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Thinking About HIV Infection

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Drs Simpkins, Siberry,
and Hutton have
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Objectives After completing this article, readers should be able to:

1. Recognize the important role that the general pediatrician plays in the prevention, detection, and care of human immunodeficiency virus (HIV)-infected and -affected patients.
2. Select the proper HIV testing plan for pediatric and adolescent patients based on age, history, and physical assessment.
3. List the clinical conditions suggestive of HIV infection.
4. Provide counseling to reduce risk behaviors as part of routine adolescent health care.
5. Discuss comprehensive primary care for HIV-exposed infants.

Case Studies

Case Study 1

A 20-year-old woman, who is a recent emigrant from Ethiopia, brings in her 4-month-old infant for a health supervision visit. The baby has had no immunizations, and his mother reports having had no prenatal care. She is breastfeeding exclusively. The infant's 25-year-old father recently died after being very sick for 2 years. The mother states that he had "bad lungs." What are your next steps?

Case Study 2

A 17-year-old honor student comes to your office with a maculopapular rash on his face, trunk, palms, and soles. He also complains of a sore throat and fever and states that he recently returned from visiting his grandmother in Georgia. During his visit, he went hunting with his uncles and his grandmother's dog. During the interview, which involves asking routine psychosocial questions in a nonthreatening manner (Table 1) to elicit sensitive information, he states that he has been sexually active with women for 2 years and with men for 6 months. He does not use condoms with either. He denies any contacts with sick persons or substance abuse, including injection drug use (IDU). What are your next steps?

Abbreviations

AIDS:	acquired immunodeficiency syndrome
CCR5:	chemokine coreceptor 5
CD4:	a glycoprotein on the surface of T helper cells
EIA:	enzyme-linked immunoassay
HIV:	human immunodeficiency virus
IDU:	injection drug use
MMR:	measles-mumps-rubella
mRNA:	messenger RNA
MTCT:	mother-to-child transmission
NNRTI:	non-nucleoside reverse transcriptase inhibitor
NRTI:	nucleoside reverse transcriptase inhibitor
OI:	opportunistic infection
PCP:	<i>Pneumocystis jiroveci</i> pneumonia
PCR:	polymerase chain reaction
PI:	protease inhibitor

Introduction

The epidemiology, diagnosis, prevention, and treatment of HIV infection and acquired immunodeficiency syndrome (AIDS) in the pediatric and adolescent population have changed dramatically over the past 25 years. In countries that have good resources, such as the United States, rates of new infections in infants have plummeted with the implementation of effective screening and prevention strategies. Children born with HIV early in the epidemic now are surviving into young adulthood, facing unpredicted challenges and opportunities in their physical health and social and emotional well-being. Today's adolescents are acquiring HIV at an alarming rate. The role of the pediatrician varies with the type of practice, the prevalence of HIV in the local commu-

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Table 1. HEEADSSS* Interview for Adolescents

Home
Education and employment
Eating
Activities
Drugs
Sexuality
Suicide/depression
Safety

*The mnemonic HEEADSSS reminds the clinician of important aspects of an adolescent's life that require inquiry. Sensitive information should be elicited in a nonthreatening manner.

nity, and the ease of access to HIV specialty care and consultation. All pediatricians should be prepared to provide care for HIV-exposed newborns and their siblings, to screen for and diagnose HIV infection in children and adolescents, and to provide routine HIV prevention counseling to adolescents. Many pediatricians provide primary care for HIV-infected children and adolescents in collaboration with HIV specialists (Table 2).

Epidemiology

Worldwide, 33.2 million people live with HIV infection, 2.5 million of whom are children younger than 15 years of age. In 2007, 2.1 million AIDS deaths occurred, of whom 330,000 were children. In the United States, 2,181 cases of AIDS were reported among children and adolescents through age 24 years for the year 2006. Only 38 of these cases were in children younger than the age of 13 years, a sharp and steady reduction from the early 1990s when nearly 1,000 children annually were reported as having AIDS. Clearly, the "pediatric" burden of infection and disease now rests in the adolescent population. Many children who had HIV at birth in the 1980s and early 1990s now are adolescents and young adults living with HIV/AIDS. In addition, the number of new cases of AIDS reported is increasing in all age categories within the 13- to 24-year-old population. Despite widespread availability of HIV testing and effective treatment, it is estimated that 25% of people living with HIV/AIDS do not know that they are infected, a proportion that increases to nearly 50% for infected adolescents.

Pathogenesis

Understanding the basics of the HIV viral life cycle can help pediatricians to employ HIV laboratory tests confi-

Table 2. The Pediatrician's Role in HIV Care

Health Maintenance Care

HIV-exposed newborns
Immunizations
Growth and nutritional status
Neurodevelopment

Acute and Chronic Illness Care

Clinical syndromes suggestive of underlying HIV infection
Common problems in HIV-infected infants, children, and adolescents

Collaboration With HIV Specialist

Evaluation and staging
Antiretroviral treatment
Prevention of opportunistic infections

Counseling and Support

Primary and secondary HIV prevention
Coping with diagnosis and prognosis
Adherence with care and treatment
School and sports participation
Transition to adult health care
Advance care planning and palliative care

Universal Precautions—Standard Precautions

dently and to understand the current approach to HIV prevention and treatment. HIV is a lentivirus in the retrovirus family. Susceptible hosts are infected when the virus enters the body and binds to CD4 receptors on host T lymphocytes. Through a complex process of specific HIV glycoprotein binding to host T-lymphocyte CD4 receptor and chemokine coreceptor 5 (CCR5) coreceptors, HIV fuses its envelope with the lymphocyte cell membrane. Viral RNA and enzymes such as reverse transcriptase enter the host cell, and the viral RNA is reverse transcribed into DNA. Viral DNA then enters the nucleus of the host cell and is integrated into the cellular genome.

