HIV AIDS Clinical Care: Testing and Assessment

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Introduction

HIV/AIDS clinical care has improved dramatically over the decades, given the availability of new medications and a better understanding of how best to use antiretrovirals and deliver primary care to persons living with HIV/AIDS. Positive change on such a massive scale, however, brings with it new demands on clinicians.

Along with innovations in HIV drug therapies, HIV/AIDS care has become more complex than ever before due to increasing comorbidities that are attributable to HIV treatment and the aging of the HIV-infected population in the United States. Patient needs also have expanded across a broad spectrum of medical, psychological, behavioral, and social issues. Notably, significant numbers of infected individuals are identified and enter care late in the course of their HIV disease, confronting clinicians with complex and immediate care challenges.

Since the early days of the epidemic, clinicians have received training in HIV/AIDS clinical care through the AIDS Education and Training Centers (AETCs) Program – the clinical training arm of the Ryan White HIV/AIDS Program that is administered by the Health Resources and Services Administration (HRSA) and its HIV/AIDS Bureau (HAB). The AETC network conducts more than 14,000 training events each year with approximately 143,000 health care providers in attendance.

The *Guide for HIV/AIDS Clinical Care* is a pillar of the Ryan White HIV/AIDS Program's mission to continuously improve HIV/AIDS clinical care. The *Guide* was first published in 1993 as a collaborative effort of several regional AETCs. It was subsequently updated and expanded in 2006 and 2011. The version before you incorporates many new insights, but the time-tested format has been retained – easy access to crucial facts for a busy clinician.

The developers of the *Guide* strive to be responsive to how HIV/AIDS clinical care is provided today.

- With more routine HIV testing in medical settings, a large number of individuals are entering care via primary care sites that have relatively limited experience managing HIV/AIDS disease.
- A notable proportion of HIV/AIDS primary care in the United States is provided by advanced practice nurses and physician assistants.
- Shortages in the health care work force are worsening. Experienced staff members are aging and retiring, a limited number of new clinicians are entering primary care and specializing in HIV/AIDS care, and fewer clinicians are available in geographic areas with limited resources.

As a result, front line primary care providers may be less familiar with management of HIV/AIDS disease, as outlined in U.S. Department of Health and Human Services treatment guidelines (available at aidsinfo.nih.gov) and clinical practices presented in this *Guide*.

By presenting best practices in the clinical management of HIV/AIDS disease, the *Guide* can help us continue the remarkable advances in HIV/AIDS care that have made the Ryan White HIV/AIDS Program a model for health care delivery for our Nation and for the world.

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Abbreviations for Dosing Terminology

BID = twice daily

BIW = twice weekly

IM = intramuscular (injection), intramuscularly

IV = intravenous (injection), intravenously

PO = oral, orally

Q2H, Q4H, etc. = every 2 hours, every 4 hours, etc.

QAM = every morning

QH = every hour

QHS = every night at bedtime

QID = four times daily

QOD = every other day

QPM = every evening

TID = three times daily

TIW = three times weekly

Important Notice

The U.S. Department of Health and Human Services (HHS) HIV/AIDS Bureau is committed to providing accurate information on the care of HIV-infected persons. It is important to be aware that management options and protocols change over time. Forthcoming HHS guidance on certain topics may differ from recommendations contained in this *Guide*. Readers are encouraged to check for updates to treatment guidelines at AIDS Info (aidsinfo.nih.gov) and for updates to drug information at Drugs@FDA (www.accessdata.fda.gov/scripts/cder/drugsatfda).

Initial History

Background

Conducting a thorough initial history and physical examination is important even if previous medical records are available. This is the best opportunity to get a complete picture of the patient's HIV disease status, comorbid conditions, and his or her physical and emotional condition, as well as to establish the basis for an ongoing relationship with the patient. Many of the conditions that put immunocompromised patients at risk of disease can be detected early, by means of a thorough assessment.

The information gathered through the initial history and physical examination will provide a comprehensive standardized database for the assessment and treatment of HIV-related problems, including acute intervention and ongoing prevention services and supportive care.

