Objectives

- Provide an overview of human immunodeficiency virus (HIV)–associated nephropathy and other pertinent renal disease in the context of pediatric HIV infection.
- Provide a basic understanding of the cardiac conditions in HIV-infected children.
- Review the causes of chronic lung disease in HIV-infected children, with a focus on lymphocytic interstitial pneumonitis (LIP).

Key Points

- Nephropathy in HIV-infected children, though rare, is a dangerous condition and can lead to end-stage renal failure and death.
- Clinicians must monitor children for clinical and laboratory signs of kidney disease and must refer and treat patients as appropriate.
- HIV-associated nephropathy is a World Health Organization Clinical Stage 4 condition, and patients with this disease require highly active antiretroviral therapy and follow-up.
- Left ventricular dysfunction and cardiomyopathy are common in children infected with HIV.
- Pericardial effusions are common and usually resolve spontaneously in HIV-infected children.
- Therapy for symptomatic congestive heart failure may require additional cardiac medications.
- Chronic lung disease, especially LIP, is common in children with HIV.
- Prednisone therapy may be beneficial in patients with severe LIP.

Renal Disease

Human immunodeficiency virus (HIV) infection is associated with several different types of renal disease. The most common clinical entity encountered in children and adults is HIV-associated nephropathy (HIVAN), a disease that leads to progressive renal damage, urine protein loss, and sometimes end-stage renal disease. HIVAN is often characterized by collapsing focal segmental glomerulosclerosis on renal biopsy, but children sometimes demonstrate clinical signs of HIVAN without underlying focal segmental glomerulosclerosis. Other less common renal manifestations of HIV infection are HIV-related immune complex glomerulonephritis and membranous nephropathy.

Though present in up to 10% of adults, HIVAN is an unusual feature of childhood HIV infection. The incidence of HIV-associated kidney disease in children is estimated at between 2% and 5% and at up to 15% in populations of African descent. Risk factors for HIVAN include high viral load, low CD4+ T-lymphocyte cell counts, and longstanding HIV disease. Many centers do not routinely perform renal biopsies on patients (adult or child) with HIV and elevated urine protein (proteinuria), and therefore the true prevalence of HIVAN is not known. Though HIVAN is believed to be the most common form of kidney disease in HIV-infected adults of African descent, biopsy data have confirmed HIVAN in only about half of suspected cases. Available data from kidney biopsy series suggest that the most common diagnoses encountered among HIV-infected individuals are the following:

- Focal segmental glomerulosclerosis, thought to be due to the direct pathogenic effect of HIV in the kidney
- Immune complex glomerulonephritis, related to the deposition of antigen–antibody complexes
- Membranous nephropathy, usually related to ongoing hepatitis B or C infection

Other non-HIVAN disorders of the kidney that sometimes occur in HIV-infected patients include

- acute renal failure resulting from hypotension or infection,
- drug-induced kidney disease (e.g., aminoglycosides, amphotericin B, some antiretroviral [ARV] drugs), and
- postinfectious glomerulonephritis due to bacterial infection.
**Clinical Presentation and Diagnosis**

Classic HIVAN can present at any stage of HIV infection and with various degrees of renal disease. Though many affected patients have urine protein loss with no symptoms, HIVAN can lead to a nephrotic syndrome characterized by high urine protein loss, low serum albumin, and edema. In children, edema is often first noticeable around the eyes (called periorbital edema) (**Figure 1**). This swelling is often incorrectly identified as an allergy because it decreases throughout the day. However, as the kidney disease progresses, the edema will become generalized and patients can develop ascites, pleural effusions, leg swelling, and/or genital swelling. Complaints of anorexia, irritability, abdominal pain, and diarrhea are common, whereas hypertension is usually not present. The differential diagnosis of edema in children, in addition to kidney disease, includes protein-loss enteropathy, protein-energy malnutrition, hepatic failure, and congestive heart failure. Some helpful clinical criteria for HIVAN include proteinuria, edema, high blood pressure, and black race. However, a laboratory evaluation is needed to distinguish HIVAN from these nonrenal causes of edema. Ray et al. (**Table 1**) used clinical criteria to help distinguish between HIVAN and other kidney lesions in HIV-infected patients, but only renal biopsy provides a definitive diagnosis.