When the host cell is activated, transcription takes place, allowing viral DNA to be converted to genomic and messenger RNA (mRNA). mRNA is translated into viral proteins that combine with copies of genomic RNA to become complete virions that subsequently are released from the host cell. The cycle of infection, replication, and release continues rapidly in the newly infected host, creating billions of virions per day.

This initial viremic phase precedes antibody response

and is the period of highest infectivity due to the very high viral load. During this time, dissemination of the virus in the body and seeding of lymphoid organs is widespread. The newly infected person may experience acute retroviral syndrome, characterized by fever, lymphadenopathy, rash, myalgia, arthralgia, headache, diarrhea, oral ulcers, leukopenia, thrombocytopenia, and transaminitis. During this “window period” between host cell infection and host antibody response, an infected person has a negative HIV antibody test result, but HIV RNA testing results are positive. Seroconversion, the demonstrated presence of HIV antibody, may occur as early as 10 to 14 days after infection but usually occurs within 3 or 4 weeks. Nearly all patients seroconvert within 6 months of acquiring the infection. Infection with HIV is lifelong because HIV infects long-lived memory T cells.

Preventing HIV Transmission to Children and Adolescents

HIV infection is transmitted by two principal modes in the pediatric age group: mother-to-child and behavioral. Mother-to-child transmission (MTCT) can occur antepartum through transplacental transfer; intrapartum through exposure to maternal blood, amniotic fluid, and cervicovaginal secretions during delivery; and postpartum through breastfeeding. MTCT is preventable in almost all cases by the proper use of combination antiretroviral therapy to achieve an undetectable viral load in the mother, intrapartum maternal zidovudine, neonatal zidovudine, and safe replacement infant feeding.

In addition, elective cesarean section prior to the onset of labor can reduce MTCT risk in women who have persistent viremia due to lack of or ineffective antiretroviral therapy during pregnancy. In the United States, MTCT now occurs in fewer than 2% of births to HIV-positive women, a decrease from 25% in nonbreastfed infants prior to the routine use of antiretroviral therapy for the prevention of MTCT. It is important to remember that some infected infants escaped detection early in the United States epidemic and now are being identified as “new” cases in the adolescent age group.

Adolescents are exposed to HIV through risky behaviors that involve the exchange of infected blood or semen, such as unprotected sex (homosexual and heterosexual) or injection drug use with sharing of needles or syringes. Factors that increase the risk of sexual transmission include traumatic sex (voluntary or involuntary), in which the genital, anal, or oral epithelium is compromised (with those reporting receptive anal sex at highest risk); active genital ulcer disease in either partner; and

(for females) douching before sex. Adolescent females are at even higher risk than adult women of acquiring sexually transmitted infections, including HIV, because of the presence and vulnerability of the cervical ectropion, an area of endocolumnar cells on the ectocervix that regresses into the endocervical canal as the adolescent matures. Behaviors that increase the likelihood of an adolescent male or female being exposed to an HIV-positive sexual partner include exchanging sex for money or drugs, having multiple sex partners, and using recreational drugs, including alcohol.

Studies of discordant partnerships (one person has HIV infection, the other does not) reveal that consistent and correct use of condoms made of latex, polyurethane, or other synthetic materials offers a high degree of protection from HIV and other sexually transmitted infections spread by the exchange of body fluids (as opposed to infections spread by direct contact with lesions, such as herpes simplex).

Testing for HIV Infection: Who, What, When?

The Tests

Several laboratory tests are approved for screening and diagnosing HIV infection (Table 3). The pediatrician must select the correct test based on the patient’s age and the clinical indication (Table 4). Most commercially available tests detect HIV antibody. For patients older than age 18 months, the confirmed presence of antibody to HIV is diagnostic of HIV infection. Standard HIV antibody testing is performed on a blood specimen in two steps: screening enzyme-linked immunoassay (EIA) is performed and if reactive, a confirmatory test such as Western blot is performed. Both steps must be positive for the overall test result to be reported as positive.

Table 3. HIV Tests

Antibody Tests in Laboratories

Enzyme-linked immunosorbent assay
Western blot
Immunofluorescence assay

Antibody Tests in Clinical Settings (Rapid Tests)

Blood
Saliva

Viral Detection Tests in Laboratories

DNA polymerase chain reaction (PCR) (qualitative)
RNA PCR (quantitative)

Table 4. HIV Screening and Diagnostic Testing

Who	What	When
Pregnant women	Antibody	Prenatal enrollment; repeat in third trimester
HIV-exposed newborns	DNA PCR Antibody	Optional at birth; 2 to 3 weeks, 1 to 2 months, at or after 4 months Optional after age 12 months to confirm seronegativity
Children of HIV+ mother	Antibody*	No maximum age
Adolescents	Antibody	Single screen at/after age 13 years; repeat annually if sexually active or injecting drugs
Clinical suspicion	Antibody**	Any age if clinical presentation is suggestive of underlying HIV infection