This chapter includes essential topics to cover during the clinic intake and examples of questions that can be used to elicit important information (the questions should be tailored to the individual patient). This can be completed during the initial visit or divided over the course of two or three early visits. For essential aspects of the physical examination to cover in an initial clinic intake visit, see chapter *Initial Physical Examination*.

HRSA HAB Performance Measures

Percentage of patients with a diagnosis of HIV who had at least **one medical visit in each 6-month period** of the 24-month measurement period with a minimum of 60 days between medical visits

(Core measure)

Percentage of patients with a diagnosis of HIV who received **HIV risk counseling** in the measurement year

(Adult and Adolescent measure)

Percentage of new patients with a diagnosis of HIV who have been screened for **substance use** (alcohol and drugs) in the measurement year

(Adult and Adolescent measure)

Percentage of patients aged 12 years and older **screened for clinical depression** on the date of the encounter using an age-appropriate standardized depression screening tool AND, if positive, a follow-up plan is documented on the date of the positive screen

(Adult and Adolescent measure)

S: Subjective

Initial History	
Category / Topics to Cover	**Sample Questions**
History of Present Illness	
HIV Testing	• What was the date of your first positive HIV test? • Did you have a previous HIV test? If so, when was the last negative result?
Treatment Status	• Where do you usually receive your health care? • Have you ever received care for HIV? • What was the date of your last HIV care visit? • What is your current CD4 (T-cell) count? • Do you know what your first CD4 count was? • What was your lowest CD4 count? • What was your highest CD4 count? • Do you know what your first viral load count was? • What is your current viral load count?

Category/Topic to Cover	Sample Questions
History of Present Illness (continued)	
HIV-Related Illnesses	• What opportunistic infection(s) have you had, if any? (PCP, MAC, cryptococcal meningitis, TB, etc.) • What year(s) were you diagnosed with these infections? • Have you had cancer(s)? • What other HIV-related illnesses have you had? Have you had zoster (shingles), oral thrush, pneumonia?
Active TB and TB Testing History	• Have you ever had tuberculosis (TB)? • When was your last TB test? • Was it a TB skin test (TST) or interferon-gamma release assay (IGRA)? • What were the results of this test? • Have you ever had a positive TB result? • What year and what health care setting? • What medications did you take and for how long?

Antiretroviral Therapy (ART) History	• Are you taking HIV medications now?
	• If so, please name them or describe them, and tell me how many times a day you take them.
	• How many doses have you missed in the past 3 days?
	  • The past week?
	  • The past month?
	• What side effects, if any, do you have now? In the past?
	• What HIV medicines have you taken in the past (names or descriptions)?
	• When did you start and stop taking them (dates)?
	• Do you know why you stopped taking these medications?
	• Do you know what your HIV viral load or your CD4 counts were while you were taking your medications?
	• Have you ever had a resistance test?
	• Did you have any side effects to past HIV medications?

Past Medical and Surgical History	
Chronic Diseases	Do you have any chronic conditions, such as the following? • Diabetes • High blood pressure • Heart disease • Cholesterol problems • Asthma or emphysema • Sickle cell disease • Ulcers, acid reflux, or irritable bowel syndrome • Thyroid disorders • Kidney or liver problems • Mental health disorders If so, do you receive medical care for these conditions?
Previous Illnesses	• Have you had any hospitalizations? Where, when, and for what reason? • Have you had any surgeries? When and where? • Have you had any major illnesses, including mental health conditions?
Hepatitis	• Have you ever had hepatitis? What type (A, B, C)? • Do you have chronic hepatitis? • Do you know whether you are immune to hepatitis A or hepatitis B? Have you been vaccinated?

