altered mental status. An imaging study of the CNS may be useful before the initial lumbar puncture and subsequently if the clinical status deteriorates. If the opening pressure is high (>25 cm H_2O), consideration should be given to reducing the pressure by repeated lumbar punctures or by insertion of a CSF drain or shunt. One approach used by experienced clinicians is to remove the volume of CSF that reduces opening pressure by 50% as often as needed by assessing clinical parameters and to resort to a shunt if symptoms of increased pressure continue to recur after many lumbar punctures. Corticosteroids, mannitol, and acetazolamide are not recommended.[8,290]

Monitoring titers of cryptococcal polysaccharide antigen in serum or CSF is of no value in determining response to therapy and is not recommended.[8,283] If new symptoms or clinical findings subsequently develop, a repeat lumbar puncture, with measurement of opening lumbar pressure and CSF culture, should be performed. Many experts would repeat the CSF culture after 2 weeks. Because a positive culture after 2 weeks of therapy predicts relapse, these experts would consider a positive culture at this time point to be an indication to extend the duration of induction therapy.

After at least 2 weeks of successful induction therapy (i.e., substantial clinical improvement and perhaps a negative CSF culture after repeat lumbar puncture), therapy with amphotericin B and flucytosine can be discontinued, and consolidation therapy can be initiated with fluconazole 400 mg daily. This therapy should continue for at least 8 weeks. Subsequently, fluconazole should be reduced to 200 mg daily and continued as long-term maintenance therapy to complete at least 1 year of azole therapy.

Maintenance fluconazole therapy can be stopped for patients who are asymptomatic, have completed 6 months of therapy, and have had a sustained increase in $CD4^+$ T-cell counts with ART to more than 100 to 200 cells/mm^3 for at least 6 months (see Table 129.3).[8] Some clinicians would repeat the lumbar puncture before stopping therapy to assess the antigen titer and the presence of viable organisms, but there is no evidence that this is necessary.

About 30% of patients with cryptococcal meningitis develop IRIS when ART is initiated.[8,291–300] IRIS can be a life-threatening complication of starting ART for patients with cryptococcal meningitis, with substantial headache, fever, photophobia, lymphadenopathy, pneumonitis or progressive obtundation, herniation, and death. The manifestations of IRIS are difficult to distinguish from treatment failure. Initiating ART at 5 weeks after diagnosis, as compared with 1 to 2 weeks after diagnosis, was shown to increase survival, although the incidence of IRIS was not significantly different between the two groups.[293]

A randomized study examined adjunctive therapy with dexamethasone in patients with cryptococcal meningitis in Asia and Africa and found that it did not reduce mortality and was associated with more adverse effects and disabilities.[297] Based on limited data in North America and on expert opinion, the optimal ART strategy is to delay initiation of ART at least until after completion of antifungal induction therapy (the first 2 weeks) and possibly until the total induction/consolidation phase (10 weeks) has been completed. Delay in ART may be particularly important for patients with increased ICP. Thus the timing of ART administration should be considered between 2 and 10 weeks after the start of antifungal therapy; the precise starting and subsequent dates of therapy should be monitored carefully for complications caused by IRIS such as elevated ICP.[8]

For nonmeningeal cryptococcosis, IRIS is much less common. ART can probably be initiated within 2 to 4 weeks of starting anticryptococcal therapy. Non-CNS, extrapulmonary cryptococcosis and diffuse pulmonary disease should be treated similarly to CNS disease. HIV-infected patients with apparent nonmeningeal disease should always have lumbar puncture to determine if subclinical meningeal disease is present. For mild-to-moderate symptoms and focal pulmonary infiltrates, treatment with fluconazole (400 mg daily for 12 months) combined with effective ART is recommended. Treatment is identical for patients with an isolated positive serum cryptococcal antigen test.[300]

Histoplasmosis is a well-recognized complication of HIV infection, often occurring as the AIDS-defining disease in patients with $CD4^+$ T-cell counts less than 150 cells/mm^3, especially in certain geographic areas such as the Mississippi and Ohio River valleys of the United States, Puerto Rico, and much of Latin America.[301] Patients with low $CD4^+$ T-cell counts, particularly patients with $CD4^+$ counts less than 150 cells/mm^3, are likely to present with extrapulmonary manifestations such as fever, meningitis, abdominal pain, diarrhea, or shock. Patients with higher $CD4^+$ counts (i.e., >300 cells/mm^3) may present with disease confined to the lungs. Diagnosis is characteristically established by direct microscopy or culture (bronchoalveolar lavage, bone marrow, or blood) or by antigen detection (urine, blood, or bronchoalveolar lavage). Although a sensitive and specific assay is available only from specialized laboratories, the sensitivity of the test most commonly used is high in urine (95%), serum (85%), bronchoalveolar lavage (70%), and CSF (50%).[301–305] *Histoplasma* meningitis can be especially difficult to document and must sometimes be treated presumptively in patients with disseminated disease.