*Use infant testing algorithm if antibody-positive and younger than age 18 months.
**Use additional HIV RNA testing if clinical presentation is suggestive of acute retroviral syndrome
PCR=polymerase chain reaction

Newer rapid tests also detect antibody; they are performed on blood or saliva and allow the clinician to provide a result to a patient in approximately 20 minutes. Positive screening results must be confirmed by standard antibody testing. Specific HIV viral detection using DNA or RNA polymerase chain reaction (PCR) is necessary in two clinical situations when antibody testing is nondiagnostic: in infants of HIV-infected mothers and in patients of any age who are suspected of having acute or early HIV infection. All infants born to HIV-positive mothers test positive for HIV antibody due to the transfer of maternal immunoglobulin across the placenta; HIV DNA or RNA PCR identifies those who have true HIV infection. Older children and adolescents who have symptoms of acute retroviral syndrome may not yet have detectable HIV antibody; HIV RNA PCR is a sensitive test for early HIV infection. A definitive diagnosis of HIV infection requires that two different specimens test positive (eg, in children older than 18 months, two antibody tests or one antibody + one RNA) using appropriate techniques based on the age of the patient and the clinical indication.

Counseling and Consent

National HIV testing guidelines recommend counseling and testing as a routine part of regular medical care in addition to continued efforts to reach out to individuals at higher risk. The goal is to identify all HIV-positive individuals, engage them in HIV care for their own health, and reduce the transmission of HIV to others. Clear, understandable information about the benefits of HIV testing should be provided in a manner that protects patient privacy and provides emotional support as needed. Key messages include that: 1) HIV infection is a treatable condition, 2) HIV infection is a serious health condition, 3) early detection of HIV infection permits

early treatment to prevent disease progression and maintain health, and 4) people who have HIV infection can prevent its transmission to others. The “opt-out” counseling approach informs patients that HIV testing will be performed as part of their routine care unless they decline, reducing barriers associated with mandatory prevention counseling and written consent. Adolescents in the United States can seek confidential testing and treatment for HIV independently, although family support is encouraged.

Parents or guardians seek care on behalf of infants and children. Children should be included in developmentally appropriate discussions about care. Anticipating the need for HIV disclosure to the child is an important component of the pediatric counseling process. Helping adult caregivers understand the importance of sharing simple and truthful information provides a strong foundation for later disclosure. The indication for diagnostic testing may help frame the conversation (eg, mother is HIV-positive, sibling is HIV-positive, child has worrisome clinical findings). Counseling messages include:

All ages: Inform child that a blood test will be performed, give simple details of the procedure, help choose a coping strategy, and offer comfort.

4 to 6 years of age: “I am worried that you keep getting sick. I need to do a blood test to help me figure out why.”

7 to 10 years of age: “I am worried that you keep getting sick. I wonder if your immune system, the part of your body that fights off infections, isn’t working the way it should. I want to do blood tests to help me figure this out.”

11 to 13 years of age: “I am worried that you keep getting sick. I wonder if your immune system, the part of your body that fights off infections, isn’t working the way it should. I want to do blood tests to help me figure this

out. One of the tests looks for HIV. Have you ever heard of that?"

The most important guideline is *never lie*. Partial truthfulness can be supplemented at later visits or at older ages. Deliberate misinformation, even under the guise of protecting the child, leads to loss of trust and is very difficult to undo.

Screening Pregnant Women

Universal HIV counseling and voluntary HIV testing using an opt-out approach is the recommended standard of care for all pregnant women in the United States. This practice provides the opportunity for HIV-positive women to access HIV care for their own health and to prevent HIV transmission to their babies. The opt-out approach informs all pregnant women receiving care that an HIV test will be performed unless she opposes testing. Initial testing is performed early in pregnancy. Repeat testing is recommended in the third trimester (before 36 weeks' gestation) for women who live in high HIV prevalence areas or for women who have specific high-risk factors (exchange sex for money or drugs, IDU, sexual partner who engages in IDU, new diagnosis of sexually transmitted infection during pregnancy).

For women who have not received prenatal care, intrapartum testing should be offered by using rapid test kits or expedited EIA. Mothers who decline screening at any of these opportunities should be offered testing again at every opportunity, including rapid antibody testing in the immediate postpartum period. Practitioners also can offer rapid antibody testing of newborns as an indicator of HIV exposure when the mother's status cannot be determined. In most cases, maternal consent is needed for testing newborns, but some states allow testing of high-risk newborns without consent.

Testing HIV-Exposed Infants

Infants born to HIV-positive mothers should undergo specific diagnostic testing; HIV DNA or RNA PCR should be used as part of their health maintenance care. Testing is recommended at age 14 to 21 days, at 1 to 2 months, and again at 4 to 6 months. Due to the low sensitivity of tests in the first 48 hours after birth, testing is optional at birth. If performed, blood samples from the umbilical cord should not be used because of possible contamination with maternal blood. In nonbreastfed infants, the sensitivity of HIV DNA PCR increases to 93% by 14 days of age. By 28 days, the sensitivity increases to 96% and the specificity is 99%. Sensitivity and specificity of the HIV RNA assay are similar. Any positive test requires repeat confirmatory testing as soon as pos-

sible. Some practitioners use HIV DNA PCR for initial testing and HIV RNA assay for confirmatory testing.