Category/Topic to Cover	Sample Questions
Past Medical and Surgical History (continued)	
Gynecologic and Women's Health	• When was your last cervical Papanicolaou (Pap) test? • What were the results? • Have you ever had an abnormal Pap test? • When was your last menstrual period? • What is the usual length of your cycle? Is it regular or irregular? • Have you noticed changes in your menstrual cycle? • When was your most recent breast examination? • Have you had a mammogram? When? • Have you ever had an abnormal breast examination or mammogram? • Do you get yeast infections? How often? • Do you get urinary infections? • Have you ever had kidney stones?
Obstetric	• How many pregnancies have you had? • How many live births? Ages of children now? • How many miscarriages or therapeutic abortions? • Were you tested for HIV during any pregnancy? What year? • Did you deliver an infant while you were HIV infected? • Was HIV medication given during pregnancy and delivery? • Do you have children? What is their HIV status? • Do you intend to become pregnant?
Anorectal History	• Have you ever had an anal Pap test? • What were the results? • Have you had anal warts? Other abnormalities?
Urologic History	Have you ever had: • Kidney stones • Urinary tract Infections • Prostate infection or enlargement • Have you had a prostate-specific antigen (PSA) test? (What were the results?)
Sexually Transmitted Diseases	Have you ever had any of the following infections? If yes, when was last episode? • Syphilis (If yes, ask about stage, treatment and date of treatment, titer follow-up, and date and result of last titer.) • Vaginitis • Genital herpes • Nongonococcal urethritis (NGU) • Gonorrhea (If yes, ask about sites of infection: oral, anal, urethral, vaginal.) • Chlamydia (If yes, ask about sites of infection: oral, anal, urethral, vaginal.) • Genital warts (HPV) • Proctitis • Pelvic inflammatory disease (PID) • Trichomoniasis

Category/Topic to Cover	Sample Questions
Past Medical and Surgical History (continued)	
Dental/Oral Care	• When was your last oral health examination? • Do you have all your natural teeth? • Do you have partials or dentures?
Eye Care	• When was your last vision examination? • When was your last dilated retinal examination? • Do you wear glasses or corrective lenses?
Medications	• What (non-ARV) medications do you take? • What herbs, vitamins, nutritional supplements, or over-the-counter (OTC) medications, do you take?
Allergies; Medication Intolerance	• Have you had an allergic reaction to any medications? What type of reaction, how severe? • Have you had allergic reactions to other types of exposures? • Have you had severe side effects from any medications?
Immunizations	When was your last vaccination for the following: • Streptococcal pneumonia (Pneumovax; PPV23, PCV13) • Tetanus/Pertussis (Tdap) • Influenza • Hepatitis A • Hepatitis B Did you have chickenpox as a child, or were you vaccinated against chickenpox? What about measles, mumps, and rubella?
Health-Related Behaviors	**Tobacco use:** • Do you smoke? How many cigarettes per day? How long have you smoked? How much have you have smoked in the past? • Besides tobacco, what do you smoke? • Do you chew tobacco? **Alcohol use:** • How often do you have a drink containing alcohol? How many drinks do you have on a typical day? How many per week? • Have you ever had a problem fulfilling work, social, or school obligations because of alcohol use? • Have you ever sought treatment for alcohol-related problems? **Drug use:** • Do you use any recreational or street drugs we haven't covered in earlier questions? Any prescription drugs or medications that were not prescribed to you? • If so, what drugs and how do you use them (inject, smoke, inhale, etc.)? **Drug use (continued):** • How often do you use substances? • Have you shared drug-use equipment with another person? • What pain relievers do you use on a regular basis? • Are you interested in treatment for alcohol or drug use? • Have you ever sought treatment? **Exercise:** • What kind of exercise do you participate in? How frequently? **Diet:** • What do you eat during a typical day? • Do you consume raw (unpasteurized) milk, raw eggs, raw or rare meat, deli meats, soft cheeses, or raw fish? • How much water do you drink during a typical day? • What is your source of water? • How much caffeine do you drink during a typical day?