Acute therapy for moderate or severe nonmeningeal disease should consist of intravenous liposomal amphotericin B for at least 14 days for most patients.[8,306–310] Meningeal disease requires a longer course of amphotericin B (i.e., at least 4–6 weeks). For patients with mild, nonmeningeal disease, itraconazole is also effective (see Table 129.2). Serum levels of itraconazole should be monitored. Serum and urine *Histoplasma capsulatum* polysaccharide antigens are useful for monitoring both the initial and the long-term phases of treatment. These tests predict treatment failure or relapse.[8,310] As with most HIV-associated opportunistic infections, patients with acute disease need lifelong maintenance therapy with itraconazole to prevent relapses unless they receive effective ART.[311]

Coccidioidomycosis can cause especially severe disease in patients with HIV infection, particularly patients with $CD4^+$ cell counts less than 250 cells/mm^3 and who have traveled to or resided in the southwestern United States and parts of Central or South America (see Chapter 265). Patients can develop focal or diffuse pneumonia, meningitis, lymphadenitis, hepatitis, or skin disease, or they can be asymptomatic with a positive serology.[312] The diagnosis is difficult to establish: direct microscopy; culture; and assays for IgG, IgM, complement-fixing antibody, antigen, and nucleic acid have been used.[313]

For patients with diffuse pulmonary infiltrates due to *Coccidioides* and $CD4^+$ T-cell counts less than 50 cells/mm^3, therapy should consist of the amphotericin B deoxycholate or the liposomal form of amphotericin B.[8] If meningeal involvement is present, therapy should consist of fluconazole or, alternatively, itraconazole; some refractory cases may require systemic and intrathecal amphotericin B twice weekly; some of these patients will require a CSF shunt. Focal coccidioidal pneumonia or other mild disease in patients with $CD4^+$ T-cell counts more than 50 cells/mm^3 and relatively mild disease can probably be treated adequately with fluconazole alone, 400 mg orally every day, or itraconazole.

Primary prophylaxis for *Coccidioides* is recommended by many experts based on a new positive IgG or IgM serology plus a $CD4^+$ T-cell count less than 250 cells/mm^3.[8] These experts would test seronegative individuals yearly if the patients reside in and travel to endemic areas.

After acute disseminated or meningeal disease due to *Coccidioides*, fluconazole or itraconazole maintenance therapy should probably be continued lifelong regardless of $CD4^+$ T-cell count, which differs from recommendations for all other HIV-related opportunistic infections; that is, for other infections, maintenance therapy can be stopped when reconstitution goals are met.[8]

Bacterial Pneumonia

Patients with HIV infection have a higher incidence of respiratory infections than patients without HIV infection (see Chapter 123).[314–319] The frequency of these infections is inversely related to the $CD4^+$ T-cell count. These respiratory infections include upper tract (sinusitis, otitis, and bronchitis) and lower tract (pneumonia, empyema) disease. *S. pneumoniae* is the most commonly identified bacterial cause. Infection due to encapsulated *Haemophilus influenzae* is not common among adults in North America. *Pseudomonas* spp. and *S. aureus* pneumonia have been reported to be frequent causative agents for respiratory disease.

Diagnosis and therapy do not differ from the approaches established for patients without HIV infection. Patients with HIV infection and

low CD4+ T-cell counts develop more severe pneumococcal disease than non–HIV-infected patients, as characterized by bacteremia and focal complications such as effusions and empyemas. Patients with higher CD4+ T-cell counts appear to have disease that is comparable in severity to patients without HIV infection.[320]

The frequency of bacterial infections is reduced by prophylactic or therapeutic regimens prescribed for other indications such as TMP-SMZ (e.g., for PCP) and azithromycin or clarithromycin (e.g., for MAC). Granulocyte colony-stimulating factor can reduce the frequency of bacterial infections in severely neutropenic (non–HIV-infected) patients with cancer, and it has been used for neutropenic patients with HIV infection. Because the frequency of pneumococcal disease can be reduced by the administration of pneumococcal vaccine to patients with CD4+ T-cell counts greater than 200 cells/mm^3, immunization with both the conjugate and the polysaccharide vaccines should be given following published guidelines (see Chapter 316).[8] Immunization should probably be repeated if the initial vaccine was administered when the CD4+ count was less than 200 cells/mm^3 and later increased to more than 200 cells/mm^3 due to ART. HIV-infected patients also should receive annual influenza immunization with the inactivated vaccine. Reducing patient exposure by immunizing family members for pneumococcus, hemophilus, and influenza is also indicated.

Mycobacterium Species Infection

Mycobacterium tuberculosis

TB is the leading cause of morbidity and mortality among people living with HIV worldwide, with 1.2 million new HIV-infected persons reported with TB and 390,000 deaths in 2015.[321] However, TB is uncommon among US-born patients who have not had exposure to known cases and who have not spent time in high-risk environments such as correctional facilities, shelters, drug treatment centers, or TB endemic areas outside the United States.[322]

Rates of TB in the United States are declining, with 2.9 new cases of TB disease per 100,000 population (9287 cases) reported in 2016, a decline of 2.7% from 2015. The incidence of HIV-related TB has declined more rapidly than the rate of active TB in the general population in part due to the widespread use of ART.