HIV infection is *reasonably* excluded when results of two virologic tests are negative, the first at 14 days or older and the second at 1 month of age or older. *Definitive* exclusion requires negative results for two virologic tests, the first at age 1 month or older and the second at 4 months of age or older. In older infants for whom early testing was not performed, an alternate strategy is to confirm the absence of HIV antibody. If infection already has been excluded definitively, HIV antibody testing between 12 and 18 months of age to confirm the loss of maternal antibody is optional.

Breastfeeding causes continued HIV exposure and is not recommended in the United States where safe replacement (formula) feeding can be provided. Testing should continue throughout the period of breastfeeding and for 6 months after cessation when an infant is breastfed.

Testing Children and Adolescents

HIV antibody tests are used for screening and diagnosis in children older than age 18 months. All children of HIV-positive mothers should be screened for HIV infection regardless of age or healthy appearance. Children or adolescents who present with clinical conditions suggestive of HIV infection should undergo HIV testing as part of the diagnostic evaluation, regardless of risk history.

All adolescents should be offered HIV testing as part of routine health care. Annual testing is recommended for those at high risk of acquiring HIV infection. Rapid tests offer the advantage of providing test results at the same visit. HIV-negative individuals can be reassured and counseled to avoid future HIV exposure. HIV-positive individuals can be engaged immediately into care and support.

If a practitioner suspects acute infection or acute retroviral syndrome, he or she should order HIV antibody and nucleic acid testing (HIV RNA) to look for evidence of infection. A positive nucleic acid test result in the presence of a negative or indeterminate antibody test result is consistent with acute HIV infection. Antibody testing is recommended 10 to 12 weeks later to confirm seroconversion.

Evaluation and Staging of the HIV-Positive Patient

Patients who have positive HIV test results should be referred to an HIV specialist for comprehensive evaluation (Table 5) so the clinical and immunologic stage of disease can be assessed and treatment recommended.

Initial evaluation of an HIV-infected pediatric patient should include the mother's medical history, child's medical history, family history, and social history. A comprehensive physical examination should be performed and documented, including a developmental evaluation. Assessment of HIV-infected adolescent patients (generally, 11 years of age and older), as for all adolescents, should include a sexual history, substance use history, and sexual maturity staging.

Initial laboratory testing in an HIV-positive patient should include CD4 percentage and absolute cell counts, plasma HIV RNA concentration (viral load), HIV genotype to assess for baseline resistance mutations, complete blood count with differential count, serum chemistries with liver and renal function tests, a lipid profile, and urinalysis. For children younger than 5 years of age, CD4 percentage is the preferred test for monitoring immune status because the absolute CD4 cell count (number of CD4 cells/mm³) in this age group varies with age-related changes in absolute lymphocyte count. Screening for hepatitis B and C infection as well as for tuberculosis is recommended for all HIV-infected patients. In addition, sexually active adolescents should be screened for *Chlamydia* infection, gonorrhea, syphilis, and human

papillomavirus infections. In contrast to the guidelines for cervical cancer screening in healthy women, cervical Papanicolaou smears are indicated routinely in all sexually active, HIV-infected adolescent girls, with colposcopy recommended for evaluation of abnormal results. Similarly, most experts perform anal Pap smears in HIV-infected adolescent men who have sex with men and HIV-infected sexually active women; anoscopy is recommended for evaluation of abnormal results.

HIV infection is a multisystem disease; clinical manifestations range from asymptomatic to complications affecting virtually every organ system (Table 6). The Centers for Disease Control and Prevention classification system designates clinical categories based on the patient's medical history and immunologic function categories based on CD4 percentage (Table 7). This information permits an estimated risk for future morbidity and mortality and provides a rationale for instituting specific opportunistic infection prophylaxis and initiating or deferring antiretroviral therapy.

HIV-specific Treatment

Antiretroviral Therapy

The goal of anti-HIV therapy is to maximize the quality and longevity of life through:

- Complete suppression of viral replication (goal of *non-detectable viral load*)
- Preservation or restoration of immunologic function (goal of *normal CD4 percentage or count*)
- Prevention of or improvement in clinical disease (goal of *asymptomatic state*)

National treatment guidelines for HIV-infected children and adolescents are updated routinely and are available on the Internet (<http://www.aidsinfo.nih.gov/Guidelines/>). Current recommendations are summarized in the text and in Table 8. The pediatric treatment guidelines updated in 2008 recommend antiretroviral treatment for *all* infected infants (<12 months old); simplifies treatment initiation recommendations into three age categories (<12 months old, 1 to 4 years old, and ≥5 years old) instead of four; places greater emphasis on simplified, age-based CD4 thresholds for treatment initiation than on viral load; and is consistent with adult guidelines for initiation of antiretroviral treatment in children 5 years of age and older. Clinical and immune statuses are key predictors of morbidity and mortality and form the basis for these recommendations. Viral load is more useful for monitoring adherence and effectiveness of therapy than as an indicator of when to initiate antiretroviral therapy.