Common abnormal lab values in patients with HIVAN are those suggestive of nephrotic syndrome: high urine protein (3+ to 4+ or a urine protein/creatinine ratio of >0.2) and low serum albumin (<2.5 g/dL). Serum cholesterol and triglycerides may be elevated, and azotemia (a high level of nitrogen-containing compounds in the blood) may be present. Urine should not have more than a few red or white blood cells; gross blood in the urine is uncommon. Renal ultrasound, if available, will probably demonstrate large kidneys that are echogenic (i.e., appear brighter than usual).

![Figure 1. Above left, a child with generalized edema caused by urine protein loss. Notice the prominent swelling around the eyes ("periorbital edema") and cheeks, the distended abdomen, and the swollen arms. Periorbital edema is often the first clinical sign of renal disease in less severe cases. Lower extremity edema (as pictured above right) can also be seen in children with kidney disease and other diseases such as kwashiorkor. Photos courtesy of http://phil.cdc.gov.](image)

**Clinical Course**

In children, renal disease associated with HIV progresses at a slower rate than in adults, with most children developing proteinuria within 2-5 years after HIV infection. After the onset of proteinuria, end-stage renal disease can develop within 3 years. However, the rate of progression depends on the underlying cause of

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical Parameters</th>
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<tr>
<td>HIVAN</td>
<td>Persistent proteinuria*</td>
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<tr>
<td></td>
<td>Abnormal microscopic examination of the urinary sediment, which might include microcysts</td>
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<td></td>
<td>Presence of enlarged echogenic kidneys by renal ultrasound on at least two different studies performed 2 mo apart</td>
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<td>Black race and clinical history consistent with the diagnosis of HIVAN</td>
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<td>Non-HIVAN</td>
<td>Macroscopic hematuria</td>
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<td></td>
<td>Microscopic hematuria without proteinuria</td>
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<td></td>
<td>Elevated blood urea nitrogen and serum creatinine levels without significant proteinuria</td>
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<td></td>
<td>Hematuria and/or proteinuria in white or Hispanic HIV-infected children</td>
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*Urine dipstick for protein above 1+ or a urinary protein creatinine clearance ratio greater than 0.1 for more than 2 months without acute infection.*
Renal, Cardiac, and Pulmonary Manifestations of HIV/AIDS

the disease and the presence of other AIDS-associated illnesses. Some children can have chronic urine protein loss without developing clinically significant edema or end-stage renal disease. Baseline screening urinalyses are helpful to identify those patients with proteinuria, but the value of treating these patients is unclear, and both screening and treatment should be guided by other symptoms.

Although nephropathy is a World Health Organization (WHO) Clinical Stage 4 disease, HIVAN and non-HIVAN are typically late manifestations of HIV/AIDS. HIV-infected children rarely die of end-stage renal disease, and a patient’s prognosis depends heavily on other Stage 3 and 4 diseases (e.g., opportunistic infections and cardiomyopathy) and whether the child is receiving highly active antiretroviral therapy (HAART). Treating HIV should take priority over treating mild or asymptomatic renal disease.

**Treatment**

Patients with HIVAN should be on HAART. HAART reduces the risk of developing HIVAN by more than half and significantly reduces the rate at which HIVAN progresses to renal failure. In the era before HAART, HIV-infected children with HIVAN died on average less than a year after the diagnosis of renal disease. HAART can slow or even stop this progression toward renal failure.