TB is a special risk in patients with HIV infection because the conversion rate from latent disease to active disease is 35 to 162 per 1000 person-years of observation for patients with HIV, as opposed to 12.9 per 1000 person-years for the general population.[8,323] TB can occur at any CD4+ T-cell count, although the risk increases with progressive immunodeficiency. ART results in a prompt and marked decrease in the incidence of TB, and this effect has been documented in settings with low and high case rates. Even when patients develop sustained viral suppression and a CD4+ T-cell count in "normal" ranges, however, HIV-infected patients remain at higher risk for developing active TB than the general population.

All persons with HIV infection should be tested for TB with either a PPD or an interferon-γ release assay (IGRA). A patient should not be assessed with both tests because of uncertainty related to interpretation of discordant results. The test should be repeated if it was negative and the CD4+ T-cell count increases above 200 cells/mm^3 from a level below that. If the patient is exposed to a known case of TB or has a high risk for exposure, the screening test should be repeated.

Latent tuberculous infection is defined by a positive IGRA or the presence of a positive tuberculin skin test (≥5 mm of induration at 48–72 hours in HIV-infected persons with no clinical or radiographic evidence of TB disease). IGRAs have higher specificity (92%–97% vs. 56%–95%), better correlation with surrogate measures of exposure to *M. tuberculosis,* and less cross-reactivity with bacille Calmette-Guérin vaccination and nontuberculous mycobacteria. Three IGRAs are approved by the US Food and Drug Administration and available in the United States. Progressive immunodeficiency reduces the sensitivity of the tuberculin skin test and IGRA.[324–326]

All previously untreated patients with a positive test for latent TB and all patients with close recent contact with active TB should be treated.[8] Treatment of latent TB should be with isoniazid or one of the recommended alternatives once the presence of active disease has been ruled out (see Table 129.1).

The manifestations of active TB among patients with HIV/AIDS depend on host immune status. For patients who have CD4+ T-cell counts greater than 350 cells/mm^3, manifestations of pulmonary disease are not substantially different from manifestations in the general population. For patients with lower CD4+ counts, lower lobe pulmonary disease, miliary disease, cavitation, effusions, adenopathy, and extrapulmonary disease are more common than in patients with higher CD4+ counts or non–HIV-infected patients.[327]

The initial evaluation of a patient suspected to have any form of HIV-related TB should always include a chest radiograph and perhaps a computed tomography scan even in the absence of pulmonary symptoms or signs. For patients with HIV infection, however, chest radiography is not a sensitive screen for pulmonary TB. Patients with low CD4+ T-cell counts can have TB culture-positive sputum despite normal chest radiographs. Sputum smear and culture are often useful in symptomatic patients being evaluated for possible TB disease who have a normal chest radiograph and patients who appear to have only extrapulmonary disease.[328]

As with non–HIV-infected patients, TB can be diagnosed by smear, culture, or nucleic acid probe of a respiratory sample or some other tissue or fluid.[8,328–330] The use of a nucleic acid amplification test is recommended on at least one specimen from all patients being evaluated for suspected pulmonary TB because this test has excellent sensitivity and specificity and can distinguish TB from nontuberculous mycobacteria.[330] Because this test is rapid, it can also guide decisions about isolation precautions. HIV infection does not alter the sensitivity of sputum culture, but patients with advanced immunodeficiency often have negative sputum smears.[8,329–332]

Because standard mycobacterial cultures for TB may take weeks to months to grow, rapid diagnosis is preferred in patients with HIV infection given the risk of rapid clinical progression and the risks of transmission to other highly susceptible individuals. Nucleic acid amplification tests provide rapid diagnosis of TB and some may also provide resistance testing for rifampin and isoniazid. These tests are useful in patients with positive and negative smears and can distinguish *M. tuberculosis* from other mycobacteria. These tests are more sensitive than AFB smear, being positive in 50% to 80% of smear-negative, culture-positive specimens with sensitivity approaching 90% if three specimens are assessed.[329,332] Nucleic acid amplification tests can also be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than in sputum specimens.

Treatment of suspected TB for HIV-infected individuals is the same as for non–HIV-infected persons.[333–335] Regimens should include an initial four-drug combination of isoniazid, rifampin, ethambutol, and pyrazinamide. If rapid drug susceptibility testing indicates resistance to rifampin, an initial multidrug-resistant TB regimen (usually including a fluoroquinolone and either an aminoglycoside or capreomycin) should be used and later adjusted once complete susceptibility results are available. All HIV-infected patients should ideally receive directly observed therapy. Drug-susceptible TB should be treated with a 2-month intensive phase of the four drugs. Ethambutol can be discontinued when susceptibility to isoniazid and rifampin has been confirmed. Isoniazid and a rifamycin are used in the continuation phase of therapy, generally recommended as an additional 4 months of treatment for uncomplicated TB. Daily regimens (5–7 days per week) are preferred over intermittent regimens (two or three times per week), which perform well in non–HIV-infected persons. For HIV-infected patients, twice-weekly or thrice-weekly dosing during the intensive phase has been associated with an increased risk of treatment failure or relapse that includes acquired drug resistance to the rifamycin class.