Treatment is recommended for: AIDS *or* severe symp-

Table 5. Evaluation and Staging

History

Physical Assessment

Laboratory Assessment

Confirm HIV infection
 HIV RNA (viral load)
 HIV resistance profile (genotype)
 CD4 percentage and absolute count
 Complete blood count with differential count
 Chemistry panel (liver transaminases, bilirubin, electrolytes, urea nitrogen, creatinine, calcium, phosphorus, glucose, cholesterol, triglycerides, amylase, lipase)
 Coinfections: cytomegalovirus, *Toxoplasma*, hepatitis B and C, varicella
 Urinalysis (dipstick and microscopic)

Tuberculin skin test

In sexually active individuals, screen for gonorrhea, *Chlamydia* infection, syphilis

Consider chest radiography, electrocardiography, dual-energy x-ray absorptiometry scan for bone mineral density

Table 6. Relative Frequency of Clinical Conditions in Untreated HIV Infection

Body System or Illness Category*	Specific Conditions	Relative Frequency	
		Common	Uncommon
Infections: recurrent, severe, or unusual (opportunistic)	Recurrent or chronic otitis, sinusitis	C	
	Recurrent or severe pneumonia	C	
	Recurrent or severe bacteremia	C	
	Opportunistic infections, such as PCP, MAC, invasive candidal infections	C	
Lymphoreticular system	Generalized lymphadenopathy	C	
	Hepatomegaly	C	
	Splenomegaly	C	
	Parotid enlargement	C	
	Lymphoid interstitial pneumonitis	C	
Growth	Failure to thrive	C	
	Weight loss, wasting	C	
	Stunting	C	
	Delayed puberty	C	
Neurologic	Neurodevelopmental delay or regression	C	
	Abnormal tone (increased or decreased)	C	
	Gait disturbance	C	
	Peripheral neuropathy		U
	Stroke		U
Pulmonary	Bacterial pneumonia	C	
	Lymphoid interstitial pneumonitis	C	
	Bronchiectasis		U
	Pneumothorax		U
Cardiovascular	Cardiomyopathy		U
	Pericardial effusion		U
	Conduction abnormalities		U
	Hypertension		U
	Vasculopathy		U
Gastrointestinal	Gastritis	C	
	Duodenitis	C	
	Hepatitis		U
	Pancreatitis		U
	Cholecystitis		U
	Diarrhea	C	
	Gastrointestinal bleeding		U
	Abdominal pain	C	
Renal	Proteinuria	C	
	Renal tubular acidosis		U
	Renal failure		U
	Hypertension		U
Hematologic	Anemia	C	
	Neutropenia	C	
	Thrombocytopenia	C	
Dermatologic	Seborrhea	C	
	Eczema	C	
	Urticaria		U
	Zoster	C	
	Herpes simplex infections	C	
	Tinea corporis, capitis, unguium	C	
	Bacterial infections	C	
	Molluscum contagiosum	C	
	Warts (HPV)	C	
	Genital/Reproductive	HPV-related dysplasia (cervical, anal)	C
Pelvic inflammatory disease		C	
Delayed puberty		C	

*Some conditions belong to more than one category. HPV=human papillomavirus, MAC=*Mycobacterium avium* complex, PCP=*Pneumocystis jirovecii* pneumonia

Table 7. HIV Clinical Classification System

Clinical Categories		
N	No symptoms*	
A	Mild symptoms (eg, generalized lymphadenopathy)	
B	Moderate-to-severe symptoms (eg, thrombocytopenia)	
C	AIDS-defining conditions (eg, <i>Pneumocystis jiroveci</i> pneumonia)	
Immune Categories		
1	Normal	CD4 ≥25%
2	Moderate suppression	CD4 15% to 24%
3	Severe suppression	CD4 <15%

*Class N in pediatric classification system only (children <13 years of age)

tored in collaboration with an HIV specialist. Strong evidence supports the use of triple-drug combination antiretroviral therapy to maximize virologic response and minimize the emergence of viral resistance. Initial therapy consists of three drugs from two categories: one non-nucleoside reverse transcriptase inhibitor (NNRTI) OR protease inhibitor (PI) PLUS two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs).

Important issues to consider when selecting specific drugs include:

toms, CD4 percentage of less than 25% (1 to 4 years) or absolute CD4 count of less than 350 cells/mm³ (5 years and older) regardless of symptoms, all infected infants younger than 12 months of age, and all pregnant adolescents.

Treatment is considered for: patients whose HIV RNA is more than 100,000 copies/mL *and* who have mild or absent symptoms *and* adequate CD4 cells (CD4 percentage of more than 25% [1 to 4 years] or absolute CD4 count of more than 350 cells/mm³ [5 years and older]).

Treatment can be deferred for: mild or absent symptoms *and* adequate CD4 values (CD4 percentage of more than 25% [1 to 4 years] or absolute CD4 count of less than 350 cells/mm³ [5 years and older]) *and* RNA of less than 100,000 copies/mL.

Antiretroviral therapy should be planned and moni-

- Age, weight, sexual maturity stage of patient
- Baseline HIV resistance pattern
- Likelihood of developing resistance to selected drugs if patient has difficulty adhering to the regimen (low versus high barrier to resistance)
- Likelihood of becoming pregnant while taking selected drugs (eg, efavirenz)
- Ease of administration (formulation, schedule, food restrictions)

Planning treatment collaboratively with the patient and family strengthens the therapeutic relationship and promotes successful adherence and HIV control. Enlisting adult support in the home is beneficial regardless of the patient's age. Frequent clinical follow-up with viral load testing allows the clinician to identify problems early and help patients and families find successful solutions.