Category/Topic to Cover	Sample Questions
Sensitive Sexual and Gender History Questions	
Gender Identity	• Do you consider yourself male or female? • Have you had or considered treatment for sex change? • Are you presently taking hormone therapy? • Have you had hormone therapy in the past? • Have you had any gender confirmation (sex reassignment) surgery?
General Sexual	• Do you have sex with men, women, or both? • In the past, have you had sex with men, women, or both? • In the past 2 months, how many sex partners have you had? • In the past 12 months, how many sex partners have you had?
Sexual Practices	• Do you have anal sex? Vaginal? Oral? • How do you protect yourself from sexually transmitted diseases, or HIV reinfection? • For men who have sex with men: • Are you the receptive or insertive partner, or both? • How often do you use alcohol or drugs before or during sex?
HIV Prevention	• Do you know the HIV status of your partner(s)? • Do you take measures to protect your partners from HIV? What measures? • In what situations do you or your partner use condoms or some other barrier? • Are there situations in which you do not use barrier protection?
Sex Trading	• Have you ever exchanged sex for food, shelter, drugs, or money?
Contraception	• What birth control measures do you use, if any? • How often do you use condoms or other latex barriers? • Do you have plans for you or your partner to become pregnant?
Family History	
	Do you have a family history of: • Heart disease? Heart attacks or strokes? • Cholesterol problems? Diabetes? • Cancer? • Mental health conditions (e.g., depression, bipolar disorder, anxiety, phobias)? • Addictions? Which family member(s), and what is their health status currently?
Social History	
Relationship Situation	• What is your relationship status (single, married, partnered, divorced, widowed)? • Do you have children? • Does your partner (and/or children) know about your HIV status?
Living Situation	• Do you live alone or with others? With whom? • How long have you lived in your residence?
Support System	• Who knows about your HIV status? • Which individual has been the most supportive since your HIV diagnosis? • Who has been the least supportive? • Have you used any community services such as support groups?

Category/Topic to Cover	Sample Questions
Social History (continued)	
Employment	• Are you currently employed? • Where do you work? • Describe your job task(s). • What setting do you work in on a daily basis? • Does your employer provide health insurance? • Does your employer know of your HIV status? • If on disability: How long have you been on disability? • What medical condition has made you disabled?
Incarceration History	• Have you ever been incarcerated? When was the last time?
Pets	• What kind of pets do you have, and who cleans up after them?
Travel	• Where have you traveled outside the United States? • When did travel take place?
Mental Health	
Coping	• How do you handle your problems/stresses? • What do you do to relax?
History	• Have ever been diagnosed with depression, anxiety, panic, bipolar disorder, schizophrenia, etc.? • Have you taken or are you taking any medications for these conditions? • Are you seeing a therapist or mental health professional? • Have you had any previous counseling or mental health problems? • Have you ever been hospitalized for a psychiatric condition? • Have you ever thought about hurting yourself? (If yes, probe for previous suicide attempts: Are you feeling that way now?) (See chapter *Suicide Risk* and prepare for immediate referral if necessary.)
Violence	• Have you ever been sexually abused, assaulted, or raped? • Has an intimate partner ever forced you to do something you did not want to do? • Has a partner, family member, or other person ever physically hurt you? • Have you lived in any situation with physical violence or intimidation? • When has this occurred? • Are you afraid for your safety now? • (If yes) Did you seek legal help, therapy, or other type of assistance?
Childhood Trauma	• Was there any alcoholism or drug abuse in your household when you were a child? • Did you experience or observe violence; physical, sexual, or emotional abuse; or neglect?

Review of Systems

For each positive answer, ask about location, characteristics, duration of symptoms, exacerbating and alleviating factors, previous diagnostic workup, and treatments tried.	
General	• Do you ever wake up feeling tired?
Fever	• Do you have fevers? How high, and for how long? How often?
Night Sweats	• Do you ever sweat so much at night that it soaks your sheets and nightclothes?
Anorexia	• How is your appetite?
Weight	• What was your weight 1 year ago? • What is a normal weight for you? • Have you lost or gained weight unintentionally?
Body Changes	• Have you noticed any changes in the shape of your body (describe)? For example, has there been an increase in your waist, collar, or breast size or a decrease in your arm, leg, or buttocks size? • Have you noticed increased visibility of veins in your arms and legs? • Have you noticed thinning of your face, especially around the cheeks?
Head, Ears, Eyes, Nose, and Throat	
Vision	• Have you noticed any changes in your vision, especially blurred vision or vision loss, double vision, new "floaters" or flashes of light? • Have you noticed this problem in one or both eyes? • When did you first notice these changes?
Mouth, Ears, Nose, Throat	• Have you noticed any white spots in your mouth or a white coating on your tongue (thrush, oral hairy leukoplakia)? • Do you ever get sores in your mouth or the back of your throat? Gum problems? • Any nosebleeds? • Do you ever experience hearing loss, ringing in your ears, or ear pain?
Cardiovascular	
Cardiac	• Any chest pain or pressure? Palpitations? • Any shortness of breath during activities or while you are lying down? • How far can you walk or run before you get short of breath? • Any swelling in your feet or legs?
Pulmonary	
Cough	• Do you have a cough? • Can you describe it? Dry or productive, amount, color, odor, presence of blood in sputum? When is it the worst?
Dyspnea	• Do you ever feel short of breath? • Does that happen when you are sitting still, lying down, or moving around? • How severe is your shortness of breath? • What does it prevent you from doing? • Do you ever wheeze??