For HIV-infected patients, regimens that include once-weekly or twice-weekly dosing during the continuation phase of therapy have also been associated with increased risks of treatment failure or relapse with acquired rifamycin resistance. Therefore daily (5–7 days per week) dosing is also recommended during the continuation phase of therapy.

The outcomes of 6-month regimens (2 months of isoniazid, rifampin, ethambutol, and pyrazinamide followed by 4 months of isoniazid and rifampin) given as directly observed therapy to patients with HIV coinfection have been comparable to outcomes in non–HIV-infected populations. Some experts prefer 9- to 12-month regimens, but there

is no compelling evidence that such longer regimens produce better results in settings where ART is available.[333–335]

Courses longer than 6 months (e.g., 9 months, 12 months, 18 months, or longer) are indicated in certain patients with high burdens of disease, slow therapeutic response, or involvement of the meninges or bone. A 6- to 8-week course of corticosteroids is indicated for patients with severe pericardial or meningeal disease.[336,337] For ART-naïve patients, ART should be started within 2 weeks after TB treatment initiation when the $CD4^+$ T-cell count is <50 cells/mm^3 and within 8 weeks of starting anti-TB treatment in patients with higher $CD4^+$ T-cell counts.[8,338–342]

IRIS is frequently associated with initiation of TB therapy in patients with HIV infection.[338–342] IRIS may manifest as clinical exacerbation at sites previously known to be involved by active disease or at sites that had been clinically silent until enhanced immunity caused clinical manifestations in response to viable or nonviable organisms. This is particularly relevant to patients with TB meningitis and pericarditis. In patients with TB meningitis and low $CD4^+$ T-cell counts, early ART may exacerbate meningeal inflammation leading to mild, moderate, or severe disease, and thus the timing of ART initiation must be based on clinical judgment.

When TB occurs in patients already on ART, treatment for TB must be started immediately. ART should be modified to reduce the risk for drug interactions and to maintain virologic suppression. Drug interactions between antituberculous drugs (especially rifamycins) and antiretroviral drugs (especially protease inhibitors and NNRTIs) need to be carefully considered and appropriate adjustments made.[8]

Patients with pulmonary TB should have monthly sputum smears and cultures to document culture conversion on therapy, defined as two consecutive negative cultures. Patients with susceptible TB should convert sputum cultures to negative by 2 months of TB therapy, although patients with advanced disease (i.e., cavitary TB) may take longer to convert sputum cultures to negative. Patients who have not had sputum culture conversion at 4 months should have sputum sent for resistance testing.

Relapse of TB is uncommon if patients have strains susceptible to all major antituberculous drugs and if they complete the recommended course of therapy. Some apparent relapses are reinfections with new, different strains of TB.[60–62]

Mycobacterium avium Complex

MAC disease was a characteristic complication of AIDS in North America for the first 25 years of the HIV epidemic. MAC has been much less common since the widespread use of ART.[1,2,8,343] MAC most often manifests as a systemic process characterized by fever, weight loss, elevated serum alkaline phosphatase levels, and substantial anemia.[343–345] Wasting, diarrhea, or lymphadenopathy may be seen. Diagnosis is most readily established by blood culture or by biopsy of affected tissue. Culture of organisms from respiratory secretions, stool, or urine does not unequivocally establish the presence of invasive disease or the need for therapy. Patients colonized with MAC do not necessarily develop disease due to MAC, although they are more likely to develop such disease than noncolonized persons with HIV infection. Therefore a positive culture of sputum, stool, or urine is not necessarily an indication for therapy.

Initial treatment regimens usually include either clarithromycin or azithromycin plus ethambutol (see Table 129.2). Testing of isolates for clarithromycin or azithromycin resistance is recommended for all clinically significant isolates, although the occurrence of such primary resistance is unusual.[8] Because there is more experience with clarithromycin than with azithromycin, the former drug is usually preferred.[8] If clarithromycin or azithromycin is used as monotherapy, relapse occurs in most patients in less than 1 year. Therefore clarithromycin plus ethambutol is the recommended regimen unless there is reason to suspect that the isolate is macrolide-resistant.[8,344,345]

Additional drugs such as rifabutin, amikacin, ciprofloxacin, moxifloxacin, or linezolid may be added if the disease is severe or extensive, if the isolate is drug-resistant, or if the patient is extremely immunosuppressed. Some experts advocate a three-drug regimen of clarithromycin, ethambutol, and rifabutin or a quinolone or an aminoglycoside.

Most patients with drug-susceptible isolates demonstrate defervescence and lower quantities of circulating MAC within 2 to 4 weeks after initiation of therapy, unless the disease is extensive, drug adherence is poor, or absorption or pharmacokinetic issues result in suboptimal serum tissue concentrations of drug. If patients do not respond within the first 1 to 2 months of therapy, MAC susceptibility testing should be repeated, and serum drug-level monitoring should be considered.