Table 8. When to Initiate Antiretroviral Therapy

Immune Status CD4 Percentage (1 to 4 years old)	Infants <12 Months of Age	Pregnant Adolescents	Children Older Than 1 Year of Age and Nonpregnant Adolescents		
			N or A (Asymptomatic or Mild Symptoms)	B (Moderate-to-severe Symptoms)	C (AIDS Conditions)
Absolute CD4 cell count (5 years and older) ≥25% ≥350 cells/mm ³	TREAT	TREAT	RNA <100,000 copies/mL DEFER	TREAT	TREAT
			RNA >100,000 copies/mL CONSIDER		
<25% <350 cells/mm ³	TREAT	TREAT	TREAT	TREAT	TREAT

Patients in whom the virus shows no drug resistance and in whom therapy is initiated with currently available medicines should achieve a nondetectable viral load within 3 to 6 months. Failure to achieve this goal strongly suggests suboptimal adherence to the recommended regimen rather than viral resistance.

Once HIV infection is controlled on a stable regimen, most patients are seen every 3 to 4 months for routine monitoring of viral load, CD4 cell response, and clinical status, including evaluation for potential medication adverse effects or toxicities. Patients who experience treatment failure have additional treatment options, including new drugs in existing classes (PIs, NNRTIs, NRTIs) as well as new drug classes such as entry inhibitors (fusion inhibitors and CCR5 antagonists) and integrase inhibitors.

Preventing Opportunistic Infections

The profound immunodeficiency caused by uncontrolled HIV infection allows serious and life-threatening infections to occur in children and adolescents. Evidence supports the primary prevention of common opportunistic infections (OIs) based on age and CD4 guidelines. Full recommendations are available at <http://aidsinfo.nih.gov>.

Pneumocystis jiroveci pneumonia (PCP) is the most common OI. Cotrimoxazole is recommended for all HIV-exposed infants until HIV infection is reasonably excluded, for all HIV-infected infants until age 12 months, and for HIV-infected children and adolescents older than 1 year of age whose CD4 values fall into the severe immune suppression category (CD4 percentage <15% or CD4 count <200 cells/mm³).

Primary prevention of *Mycobacterium avium* complex by using azithromycin or clarithromycin is recommended at lower CD4 values (≥ 6 years old with CD4 count of <50 cells/mm³; ages 2 to 5 years with CD4 count of <75 cells/mm³; 1 to 2 years with CD4 count of <500 cells/mm³; <1 year old with CD4 count of <750 cells/mm³).

Toxoplasmosis is less common in children than in adults, but its prevention with daily cotrimoxazole is recommended in HIV-infected children and adolescents who are *Toxoplasma* immunoglobulin G-seropositive and have severe immunosuppression (CD4 percentage <15% for children <6 years old; CD4 count <100 cells/mm³ for children ≥ 6 years old).

Immunizations

The 2009 immunization schedule for HIV-exposed infants and for HIV-infected infants, children, and adolescents is the same as for their healthy peers, with only a few

exceptions. Patients who have severely symptomatic illness or CD4 percentages of less than 15% or CD4 counts of less than 200 cells/mm³ should not receive measles-mumps-rubella (MMR) or varicella vaccines due to the risk of opportunistic disease from the live attenuated virus strains in the vaccines. HIV-infected children who have higher CD4 counts should receive MMR and varicella separately, not as the combined MMR-V. The higher titer of varicella in MMR-V has not been tested for safety in HIV-infected children. Annual influenza immunization is recommended for all children older than age 6 months, but only the killed, injectable formulations of the influenza vaccine are recommended for HIV-infected children and adolescents.

HIV-infected children and adolescents need certain additional vaccines and doses. Pneumococcal polysaccharide vaccine is recommended in addition to the regular pneumococcal conjugate vaccine series. Specific and comprehensive recommendations for immunizations in HIV-infected children, adolescents, and adults are available at <http://aidsinfo.nih.gov/>.

Counseling and Support

Primary and Secondary Prevention of HIV Infection

Health education messages to avoid HIV infection and to prevent its spread to others should be routine in every pediatric and adolescent practice. It is important for clinicians to be prepared to offer prevention counseling, including abstinence and safe sex as best options for preventing HIV transmission. Clinicians should be able to teach all adolescents about correct use of male latex condoms and emphasize that consistent use is essential for prevention. Screening all patients ages 13 years and older for HIV infection identifies asymptomatic patients unaware of their HIV infection status, providing them the opportunity to enroll in HIV-specific care for their own benefit and to reduce the risk of transmitting HIV to others. HIV-negative adolescents who engage in behaviors through which HIV can be transmitted should be tested at least annually.

Coping With the Diagnosis and Prognosis

Learning of a new diagnosis of HIV infection for oneself or one's child is emotionally devastating for most people. While providing a listening ear and emotional support, clinicians also can offer hope and reassurance about the availability of effective treatment that can result in improved quality of life and survival for people living with HIV infection in the United States. Referral to the HIV

specialist allows prompt access to specific medical care and psychosocial supports.

Disclosure of HIV Infection Status

HIV infection remains a stigmatizing diagnosis. Ignorance, misinformation, and fear in families and communities cause people living with HIV infection to keep their status a secret. However, this practice has negative consequences, such as isolating the HIV-positive individual from social support and risking additional spread of HIV to sexual partners. Planned disclosure to family members and friends can increase practical and emotional support for the HIV-positive person. Sexual partners can make informed decisions about how to protect themselves from exposure to HIV.

In contrast to adolescents and adults, disclosure of HIV status to children should be undertaken over time, providing sequential pieces of practical health information that match the developmental capacity of the child. This process builds a strong foundation for children to participate meaningfully in their HIV care.