Gastrointestinal	
Dysphagia	• Do you have any problems with food sticking in your throat or being difficult to swallow? • Do you gag or get nauseated when trying to eat? • Do you notice it is easier to swallow liquids or solids? • Do you have difficulty swallowing pills?
Odynophagia	• Do you have pain in your throat, esophagus, or behind your breastbone when you swallow?
Dyspepsia/Reflux	• Do you ever have heartburn (or a burning feeling rising from the stomach to behind the breastbone)? • When does it happen – after eating, lying down, on an empty stomach? • Do you get the taste of stomach acid in your mouth?
Nausea/Vomiting	• Do you have nausea or vomiting? • When? Are there specific things that cause this?
Diarrhea	• Do you have diarrhea, or more than 3-5 unformed stools a day? • Stool characteristics: bloody, pus, mucus? • Pain or cramping with diarrhea? Tenesmus?
Bowel Habits	• How frequently do you have bowel movements? • Do you have problems with constipation, blood in the stools, or other? • Do you have problems with flatulence or belching after eating?
Genitourinary	
Genital	• Do you have any lesions or sores on your genital area now, or have you in the past? • Have you ever had genital herpes? If yes, how often do you have outbreaks? • When was the most recent outbreak?
Women	• Have you had any lower abdominal pain? • Have you noticed a vaginal discharge or odor? • Do you have any burning or pain on urination? • Frequent urination? • Do you lose control of your urine or have problems getting to the bathroom before you start to urinate?
Men	• Have you noticed any swelling or testicular pain? • Do you have difficulty starting your stream of urine? • Are you getting up at night to urinate? • Have you had burning or pain on urination? • Do you lose control of your urine or have problems getting to the bathroom before you start to urinate? • Do you have any difficulty developing or maintaining an erection? • Any discharge from your penis?

Musculoskeletal	
	• Do you have any muscle aches or pains? Joint pain or swelling? • Back pain? • Have you ever broken any bones? • Do you have chronic pain? • Describe the pain – location, duration, rating (scale of 1-10), alleviating factors.
Skin	
Skin Lesions	• Have you noticed any rash or skin problems? If so, where? • Have you noticed any new moles, bruises, or bumps on your skin? • Do you have any moles that have changed shape, size, or color?
Tinea	• Do you have fungal infections on your skin, especially groin, fingernails, toenails, or feet?
Folliculitis	• Do you have any itchy bumps on your face, back, or chest?
Seborrhea	• Do you have flaking or itching on your skin or scalp?
Neurologic	
Headache	• How often do you get headaches? • Describe the headaches – location, timing, duration, alleviating or aggravating factors. • Do they cause nausea or vomiting? • Does sensitivity to light lead to headaches?
Neuropathy	• Do you have any numbness, tingling, burning, or pain in your hands or feet?
Weakness	• Do you have or have you had any weakness in your arms or legs?
Gait	• Have you noticed any changes in the way you walk?
Memory	• Do you have difficulty with your memory or ability to concentrate? If so, describe.
Seizures	• Have you ever had a seizure or "fit"? • If so, describe the seizure – When? How long did it last? Did you experience loss of consciousness? Did you receive medical care?
Endocrine	
Diabetes	• Have you had any increase in thirst, hunger, or urination?
Thyroid	• Have you noticed changes in your energy level? • Do you have intolerance to heat or cold? • Have you noticed changes in your hair (thinning, coarse texture)?
Sex Steroids	• Have you noticed any changes in your libido? In your energy level, mood?
Hematologic/Lymphatic	
Adenopathy	• Do you have swollen glands? • If so, describe – location, pain, size.
Bruising or Bleeding	• Have you noticed easy bruising or prolonged bleeding after injury? • Nosebleeds or bleeding gums?