If MAC bacteremia recurs after a period of clinical and mycobacterial improvement, organisms have often become resistant to the drugs used in the treatment regimen. It is logical to choose a new regimen based on susceptibility results, although, as noted, such testing has not been validated as clinically useful for most drugs. A multidrug regimen is typically recommended, although there are no adequately powered trials to provide evidence-based guidance. Whether the macrolide should be continued despite clinical or in vitro resistance is controversial.

A repeat blood culture during therapy is necessary only if patients have not responded clinically after 4 to 8 weeks. Therapy should be continued for a minimum of 12 months based on trials done before the era of effective ART. Therapy can be discontinued after 12 months in patients who are asymptomatic and have had an ART-induced increase in $CD4^+$ T-cell counts to greater than 100 cells/mm^3 for at least 6 months.[8]

For patients with disseminated MAC who are ART-naïve, many clinicians would not initiate ART for the first 2 to 4 weeks of anti-MAC therapy to reduce the likelihood of IRIS and simplify assessment of management strategy if adverse events occur.[8] Most MAC disease seen in the United States currently is not due to disseminated disease with bacteremia, but is rather due to IRIS syndromes after ART initiation. MAC is probably the most common cause of lymphadenopathy following ART initiation. The enlargement of lymph nodes leads to local symptoms and physical findings. Biopsy of affected nodes or organs is usually necessary to be certain that the pathology is not due to active fungal disease, TB, or a malignant neoplasm such as lymphoma. Patients with IRIS due to MAC are not usually bacteremic, although biopsy of the affected node or organ usually demonstrates MAC by histology or culture or both. There is no consensus about whether such patients need to be treated for MAC rather than continuing ART alone, but most clinicians do treat MAC for several months with one of the above-described regimens.

Chemoprophylaxis for MAC is no longer recommended because all patients should be on ART promptly, which has greatly reduced the incidence of MAC. Chemoprophylaxis for MAC disease in previous years had been a logical management strategy in the United States because this disease was frequent, severe, and difficult to treat in the long term and because there are parameters for identifying patients who are at highest risk.[36,37,346,347] Patients at risk include patients with a $CD4^+$ T-cell count less than 50 cells/mm^3 and patients with a respiratory or gastrointestinal tract that is colonized with MAC. Clarithromycin, azithromycin, and rifabutin are effective chemoprophylactic agents in terms of reducing the incidence of disease and reducing mortality.

Enteric Pathogens: *Salmonella, Shigella,* and *Campylobacter* Species and *Clostridiodes difficile* (formerly *Clostridium difficile*)

Rates of bacterial enteric infections are at least 10-fold higher among HIV-infected adults not treated with ART compared with the general population.[69,348–350] These rates decline when patients are administered ART. The risk of bacterial diarrhea varies inversely with the $CD4^+$ T-cell count and is especially high among patients with $CD4^+$ counts <200 cells/mm^3. As with non–HIV-infected persons, the most common isolates are *Salmonella, Shigella,* and *Campylobacter*. *Clostridiodes difficile* (formerly *Clostridium difficile*) infection is also common among HIV-infected patients; a low $CD4^+$ T-cell count is an independent risk factor for *C. difficile* disease.

The most likely source for most enteric infections in HIV-infected patients is ingestion of contaminated food or water. However, sexual activity is well documented to have the potential for direct or indirect fecal-oral exposure, thus increasing the risk of infections, especially with *Shigella* and *Campylobacter*.[348–350]

For *Salmonella, Shigella,* and *Campylobacter,* patients with HIV infection present with acute, self-limiting gastroenteritis, diarrhea, or bacteremia with or without extraintestinal involvement. Initial therapy

is similar to therapy for non–HIV-infected persons. Patients with HIV infection, especially patients with low $CD4^+$ T-cell counts, may have more persistent diarrhea, more severe diarrhea with bloody stools, and more bacteremia. Whereas 7- to 14-day courses of therapy may be sufficient for patients with mild-to-moderate disease, other patients may require longer courses of therapy. Although there are no well-defined guidelines, 2- to 6-week courses of therapy are used by many experts.

Relapses after therapy are common with *Salmonella* spp. and probably other enteric bacterial infections as well.[348–350] For such patients, prolonged long-term antibacterial suppressive therapy may be appropriate until the $CD4^+$ T-cell count increases to greater than 200 cells/mm^3.

Patients with HIV infection are predisposed to enteric infections with non-*jejuni,* non-*coli Campylobacter* spp. such as *Campylobacter fetus* as well as *Helicobacter* spp. such as *Helicobacter cinaedi* and *Helicobacter fennelliae.* These organisms require special techniques to be identified and are more likely to be reported from blood rather than from stool.