Prednisone is the medication of choice for treating children with nephrotic syndrome. Prior to using prednisone therapy, however, the clinician should have excluded tuberculosis (TB) as a cause of the renal problems or have the patient on appropriate therapy for TB. Prednisone therapy readily reduces the edema, proteinuria, and serum cholesterol level. Patients in the early stages of HIVAN, however, usually have normal or low serum cholesterol levels and no significant edema. The potential beneficial effect of prednisone therapy in HIVAN is limited to improving the proteinuria and reducing the underlying renal inflammation, but there are few conclusive data supporting its use and some centers have found that the response in patients is minimal.

If the use of prednisone is indicated, the recommended dose is the same as that for other types of nephrotic syndrome: 60 mg/m² of body surface area/day divided into two to three daily doses for 4-6 consecutive weeks, with a maximum daily dose of 80 mg. In patients who respond to prednisone therapy, the urine should become negative for protein or remain only trace positive for 3 consecutive days after 2 weeks of therapy. After the initial 4- to 6-week course of prednisone, the dose should be tapered to 40 mg/m²/day given every other day as one dose. This alternate-day dosing can then be slowly tapered and discontinued over the next 2-3 months. Patients who continue to have proteinuria (≥2+) after 4-8 weeks of prednisone therapy should be considered steroid resistant. Such resistance is common in HIVAN and non-HIVAN nephropathy.

Several smaller retrospective studies in adults with HIVAN have demonstrated that another class of drug, angiotensin-converting enzyme inhibitors (ACEIs), can reduce proteinuria and hypertension during late-stage HIVAN. The exact mechanism by which ACEIs help improve renal function is unknown. To date, no prospective, randomized, controlled trials have proven the benefits of HAART, prednisone, or ACEIs in the treatment of renal disease in HIV-infected children. On the basis of available data, however, HAART is the current drug regimen of choice to limit progression of this life-threatening WHO Stage 4 condition. Many experts recommend adding an ACEI and using a trial of prednisone in these patients. There are differences between ACEIs and their interactions with ARVs. For instance, lopinavir–ritonavir is a strong inducer of CYP2D6, affecting levels of captopril (but not enalapril), whereas efavirenz induces CYP3A4, affecting levels of enalapril (but not captopril). If available, hemodialysis and renal transplantation are therapeutic options for those patients who progress to end-stage renal disease.

**ARV Drugs and Nephrotoxicity**

ARV drugs are a rare cause of significant nephrotoxicity, but renal side effects can occur. Ritonavir has been associated with acute renal failure and indinavir has caused some adverse renal and urological effects, including stone formation. Also, tenofovir has caused tubular dysfunction leading to renal toxicity. All these complications of ARVs are uncommon.

**Cardiac Disease**

Children infected with HIV might develop a wide range of cardiovascular problems from the subclinical (e.g., electrocardiographic changes) to the life threatening (e.g., cardiomyopathy). The exact causes of many of
these cardiac abnormalities are unknown and probably multifactorial. In the era of HAART and increased life expectancy, cardiac complications are increasingly recognized as important health problems in children. In HIV-infected children, death from cardiac disease becomes more common with increasing age. It is uncommon in infants and younger children but is responsible for up to 25% of deaths in children older than 10 years who die of an HIV-related illness. Half these children suffer from chronic cardiac disease prior to death. Risk factors for cardiac complications in children with HIV infection include rapid progression of HIV infection, wasting, low CD4 count, previous serious cardiac event, and advanced neurologic disease (e.g., encephalopathy). Therefore, routine cardiac evaluation is recommended, which should include a complete physical examination, electrocardiograph (ECG), and ideally echocardiography. Aggressive treatment of cardiac complications is also essential.