Psychiatric	
Mood	• Depression screening: Have you experienced a decrease in your interest or pleasure in your activities? Have you felt depressed, down, or hopeless? • Do you feel more angry, sad, depressed, numb, irritable, or anxious than usual? • Have any major life events have occurred to cause you to feel sad or depressed? • When did these events occur?
Sleep	• How is your sleep? • How many hours do you sleep each night? • What is your sleeping schedule – time to bed and time to rise? • Do you take naps?

HIV Research

Sample Questions	
	• Have you participated in any research protocols? What studies, and when? • Would you be interested in participating in research studies (if available)?

O: Objective

- Conduct a physical examination, focusing on subjective findings elicited in the history. (See chapter *Initial Physical Examination*.) Note: If significant time has elapsed between the review of symptoms (ROS) and the physical examination, perform another ROS.

A/P: Assessment and Plan

- Arrange for baseline/intake laboratory work. (See chapter *Initial and Interim Laboratory and Other Tests*.)
- Compose a problem list. Initiate a medication list (if appropriate).
- Refer the patient to social services, mental health care, local health department partner services, community and other resources, or other clinic services as needed.

During the current visit or a future visit:

- Perform immunizations for pneumonia (Pneumovax), influenza (as appropriate), and other immunizations as indicated. (See chapter *Immunizations for HIV-Infected Adults and Adolescents*.)
- Provide counseling on prevention of HIV transmission (e.g., safer sex and injection practices), as appropriate. See chapter *Preventing HIV Transmission/Prevention with Positives*.

Patient Education

A very important aspect of caring for HIV-infected individuals is educating patients about HIV infection, including goals of care and ways of achieving those goals.

Review the following with each patient:

HIV disease

- Disease course
- Significance of CD4 cell count and HIV viral load
- Possible treatment approaches, including initial discussion about the importance of ART for the patient's own health and for reducing risk of HIV transmission
- Disclosure (e.g., whom the patient may need to tell about HIV status, relevant legal requirements, approaches to disclosure)

HIV transmission prevention and risk reduction for HIV-infected individuals

(see chapter *Preventing HIV Transmission/ Prevention with Positives*)

- Strategies to prevent transmission of HIV to uninfected partners and to prevent acquisition of sexually transmitted diseases, hepatitis, and other infections
- Safer-sex approaches, including the use of condoms or other latex barriers during sexual contacts
- Safer use of recreational drugs

Nutrition

- Maintaining a healthy weight
- Nutritional support resources, if appropriate
- Importance of including a nutritionist in medical care

Mental health

- Stress reduction
- Rest and exercise to enhance a healthy mental state

Adherence

- Importance of keeping medical appointments
- Need for adhering to any medication regimen and the consequences of missed HIV medication doses

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Initial Physical Examination

Background

Many of the conditions that put immunocompromised patients at risk of disease can be detected early, by means of a thorough history and physical evaluation.

HRSA HAB Performance Measures

Percentage of female patients with a diagnosis of HIV who have a **Pap screening** in the measurement year

(Adult and Adolescent measure)

S: Subjective

See chapter *Initial History.*

O: Objective

Assess the patient's general appearance, affect and demeanor in answering questions, body language, and other relevant characteristics. Measure vital signs; perform a physical examination.

Table 1. Vital Signs
(These measurements establish a baseline against which future measurements can be compared.)