HIV-infected patients with gastrointestinal infections require no different approaches to diagnosis or initial therapy than non–HIV-infected persons. Given their enhanced susceptibility to enteric pathogens, HIV-infected patients should be particularly careful about exposures to high-risk foods (e.g., raw eggs, undercooked seafood or poultry) or high-risk pets (e.g., stray animals or dogs or cats younger than 6 months) or to pathogen transmission involved with exposure to infants and children (e.g., daycare).[8]

Cryptosporidium, Cystoisospora, Cyclospora, and *Microsporida* Species

Cryptosporidium, Cystoisospora, Cyclospora, and *Microsporida* spp. all cause chronic diarrheal syndromes in HIV-infected patients with low $CD4^+$ T-cell counts.[351–354] Each can cause biliary and pancreatic disease by infecting the biliary-pancreatic ducts as well. Some *Microsporida* spp. (see Chapter 282) can also cause systemic disease, and certain species can produce keratitis. These pathogens can be identified in stool by a variety of tests depending on the specific pathogen including direct microscopic techniques, antigen tests, nucleic acid amplification tests, and tissue biopsy. For corneal disease, microsporidia can be identified by corneal scrapings.

The results of therapy for cryptosporidiosis (see Chapter 282) have been disappointing. No pharmacologic or immunologic therapy directed specifically against *Cryptosporidium* has been shown to be consistently effective in patients with HIV infection when used without ART. Some clinicians use paromomycin therapy, but clinical trials have not shown benefit.[355] Nitazoxanide may be effective in some patients.[356] For cryptosporidiosis and microsporidiosis, the use of antimotility drugs, combined with enhancing immune function with ART, is currently the best option.[8,357]

Prevention of cryptosporidiosis should focus on environmental control because no drugs are known to be effective for chemoprophylaxis.[8] In some areas where outbreaks have been linked to the local drinking water supply or where contamination of water is likely, water for drinking should be boiled for 1 minute or filtered through a device capable of removing particles as small as 1 mm in diameter. Individuals at risk should also avoid contact with farm animals, infected humans, or pets that are at high risk (e.g., dogs and cats younger than 6 months, stray animals, animals with diarrhea).[8]

Cystoisospora and *Cyclospora* infections (see Chapter 283) can be treated effectively with TMP-SMZ.[358] Patients usually respond symptomatically within 7 to 10 days, but the relapse rate is high unless TMP-SMZ is continued lifelong for patients whose $CD4^+$ T-cell counts remain low. If patients respond to ART with sustained increases in $CD4^+$ counts and sustained suppression of HIV viral loads, it is logical to presume that long-term maintenance therapy for isosporiasis or cyclosporiasis can be discontinued. Ciprofloxacin is also active against *Cyclospora.*[358]

Albendazole has activity in vitro and in vivo against some microsporidia. Albendazole can have a beneficial effect on diarrhea caused by *Encephalitozoon intestinalis,* disseminated disease caused by *Encephalitozoon hellem* or *Encephalitozoon cuniculi,* and disease caused by *Nosema* spp. or *Trachipleistophora* spp.[359,360] Albendazole has not been as effective in treating the major cause of microsporidial diarrhea, which is *Encephalitozoon bieneusi.* Some patients with *E. bieneusi* diarrhea experience transient symptomatic improvement after albendazole therapy, but there is little evidence for microbiologic improvement or improvement in absorption, and relapse often occurs promptly after drug therapy is discontinued.

Microsporidial keratitis has been treated successfully with prolonged topical administration of fumagillin.[361] Patients with microsporidial keratitis should be assessed for systemic microsporidiosis, and systemic therapy with albendazole should be considered. Because little is known about the transmission of microsporidia to humans, no specific recommendations for prevention can be made. It is logical to presume that prevention of food and water contamination by animals would decrease transmission of this organism.

Treponema pallidum

Syphilis is often recognized in HIV-infected patients either because of characteristic lesions of primary or secondary disease or because a screening serology result for *Treponema pallidum* is positive. There is currently a resurgence of syphilis in HIV-infected patients in many areas. The clinical manifestations of syphilis as well as its diagnosis and treatment do not differ dramatically in HIV-infected patients and non–HIV-infected patients (see Chapter 237).[362–365] Reports of ocular syphilis among patients with HIV infection have led to speculation about overrepresentation of this syndrome among HIV-infected patients.[366,367]

Syphilis can have diverse manifestations of primary, secondary, and tertiary disease. *T. pallidum* should enter into the differential diagnosis of dermatologic, ocular, and neurologic syndromes.

Neurosyphilis in patients with HIV infection presents special challenges. Neurosyphilis can occur at any stage of syphilis. Manifestations of neurosyphilis in patients with HIV infection are similar to manifestations in patients who do not have HIV infection. However, clinical manifestations of neurosyphilis, such as concomitant uveitis or meningitis, may be more common in patients with HIV infection.[368–370]

No single laboratory test can be used to establish a definitive diagnosis. The diagnosis of neurosyphilis depends on a combination of CSF tests (CSF cell count or protein and CSF Venereal Disease Research Laboratory) in the setting of reactive serologic test results and neurologic signs and symptoms. CSF abnormalities are common in patients with early-stage syphilis and are of unknown significance in the absence of neurologic signs or symptoms.