**Left Ventricular Dysfunction and Cardiomyopathy**

Cardiomyopathy is common in HIV-infected children and initially manifests itself as left ventricular (LV) dysfunction. A recent study demonstrated that as many as 28% of children developed a decrease in cardiac function over 5 years, whereas as many as 39% developed cardiomegaly. LV dysfunction is characterized by a decrease in the shortening fraction (SF) and the ejection fraction (EF) of the LV. The SF measures the change in the diameter of the LV between the contracted and relaxed states. Unlike the SF, the EF measures the amount of blood pumped out of the LV with each heartbeat. Healthy individuals have an SF between 28% and 40% and EFs greater than 55%. Many children develop LV hypertrophy and/or LV dilation in the context of LV dysfunction, both of which increase LV mass. LV dysfunction is commonly asymptomatic early in the course but may result in heart failure with progression. Children with depressed LV SF and contractility, increased LV dimensions, and increased LV mass at baseline have a higher mortality, particularly in children with rapid progression of HIV infection. The etiology of HIV cardiomyopathy remains unknown. It is probably a result of a combination of several mechanisms such as a complication of secondary viral or bacterial infections, certain ARV medications (e.g., zidovudine), chemotherapeutic agents that HIV-infected patients may have received (e.g., doxorubicin), nutritional deficiencies that are common in HIV-infected children from resource-limited areas (e.g., beriberi disease, wasting syndrome), anemia, or a combination of these factors. Although there has been significant correlation between the SF and CD4+ cell counts at baseline, the rates of CD4+ cell decline do not appear to be as useful as the viral load as a potential marker for cardiac deterioration.

**Myocarditis**

A common cause of LV dysfunction, myocarditis is signified by inflammation of the cardiac muscle. This inflammation can be the result of infection of the myocardium with certain viruses. Several studies have identified HIV particles in myocardial muscle cells, but the level of infection is commonly low, suggesting that HIV infection plays only an indirect role. Other viruses commonly encountered in HIV-infected individuals, such as parvovirus, cytomegalovirus, enterovirus, and adenovirus, have been implicated. Most recently however, certain alterations of the immune system are recognized to be associated with cardiomyopathy. Certain cytokines are part of an inflammatory response of the body and have been associated with cardiomyopathy and heart failure. In HIV-infected individuals, these cytokine pathways are more active than those in uninfected individuals, suggesting a direct role in the development of cardiomyopathy.

**Pulmonary Arterial Hypertension**

The incidence of pulmonary arterial hypertension (PAH) in adults with HIV infection is 0.5%, which is higher than that in the general population, whereas the incidence in HIV-infected children has not been established. As in myocarditis, the etiology of HIV PAH has not been well established but is probably related to an immunological process related to HIV infection, leading to chronic changes in pulmonary vasculature with resultant increase in pulmonary vascular resistance. However, other factors such as repeated pulmonary infections, severe lymphocytic interstitial pneumonitis (LIP), and LV failure may play a role. Longstanding PAH can lead to right ventricular failure and cor pulmonale.

**Pericardial Effusions**

Pericardial effusions can be found on echocardiography in approximately 10%-20% of HIV-infected patients. Pericardial effusions in HIV-infected patients might be related to opportunistic infections, malignancies (e.g., Kaposi sarcoma, non-Hodgkin’s lymphoma), or HIV itself, or it might be idiopathic. Pericardial effusions might present with a pericardial friction rub (if the effusion is small) and distant heart sounds on cardiac
auscultation or signs of hemodynamic compromise with impending cardiac tamponade. Most patients with pericardial effusions are asymptomatic because of the slow accumulation of fluid, and the fluid collection will usually resolve spontaneously. Evaluation of pericardial effusions by pericardiocentesis should be considered in certain situations, including the following:

- Systemic symptoms due to the pericardial effusion
- Large effusions
- Concern for purulent pericarditis
- Diagnostic evaluation of systemic illness
- Cardiac tamponade (hemodynamic compromise)

Appropriate therapy should be promptly initiated if an infectious cause for pericardial effusion is identified. Mortality rates for HIV-infected patients with pericardial effusions are higher even when the effusion resolves spontaneously. The effects of HAART on pericardial effusions are unknown.