Vital Sign	Recommendation/Notes
• Height	• Should be measured at baseline and annually.
• Weight	• Record at each visit.
• Temperature	• Record at each visit.
• Blood pressure	• Record at each visit. The BP cuff size should be appropriate for the patient's arm circumference.
• Heart rate	• Record at each visit.
• Respiratory rate	• Record at each visit.
• Oxygen saturation	• Record at each visit.
• Waist, hip circumferences	• Waist and hip circumference should be measured at baseline for comparison in case the patient later develops obesity or lipoaccumulation related to antiretroviral therapy (ART); repeat as indicated. **Abdominal circumference:** >102 cm (39″) in men = abdominal obesity >88 cm (35″) in women = abdominal obesity **Waist-hip ratios:** >0.95 in men = increased risk of coronary heart disease (CHD) >0.85 in women = increased risk of CHD

Body mass index (BMI)	BMI can be helpful in assessing underweight or overweight conditions, HIV/AIDS-related weight loss, and ART-related weight gain. Perform at baseline and upon changes in weight. **BMI calculation:** $\frac{\text{(weight in pounds)}}{\text{(height in inches) x (height in inches)}}$ x 703 **or,** $\frac{\text{(weight in kilograms)}}{\text{(height in meters) x (height in meters)}}$ **BMI:** <18.5 = underweight 18.5-24.9 = normal range 25-29.9 = overweight ≥30 = obese

Table 2. Physical Examination

Regions	Recommendation/Notes
General	• State of nourishment, physical appearance, well or ill appearing
Eyes	• Examine visual acuity by Snellen chart, visual fields by confrontation. • Test extraocular movements and pupillary size and reactivity. • Perform funduscopic examination, with or without mydriatics. Note any retinal lesions, white or yellow retinal discoloration, infiltrates, or hemorrhages (could indicate cytomegalovirus retinitis, retinal necrosis, or ocular toxoplasmosis). • Referral to ophthalmologist for retinal examination every 6 months if the CD4 count is <50 cells/μL. • Refer immediately if the patient has retinal lesions or new visual disturbances.
Ears/Nose	• Examine ear canals and tympanic membranes. • Visualize nasal turbinates. • Palpate frontal and maxillary facial sinuses.

Oral Cavity	• Good lighting is essential for this examination.
	• Examine:
	  • Gingiva and teeth (note loss of teeth, decay, or inflammation)
	  • Mucosal surfaces (with dentures removed) (note any lesions or discolorations)
	  • Posterior tongue
	  • Tonsils (note absence or presence; any abnormality in tonsil size)
	  • Pharynx (note lesions or exudate)
	• Refer to oral health specialist for examination.

Endocrine	• Check thyroid for enlargement, tenderness, nodules, and asymmetry.
Lymph Nodes	• Document site and characteristics of each palpable node. **Node Sites:** • Posterior cervical chain • Anterior cervical chain • Submandibular • Supraclavicular • Submental • Axillary • Epitrochlear • Inguinal • Femoral **Characteristics:** • Size (two dimensions, in millimeters) • Consistency (hard, fluctuant, soft) • Tenderness • Mobility • Definition (discrete, matted) • Symmetry

Table 2. Physical Examination (continued)