Adherence to Care and Treatment

Most people do not adhere to the treatment recommendations of their health-care practitioners all of the time. Adolescence is a particularly vulnerable age for nonadherence in those who have chronic health conditions such as HIV infection. Poor adherence leads to poor health outcomes in many diseases such as asthma and diabetes. However, HIV treatment is unique in its requirement for 90% to 100% adherence to drug regimens to avoid the development of viral resistance and the loss of future efficacy of anti-HIV drugs. The need for intensive education and support for children and adolescents living with HIV infection cannot be overstated.

School and Sports Participation

Children and adolescents who have HIV infection can participate fully in the educational and extracurricular activities in school. There is no obligation to notify school personnel of a student's HIV infection status. Any sport may be played if the student's health status allows. For all athletes, regardless of HIV infection status, skin lesions should be covered properly, and athletic personnel should use standard precautions when handling blood or body fluids that have visible blood. Certain high-contact sports (such as wrestling and boxing) may create a situation that favors viral transmission (likely bleeding plus skin breaks). Some experts advise athletes who have a detectable viral load to avoid such high-contact sports.

Transition to Adult Health Care

Children born with HIV infection in the United States during the 1980s are now young adults. They continue to be the pioneers who challenge our assumptions and identify unmet needs for care and support services. No one anticipated the current need to develop and implement programs to transition youth successfully to adult HIV health-care clinicians. Practical concerns such as transmitting a complete and coherent medical record and psychological concerns such as the loss of long-term supportive relationships must be addressed.

Advance Care Planning and Palliative Care

Advance care planning is recommended for all who live with chronic and life-threatening conditions. HIV-infected parents should plan for the care of their dependent children. HIV-infected adolescents and young adults should designate a person they trust to make health-care decisions for them if they should become unable to speak for themselves due to illness or injury. One approach is to normalize this decision as part of routine health care when reaching adulthood. This practice is particularly important for youth who have no clearly identified next of kin, such as those who are orphaned and have experienced sequential foster homes.

There continue to be patients who experience distressing medical complications of HIV infection that, if not reversed, lead to death. Integrating palliative care with HIV-specific care reduces distress by managing specific physical and emotional symptoms, encouraging clear communication, and promoting effective decision-making. This approach provides the best opportunity to improve a patient's quality of life regardless of how long the patient survives.

Managing Potential HIV Exposure

The pediatrician may be called on to respond to questions about HIV exposure. Such questions may be about occupational exposures, such as a needle stick injury to a health-care worker, or nonoccupational, such as a child finding a discarded needle and syringe or an adolescent who is a victim of sexual assault. The basic approach to any of these scenarios is to assess the likelihood that exposure to potentially infectious fluids actually occurred, determine how severe or extensive the exposure was, and evaluate the likelihood that the fluids are HIV-contaminated. If the exposure is of high risk and the source is known to be HIV-infected, postexposure prophylaxis with antiretroviral drugs should begin as soon as possible after the exposure, but no later than 72 hours. Guidelines for evaluating risk and recommending post-

exposure prophylaxis can be found at <http://aidsinfo.nih.gov>.

Having a High Degree of Suspicion

In case study 1, the clinician is presented with a 4-month-old infant of immigrant African parents whose father died as a young man with “bad lungs” and whose mother is breastfeeding exclusively. The clinician’s next steps include performing a careful history and physical examination to assess the infant’s growth and development and to look for conditions suggestive of HIV infection. HIV antibody testing should be recommended to the mother for her own health and for planning the care of her baby. If such testing cannot be arranged promptly, testing the infant for HIV antibody would indicate the mother’s HIV infection status. If the mother is HIV antibody-negative and not engaging in risky behaviors, the infant does not need additional HIV testing. However, if the mother is HIV-positive, virologic testing of the infant with HIV DNA or RNA PCR is indicated throughout the period of breastfeeding and for 6 months after cessation. Counseling should be provided about the availability of safe and affordable formula feeding and prompt weaning recommended. Age-appropriate immunizations should be administered and cotrimoxazole prescribed for PCP prophylaxis until HIV infection is excluded.

Case study 2 involves a 17-year-old male who has a rash, fever, and sore throat and recently has traveled to Georgia, a trip that included a hunting trip. In addition, the patient reports having sex with both females and males and no condom use. The scenario leads to consideration of Rocky Mountain spotted fever in the differential diagnosis. However, it is important to remember that acute retroviral syndrome in adolescents presents with fever 96% of the time and both rash and pharyngitis 70% of the time. Additional signs and symptoms include lymphadenopathy, myalgia, arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, and transaminase elevation. In this patient, HIV antibody testing and HIV RNA testing are indicated as part of the medical evaluation. Counseling should be provided to reduce the risk of sexually transmitted infections.

Conclusion

Although it is important to remember that HIV infection is a multisystem disease requiring regular medical attention, including health maintenance care, it is equally important to remember that some of the greatest chal-

lenges young people face have little to do with their physical illness. Many are in the midst of social complexities that neither they nor their families can begin to navigate without support. Despite these challenges, HIV-positive young people are resilient, strong, caring, appreciative, and worthy of our respect. They are our teachers, presenting diagnostic, therapeutic, and psychosocial challenges that open new avenues for clinical investigation, stimulate our continuous professional development, and remind us of our core human values. They lead the way as we strive to find better ways to manage their illness and improve the quality of their lives.