Patients with HIV infection with neurosyphilis (or ocular or otic syphilis) should receive intravenous aqueous crystalline penicillin G or procaine penicillin for 10 to 14 days.[8] Following therapy for syphilis, retreatment should be considered for patients with early-stage syphilis who have persistent or recurring clinical signs or symptoms of disease or a sustained fourfold increase in serum nontreponemal titers after an initial fourfold decrease following treatment. True treatment failure is probably an unusual event for any stage of syphilis.

Bartonella Species

Bartonella henselae, the cause of cat-scratch disease, and *Bartonella quintana,* the cause of trench fever (see Chapter 234), cause a spectrum of almost unique clinical syndromes in patients with HIV infection.[371–373] *B. henselae,* associated with cat exposure and also transmitted by fleas, causes disease primarily in patients with $CD4^+$ T-cell counts less than 50 cells/mm^3. Manifestations may be acute or very indolent and include cutaneous and subcutaneous angiomatous papules, which can be confused with Kaposi sarcoma, and angiomatous masses in the liver (peliosis hepatis), lymph nodes, lungs, and CNS, which can manifest as mass lesions. Bartonellosis can also manifest as fever alone.

B. quintana, transmitted by body lice, causes fever, cutaneous lesions, bone lesions, and endocarditis. *B. quintana* is epidemiologically very different from *B. henselae* because it is associated with lice and homelessness. This organism rarely, if ever, causes peliosis hepatis.

The diagnosis of bartonellosis is usually established by Warthin-Starry stain of tissue, by culture of blood or tissue using enriched agar, or by PCR assay of serum.[8] Antibody titers can be useful if patients seroconvert, although antibody synthesis may be deficient in patients with low $CD4^+$ T-cell counts, and elevated titers may not be seen for many weeks or months after the acute event.

Most experience with therapy has been with either erythromycin or doxycycline, although azithromycin is frequently substituted for erythromycin. At least 2 g daily of erythromycin base should be given for at least 12 weeks for patients with cutaneous disease.[8] Doxycycline with or without rifampin is preferred for CNS disease and severe manifestations and should be given at a dose of 100 mg every 12 hours. Clinical response may be seen during the first week. Cutaneous lesions may require 1 to 2 months to resolve; hepatic lesions may require 2 to 3 months. Hepatic and osseous lesions should be treated initially with intravenous erythromycin. Rifampin may be useful as an adjunct to the primary drug. A Jarisch-Herxheimer reaction can be seen in response to the first few drug doses. Treatment failures and relapses occur.

Prevention of bartonellosis should focus on reducing exposure to the vectors—the body louse (for *B. quintana*) and cats (especially young cats and stray cats) and cat fleas (for *B. henselae*).

Kaposi Sarcoma and Human Herpesvirus 8

Seroprevalence of HHV-8 is 1% to 5% in the general population but higher in certain geographic areas and among men who have sex with men (13%–35%).[374–377] Most patients with chronic HHV-8 infection are asymptomatic. HHV-8 is associated with Kaposi sarcoma as well as less common neoplastic processes including primary effusion cell lymphoma, Kaposi sarcoma herpesvirus inflammatory cytokine syndrome, and multicentric Castleman disease (see Chapter 140).

Seropositive patients with HHV-8 viremia have a markedly increased likelihood of developing Kaposi sarcoma.[376,377] Serologic testing for antibody to HHV-8 is not routinely performed. A PCR assay to quantitate circulating HHV-8 in peripheral blood is useful primarily for diagnosis and management of patients with multicentric Castleman disease.

Kaposi sarcoma and primary effusion cell lymphoma occur most commonly in patients with $CD4^+$ T-cell counts less than 200 cells/mm^3, whereas multicentric Castleman disease can occur at any $CD4^+$ T-lymphocyte count. Since the introduction of ART, Kaposi sarcoma has become less frequent in the United States and Western Europe.[27,28]

HHV-8 is inhibited by ganciclovir, foscarnet, and cidofovir in vitro. Ganciclovir may have a role in treating multicentric Castleman disease but has no role in treating other HHV-8–associated malignancies.[378–381]

The presence of Kaposi sarcoma does not necessarily mandate institution of specific therapy, especially if lesions are few and inconspicuous. Lesions may regress in patients who respond to ART. Local measures can be useful, including excision, irradiation, and intralesional injection with chemotherapy. Kaposi sarcoma can cause life-threatening disease by obstructing a vital structure such as the larynx, bronchus, biliary tract, or bowel. Kaposi sarcoma can occasionally infiltrate a vital organ such as the lung and cause fatal hypoxemia. In these life-threatening situations, either radiation therapy or cytotoxic chemotherapy is necessary to produce a rapid and substantial response.