**Other Cardiac Abnormalities**

Congenital heart disease occurs in from 2% to 5% of HIV-infected children, which is greater than that of the general population (0.8%). The most common lesions described to date have been ventricular and atrial septal defects. Congenital heart disease may be slightly more prevalent in HIV-infected children, although this may not be a result of HIV infection itself but rather of maternal risk factors such as smoking, drug abuse, and coinfection with other viruses. Sinus tachycardia also occurs more commonly in HIV-infected children than in uninfected children. The mechanism is unknown. No dysrhythmias have been noted to occur more commonly in HIV-infected children. Coronary artery disease and abnormalities of the great vessels also occur in children and adults living with HIV/AIDS. A recent pathologic study revealed coronary arteriopathy in half of children who died from HIV infection. Sixty-four percent of this cohort showed arteriopathy of the aorta and pulmonary arteries. Aortic root dilation can occur in children with HIV infection. The clinical relevance of these findings in children is unclear, but as life expectancy increases this may become relevant.

**Abnormalities Associated with ARV Therapy**

Certain ARV agents (e.g., zidovudine [AZT]) have been implicated to cause skeletal muscle myopathies as well as cardiomyopathy; however, a recent study failed to confirm this finding in children. Furthermore, the suspected adverse effects of fetal exposure to zidovudine could not be corroborated. In adults, metabolic derangements caused by protease inhibitors have been associated with an increase in coronary artery disease, in particular hypercholesterolemia, hypertriglyceridemia, insulin resistance, and impaired glucose tolerance. However, this complication is generally treated with dietary and lifestyle adjustments.

**Evaluation and Investigation**

The evaluation of HIV-infected children with suspected cardiac disease does not differ from that for the uninfected child. A thorough history and physical examination should be performed prior to other evaluations. In particular, patients should be evaluated for signs and symptoms of congestive heart failure, which include the following:

- Abdominal pain
- Bibasilar rales
- Chronic cough not associated with an infection
- Dyspnea on exertion
- Difficulty breathing
- Easy fatigability
- Gallop rhythm
- Generalized edema
- Hepatomegaly
- Holosystolic murmur
- Jugular venous distention
- Orthopnea
- Tachycardia
- Tachypnea
- Weight gain (poor weight gain more common in infants)

Patients who require further evaluation should have a chest radiograph and an ECG if available. The chest radiograph (Figure 2) will provide information on the heart size and shape, pulmonary blood flow, pulmonary edema, and other potential congenital abnormalities (e.g., abnormal...
Vertebral. The ECG demonstrates anatomic and hemodynamic features by changes in the QRS and T-wave morphologies. A 13-lead ECG is recommended for use in children, including either lead V3R or V4R. The ECG is of only limited use in children for evaluating LV hypertrophy and is not a sensitive indicator of LV dysfunction; however, lead V1 and V3R may be useful for evaluating for right ventricular hypertrophy. Furthermore, the ECG allows evaluating the heart rhythm and may indicate abnormalities such as myocarditis (low QRS voltage and ST segment and T-wave abnormalities, as well as sinus tachycardia) and pericarditis (e.g., low QRS voltage from the effect of pericardial fluid in pericardial effusions).

For children with suspected LV dysfunction or any other child with significant cardiac disease, an echocardiogram is indicated. Echocardiography allows evaluating the cardiac structure, and it can noninvasively estimate intracardiac and pulmonary pressures, quantitate cardiac contractile function (e.g., SFs, EFs), and detect cardiac vegetations and pericardial effusions. Echocardiography, where available, should be performed at baseline and at reasonable intervals (in particular in patients with advanced disease or rapid progression) to evaluate cardiac function and structure, as well as for pericardial effusion.