Summary

- Mother-to-child transmission of HIV can occur during pregnancy, labor, delivery, and breastfeeding. Evidence-based interventions (routine screening of pregnant women, initiation of antiretroviral drugs for mother’s treatment or prevention of MTCT, and avoiding breastfeeding) have reduced transmission rates in the United States from 25% to 30% to less than 2%.
- Triple-drug combination antiretroviral therapy effectively controls HIV infection and improves survival and quality of life for HIV-infected children and adolescents. Initial regimens use combinations of two NRTIs together with an NNRTI or a ritonavir-boosted PI. These regimens have been shown to increase CD4 counts and achieve virologic suppression.
- Prevention of serious and opportunistic infections reduces morbidity and mortality in children and adolescents who have HIV infection. Recommendations for immunizations and chemoprophylaxis vary with the patient’s CD4 count.
- Condoms made from latex, polyurethane, or other synthetic materials have been shown to decrease the transmission of STIs, including HIV infection.

Suggested Reading and Useful Websites

HIV Epidemiology

Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report, 2006*. Vol 18. Atlanta, Ga: United States Department of Health and Human Services, Centers for Disease Control and Prevention; 2008:1–55. Available at: <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/>. Accessed June 2009

HIV Disease Classification

1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR Recomm Rep*. 1994;43(RR-12):1–10. Available at: <http://www.cdc.gov/MMWR/preview/MMWRhtml/00032890.htm>. Accessed June 2009

1993 revised classification system for HIV infection and expanded surveillance case definition for aids among adolescents and adults. *MMWR Recomm Rep.* 1992;41(RR-17). Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm>. Accessed June 2009

National HIV Treatment and Prevention Guidelines (<http://aidsinfo.nih.gov>):

- Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection
- Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents
- Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States
- United States Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis
- Management of Possible Sexual, Injection-Drug-Use, or Other Nonoccupational Exposure to HIV, Including Considerations Related to Antiretroviral Therapy
- Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents
- Guidelines for Prevention and Treatment of Opportunistic Infections among HIV-Exposed and HIV-Infected Children
- Incorporating HIV Prevention into the Medical Care of Persons Living with HIV
- Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

American Academy of Pediatrics Statements

- Committee on Pediatric AIDS. Disclosure of illness status to children and adolescents with HIV infection. *Pediatrics.* 1999;103:164–166
- Committee on Pediatric AIDS. HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. *Pediatrics.* 2008;122:1127–1134
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- Read JS and the Committee on Pediatric AIDS. Diagnosis of HIV infection in children under 18 months of age in the United States. *Pediatrics.* 2007;120:e1547–e1562
- Rice SG and the Council on Sports Medicine and Fitness. Medical conditions affecting sports participation. *Pediatrics.* 2008;121:841–848

National Palliative and Supportive Care Guidelines

- National Consensus Project for Quality Palliative Care. *Clinical Practice Guidelines for Quality Palliative Care.* 2nd ed. Pittsburgh, Pa: National Consensus Project; 2009. Available at: <http://www.nationalconsensusproject.org>. Accessed June 2009
- O’Neill JF, Selwyn PA, Schletinger H, eds. *A Clinical Guide on Supportive and Palliative Care for People with HIV/AIDS, 2003.* Available at: <http://hab.hrsa.gov/tools/palliative/>. Accessed June 2009

PIR Quiz

Quiz also available online at pedsinreviews.aappublications.org.

5. A Sudanese woman who is newly arrived in the United States is Western blot-positive for HIV and is in her seventh month of pregnancy. Assuming she is begun on appropriate combination antiretroviral medications and takes them as directed during the remainder of gestation, which of the following is the *most* appropriate method of establishing the presence of HIV infection in her neonate?
 - A. Measure HIV DNA PCR in the infant's cord blood.
 - B. Measure HIV DNA PCR in the infant's venous blood.
 - C. Measure the HIV viral load in the mother.
 - D. Measure the infant's HIV antibody concentration.
 - E. Measure the titer of HIV antibody in the mother.
6. An 18-year-old homosexual male presents with a history of fever, malaise, myalgia, and headache for the past week. Your differential diagnosis includes HIV infection. Assuming this represents the acute retroviral syndrome, you would expect to find which of the following sets of results on testing his blood?
 - A. Negative HIV EIA, negative HIV RNA PCR.
 - B. Negative HIV EIA, positive HIV RNA PCR.
 - C. Positive HIV EIA, negative HIV RNA PCR.
 - D. Positive HIV EIA, negative Western blot.
 - E. Positive HIV EIA, positive Western blot.
7. Proper immunization of children who have HIV is imperative. An HIV-infected 12-month-old boy who has a CD4 percentage of more than 25% should:
 - A. Not receive the MMR vaccine.
 - B. Not receive the varicella vaccine.
 - C. Receive neither the MMR nor the varicella vaccine.
 - D. Receive separate varicella and MMR vaccines.
 - E. Receive the combined MMR-V vaccine.
8. You are conducting a health maintenance examination on a 15-year-old girl. As part of counseling her about prevention of blood- and semen-borne sexually transmitted infections, your *most* correct statement is that:
 - A. Anal intercourse is the safest form of receptive sex.
 - B. Condoms, properly used, protect against HIV.
 - C. Douching before sex is useful in preventing HIV.
 - D. Adolescent girls have a lower risk of acquiring HIV through vaginal sex than do adult women.
 - E. HIV acquisition is not associated with fellatio.

Thinking About HIV Infection
Evelyn P. Simpkins, George K. Siberry and Nancy Hutton
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