The optimal mode of therapy depends on the location and extent of Kaposi sarcoma. A variety of chemotherapeutic regimens have been used to treat extensive or life-threatening disease with some success. Liposomal doxorubicin and paclitaxel demonstrate similar response rates and progression-free survival, although liposomal doxorubicin exhibits less high-grade toxicity relative to paclitaxel. Therefore paclitaxel is generally preferred as first-line therapy. For multicentric Castleman disease and for Kaposi sarcoma herpesvirus inflammatory cytokine syndrome, there is no standardized therapy. There may be a role for antibody therapy against interleukin-6.[382,383]

Viral Hepatitis

Liver disease is an increasingly important cause of morbidity and mortality in patients with HIV infection.[17,19,384–387] HCV and HBV are commonly recognized causes of liver disease in patients with HIV infection, but alcohol; antiretroviral drugs; and a host of other infectious, neoplastic, and toxic processes can adversely affect the liver (see Chapter 117). All HIV-infected patients should be screened for hepatitis A, B, and C.[8]

The incidence of HCV among HIV-infected patients depends on the specific population being evaluated; because this virus is more efficiently spread by blood exposure than sex, intravenous substance users and recipients of unscreened blood products are more likely to be infected than men who have sex with men. Cirrhosis develops within a median of 20 years of HCV acquisition among HIV-infected persons, although the range of onset is highly variable. The natural history of HCV is clearly accelerated among patients with HIV coinfection. Cirrhosis is more likely to occur in older patients, male patients, alcohol users (>20 to 50 g/day), and patients with decreased $CD4^+$ T-cell counts.[388–392]

All patients with HIV infection should be screened for HCV using immunoassays to detect antibody. If the antibody test is negative and there is high suspicion for HCV infection, testing for HCV RNA should be performed. All coinfected patients should be treated for both HIV and HCV. The goal of therapy of the individual patient is prevention of fibrosis, cirrhosis, hepatocellular carcinoma, and death. Updated guidance for the management of HCV in monoinfected (HCV) and coinfected (HIV/HCV) patients, sponsored by the Infectious Diseases Society of America and the American Association for the Study of Liver Diseases, is available at http://www.hcvguidelines.org.[393] This guidance is updated online because new drug approvals and new studies are appearing rapidly in the current era. Recommended regimens rely on directly acting agents alone. There is no role for interferon therapy and only limited roles for ribavirin. Drug interactions between ART and directly acting agents against HCV must be considered when initiating HCV therapy. The regimens for treating HCV in HIV-infected patients are no different from the regimens in non–HIV-infected patients. The response rates are also similar and are not affected by $CD4^+$ T-cell count. Recommendations for treatment are discussed in detail in Chapters 117, 145, and 154.

HBV is a major cause of HIV-associated liver disease worldwide.[387,394–396] In the United States, however, it is much less common than HCV among HIV-infected patients, occurring in 5 to 10 of HIV-infected patients nationally. HBV is transmitted neonatally as well as by blood and by sex.

Initial testing for patients with HIV infection should include serologic testing for HBsAg, HBc antibody (anti-HBc total), and HBs antibody (anti-HBs). If the patient has acute infection, HBsAg can be detected 4 weeks (range, 1–9 weeks) after exposure, and anti-HBc IgM is usually detectable when the patient is initially symptomatic.

Chronic HBV infection is defined as HBsAg detected on two occasions at least 6 months apart. Patients with chronic HBV infection should be tested for HBV e antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA. Active disease, which can be HBeAg negative or positive, can be distinguished from inactive disease by the presence of serum HBV DNA and persistent or fluctuating alanine aminotransferase elevation. Patients with past infection that has cleared are HBsAg negative with positive anti-HBs and anti-HBc (see Chapter 145).

Some patients test positive for anti-HBc alone (i.e., negative anti HBs and serum HBV DNA negative). This may represent individuals with resolved infection who were anti-HBs and anti-HBc antibody positive, but whose anti-HBs titers have fallen below the level of assay detection. Alternatively this may signify active infection in the liver. This may also represent a false-positive result. There is no convenient method to detect which of these alternatives is applicable to an individual patient.

Before ART is initiated, all persons who test positive for HBsAg should be tested for HBV DNA. After ART is initiated, the test should be repeated every 3 to 6 months to ensure effective HBV suppression during ART, or patients should be treated with an ART regimen that contains two drugs with anti-HBV activity (e.g., tenofovir and lamivudine or tenofovir and emtricitabine).

Because HBV reactivation has been observed in patients with HBV infection during HCV treatment, patients with HCV/HIV coinfection and active HBV infection (i.e., positive HBsAg test or positive circulating bDNA and perhaps with HBc antibody positivity alone) should receive ART that includes two agents with anti-HBV activity before initiating HCV therapy. HBV reactivation should be considered in patients with current HBV infection who develop elevated liver enzymes during or immediately after HCV therapy.

The treatment of HBV is discussed in Chapters 117 and 145. For patients who are coinfected with HIV and HBV, any ART regimen should include two agents that are active against HBV with two goals: to prevent exacerbation of HBV hepatitis due to initiation of ART (IRIS) and to prevent progression of HBV liver disease.

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