**Therapy**

Patients with symptoms of congestive heart failure may require treatment with cardiac medications. Diuretics initially are the mainstay of therapy and are usually introduced first. The goal is relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema, by increasing the excretion of excess fluid via the urine. Diuretics may also be given in combination with other cardiac and ARV medications. The most widely available diuretic is furosemide and can be used both intravenously and orally. For acute treatment, a dose of 1-2 mg/kg intravenously usually results in rapid diuresis and prompt improvement of the patient’s clinical status. This treatment may be performed as often as four times daily. Chronic furosemide dosing is 1-2 mg/kg/dose given between one and four times a day orally (maximum dose, 6 mg/kg/day). One must monitor serum electrolytes, however, because furosemide might cause significant loss of serum potassium into the urine. Most patients on daily furosemide therapy will also require potassium supplementation or addition of spironolactone, a potassium-sparing diuretic. Care should be taken in patients who are also receiving digoxin because hypokalemia can potentiate digoxin toxicity.

In developed countries, most clinicians will use an ACEI (e.g., enalapril, captopril) during or after the optimization of diuretic therapy. In children, therapy should be started with low doses to reduce the likelihood of hypotension and azotemia. Blood should be obtained in all patients 1-2 weeks after starting or changing a dose and periodically thereafter to assess the plasma potassium concentration and renal function. The dosage for both enalapril and captopril needs to be reduced for patients with decreased renal function. There are differences between ACEIs and their interactions with ARVs. For instance, lopinavir–ritonavir is a strong inducer of CYP2D6, affecting levels of captopril (but not enalapril), whereas efavirenz induces CYP3A4, affecting levels of enalapril (but not captopril). For older adolescent and adult patients who cannot tolerate an ACEI, an angiotensin II receptor blocker can be used (e.g., candesartan, losartan). Many clinical trials in adults have shown that β blockade can be beneficial in the treatment of congestive heart failure. Studies have shown an increase in EF and a decrease in hospitalization in patients using β blockers. Studies in children have shown similar findings.

The angiotensin II receptor blocker losartan can be affected by the use of the CYP3A4 inducers nevirapine and efavirenz, whereas candesartan does not appear to be affected by these medications. Providers can also start patients on β blockers such as carvedilol after the patients are stable on ACEIs, again beginning at low doses with titration to higher doses as tolerated. Protease inhibitors that induce CYP2D6 (e.g., lopinavir–ritonavir) can affect the levels of β blockers and may not be appropriate to use.

Digoxin (Table 2) has been the mainstay of medical therapy for children with heart failure for decades but in developed countries is now added only when patients

**Table 2. Oral digoxin dosing**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose (μg/kg/24 h)</th>
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<tbody>
<tr>
<td></td>
<td>Loading*</td>
</tr>
<tr>
<td>Full term</td>
<td>30</td>
</tr>
<tr>
<td>&lt;2 yrs</td>
<td>40-50</td>
</tr>
<tr>
<td>2-10 yrs</td>
<td>30-40</td>
</tr>
<tr>
<td>&gt;10 yrs (and &lt;100 kg)</td>
<td>10-15</td>
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*Give half the total digitalizing dose (TDD) and then 1/4 of the TDD every 8-18 h for two doses; obtain ECG 6 h after each dose to assess for toxicity.
†Maintenance dose is started approximately 12 h after TDD is completed (for patients <10 years, divide into two daily doses). Slow initiation of digoxin can be achieved without the loading dose by initiating the maintenance dose but requires 7-10 days to reach maximum efficacy.
are failing the preceding regimen. In resource-limited areas, however, digoxin may be the only medication that is available to be used in addition to a diuretic. The kidneys eliminate digoxin, so dosing should be adjusted according to renal function. Baseline serum electrolytes should be measured before and after digitalization because hypokalemia, hyponatremia, hypomagnesemia, and hypercalcemia can exacerbate digoxin toxicity. Measurement of serum digoxin levels is recommended for chronic use in children. Therapeutic levels are 2–4 ng/mL in infants and 1-2 ng/mL in older children. Cardiac toxicity in children generally manifests as atrioventricular block, but any cardiac arrhythmia can be caused by digoxin toxicity (e.g., ST segment changes). Systemic symptoms include central nervous system disturbances, visual disturbances, anorexia, and vomiting. If toxicity is suspected, digoxin should be stopped immediately. Many medications interact with digoxin; some raise digoxin levels (e.g., tetracyclines), some lower digoxin levels (e.g., rifampicin), and some potentiate toxicity by causing electrolyte disturbances, especially hypokalemia (e.g., furosemide). The nucleoside reverse transcriptase inhibitors and nonnucleoside reverse transcriptase inhibitors do not appear to have significant interactions with digoxin, whereas one must take care with the use of protease inhibitors because these may increase digoxin levels. Because of all these potential complications, one should carefully consider the use of digoxin in a resource-limited setting.

Morbidity and mortality in heart failure is also influenced by commonly associated conditions, including arrhythmias, thromboembolism, and anemia. Therefore, management should also be directed at identifying and correcting these factors where possible.

**Pulmonary Disease**

Chronic lung disease is common in children with HIV and AIDS. Recurrent or chronic pulmonary infections can be caused by bacteria (e.g., Streptococcus pneumoniae), fungi (e.g., candidiasis, histoplasmosis, Pneumocystis jirovecii), viruses (e.g., cytomegalovirus and adenovirus), and mycobacteria (e.g., Mycobacterium tuberculosis and M. avium complex). Such infections can lead to chronic structural abnormalities, including bronchiectasis—the permanent dilation and scarring of the lungs’ bronchi (large airways) and bronchioles (small airways). In addition to infectious causes, malignancies (e.g., non-Hodgkin’s lymphoma, Kaposi sarcoma), immune reconstitution inflammatory syndrome and nonspecific interstitial lung disease may also contribute to the development of chronic lung disease. Of this long list of pulmonary manifestations of HIV, the most common chronic lower respiratory tract abnormality is LIP. Because the other pulmonary diseases listed are discussed in some detail elsewhere in this volume, the rest of this section will focus on this common and potentially fatal condition.

**Epidemiology**

LIP, a form of pulmonary lymphoproliferative disease, occurs in approximately 25%-40% of vertically infected children and usually presents in the second or third year of life. Adults with HIV are also affected, but adult LIP is less common and better tolerated. The etiology of this disorder is unknown, although serologic data suggest that an HIV–Epstein-Barr virus coinfection may be responsible. Other possibilities include an exaggerated immune response to inhaled or circulating antigens, the direct effect by HIV itself, immune dysregulation, or a combination of these factors. LIP occasionally occurs in children and adults without HIV, particularly those with autoimmune disorders.

**Clinical Presentation**

LIP is the result of a chronic process called pulmonary lymphoid hyperplasia (PLH) within the lining of the bronchi and bronchioles. Because lymphoid hyperplasia is a spectrum that results in LIP, many texts use the two terms together—LIP/PLH—when discussing patients with clinical features of a chronic lymphoproliferative pulmonary disease. When LIP/PLH occurs, the airway epithelium becomes congested with lymphoid cells, often leading to progressive blocking of the nearby capillaries. As the disease worsens and lung tissue is progressively damaged, many affected patients develop a chronic cough, rapid respirations, and low blood oxygen levels. On pulmonary examination, they may have few or no abnormal findings, though sometimes rales, or crackles, can be heard. Clubbing of the fingers and toes will be present in more advanced disease, probably representing low blood oxygenation (Figure 1). The proliferation of the lymphoid cells responsible for LIP may also affect other organs and cause findings such as generalized adenopathy, bilateral nontender parotid enlargement, and an enlarged liver and spleen (hepatosplenomegaly). The changes that accompany LIP occur slowly. Although most children present at approximately 18-24 months of age, a wide age range has been described (5-60 months).
Even though the onset is relatively late, LIP may be the first manifestation of advanced pediatric HIV disease that a clinician recognizes.

**Diagnosis**
The complete workup of pulmonary illness in the context of HIV requires a careful history and physical exam and, where available, laboratory studies and radiologic imaging. If feasible, pulmonary function tests and tissue biopsy are also sometimes indicated and diagnostically helpful. Differentiating LIP from other pulmonary illnesses can be difficult. Patients with acute bacterial lower respiratory tract infections typically have a rapid onset of illness with fever. Pneumocystis pneumonia usually has a rapid onset but typically does not cause fever and brings with it an acute and severe oxygen requirement. In comparison, LIP has a gradual onset. TB also has a gradual onset and is easily confused with LIP. However, on physical exam, patients with both Pneumocystis jirovecii pneumonia (formerly called Pneumocystis carinii pneumonia [PCP]) and TB are less likely to have digital clubbing and parotid swelling than are patients with LIP. LIP has x-ray findings that are often difficult to differentiate from common bacterial pneumonia, PCP, and miliary TB. On chest x-ray, common bacterial pneumonia often appears as a focal abnormality, but LIP, PCP, and miliary TB can all appear as bilateral, diffuse interstitial opacities (Figure 3).

Though x-rays of LIP are less likely than TB to have hilar adenopathy, distinguishing these pulmonary conditions is not possible on x-ray alone. Where available, high-resolution computed tomography of the chest may be helpful if the diagnosis of LIP is in question. Computed tomography will typically reveal micronodules (1-3 mm in diameter) with a perilymphatic distribution as well as subpleural nodules. In LIP, radiographic findings may improve even as the patient’s immune status worsens. If a lung biopsy is performed, microscopic inspection of the lung tissue will demonstrate abnormal collections of lymphocytes surrounding the airways. Pulmonary function testing in LIP patients typically demonstrates a pattern of restrictive disease, with reduced forced vital capacity (FVC), reduced FVC in 1 s (FEV1), and a normal FEV1/FVC ratio.

**Clinical Course and Treatment**
The clinical course of LIP varies and spontaneous remission occurs occasionally. Intercurrent respiratory illnesses can exacerbate existing disease, and when severe, LIP can cause progressive hypoxia and respiratory failure. Measuring oxygen saturation with pulse oximetry helps determine the severity of illness and the need for oxygen therapy. Some affected patients require continuous oxygen. Antibiotics may be required for acute pulmonary infections, and inhaled bronchodilators (e.g., albuterol or salbutamol) may provide some relief when LIP symptoms worsen. Although there are few data for its use, most patients respond to oral corticosteroid therapy and it is recommended for those with LIP and a chronic oxygen requirement. In affected children, prednisone (2 mg/kg/day) can be prescribed for 2-4 weeks or until the oxygen requirement improves, at which time the prednisone should be decreased to a dose of 0.5-0.75 mg/kg every other day. In severe disease, tapering is sometimes not possible and corticosteroid therapy may be required indefinitely. The most effective dose and treatment duration of corticosteroid therapy remains uncertain, and more studies are needed. Hydroxychloroquine is an alternative to oral corticosteroid therapy and is effective in some cases. The recommended hydroxychloroquine dose in children is 10 mg/kg per day. In addition to symptomatic therapy, HAART may also provide some improvement. Although LIP is a Stage 3 WHO disease, it is one of the four Stage 3 diseases (LIP, thrombocytopenia, pulmonary TB, and oral hairy leukoplakia) that do not require immediate initiation of ARV therapy, provided that the CD4+ cell count is adequate. Secondary infections (due to HIV-mediated or drug-mediated immunosuppression) are common in patients with LIP; without monitoring, diagnosis, and treatment, they can be life threatening.
**References**

**Renal Disease**


**Cardiac Disease**


**Pulmonary Disease**