Regions	Recommendation/Notes
Lungs	• Inspect, auscultate, and percuss. • Note any abnormal sounds including crackles or wheezes (e.g., signs of infections, asthma, and congestive heart failure). • Note any absence of air movement (e.g., pneumothorax, pleural effusion).
Heart	• Examine for jugular venous distention (JVD). • Palpate for point of maximal impulse (PMI). • Note rate and rhythm, heart sounds, murmurs, extra heart sounds.
Breasts	• Palpate for breast masses in both men and women. • Check for symmetry, nipple discharge, dimpling, and masses.
Abdomen	• View: examine for distention, obesity, undernutrition, vascular prominence, petechiae. • Auscultate; note bowel sounds. • Percuss; record liver size. • Palpate for hepatomegaly, splenomegaly, masses, tenderness or rebound tenderness.
Genitals / Rectum	• Inspect the genitalia and perirectal area; note lesions, warts, etc. • Look for discharges, ulcerative lesions, vesicles, or crusted lesions; take samples for diagnostic studies (e.g., for chlamydia, gonorrhea, herpes simplex virus, syphilis, chancroid, as appropriate).
Female Patients	• Perform speculum examination; note any lesions on vaginal walls or cervix. • Obtain a Papanicolaou (Pap) test. • Obtain endocervical swab for gonorrhea and chlamydia, and a posterior pool swab for wet mount evaluation for trichomoniasis, candidiasis, and bacterial vaginosis. • Consider anal Pap test, especially if the patient has a history of an abnormal cervical Pap test or genital warts (perform before introduction of lubricant).* • Bimanual examination; note size of uterus and ovaries, shape, and any tenderness or pelvic pain. • Rectal examination (e.g., for anorectal lesions, warts) and evaluation of posterior uterine abnormalities.
Male Patients	• Examine external genitalia; note whether patient is circumcised; note any lesions, discharge, or other abnormalities, as above. Perform testicular examination for masses, tenderness. • Consider anal Pap test (perform before introduction of lubricant).* • Digital rectal examination to evaluate rectal tone, discharge or tenderness, masses, or lesions; perform prostate examination if appropriate.
Extremities / Musculoskeletal	• Joints; note any enlargement, swelling, or tenderness. • Muscles; for the major muscle groups, evaluate muscle bulk (normal or decreased), tenderness, or weakness. • Look for evidence of peripheral fat atrophy. • Consider measuring baseline arm, thigh, and chest circumferences for later comparison. • Note nail changes (clubbing, cyanosis, thickening, discoloration). • Assess for pedal or leg edema.
Habitus	• Look carefully for signs of lipoatrophy or lipohypertrophy, wasting, or obesity. • Subcutaneous fat loss (face, extremities, buttocks). • Central fat accumulation (neck, dorsocervical area, breasts, abdomen).

Table 2. Physical Examination (continued)

Regions	Recommendation/Notes
Skin	• Examine the entire body, including scalp, axillae, palms, soles of feet, and pubic and perianal areas. • Describe all lesions (e.g., size, borders, color, symmetry/asymmetry, distribution, raised/flat, induration, and encrustation). • Note evidence of folliculitis, seborrheic dermatitis, psoriasis, Kaposi sarcoma, fungal infections, prurigo nodularis, etc. • Note any tattoos or body piercings.
Neurologic	**Assess the following:** • Mental status, including orientation, registration, recent and remote memory, and ability to calculate (serial subtraction) • Cranial nerves • Peripheral sensory examination, including pinprick, temperature, and vibratory stimuli • Extremity strength and gait to discern myopathy, neuropathy, and cerebellar disease • Fine motor skills such as rapid alternating movements (often abnormal in dementia) • Deep tendon and plantar reflexes
Psychiatric	• Assess the patient's general mood (e.g., depressed, anxious, hypertalkative). • Note verbal content (e.g., whether the patient answers questions appropriately; unusual or odd content). • Note inappropriate or unusual behavior, such as extremes of denial, hostility, or compulsiveness. • See section *Neuropsychiatric Disorders* for more complete information on common pathologies. • If the possibility of an emergency situation exists (e.g., potential suicide or violence), refer to crisis mental health services for immediate evaluation.

* Anal Pap test: Consider this test if follow-up evaluation of an abnormal Pap test result is available. Rates of anal dysplasia and anal cancer are higher in HIV-infected women and men than in HIV-uninfected individuals; see chapter *Anal Dysplasia*.

A/P: Assessment and Plan

After completing the initial history and physical examination, do the following:

- Enter the information garnered through the history and physical examination into the patient's chart or database.
- Continue to develop the problem list, assessment, and plan for patient care.
- Complete follow-up or laboratory studies suggested by the history and physical examination. (See chapter *Initial and Interim Laboratory and Other Tests*.)
- Prescribe opportunistic infection prophylaxis as appropriate. (See chapter *Opportunistic Infection Prophylaxis*.)
- Arrange for any appropriate vaccinations. (See chapter *Immunizations for HIV-Infected Adults and Adolescents*.)
- Refer for dental, nutrition, and social services, as well as case management and mental health care, as appropriate.
- Refer for any additional specialty care needs identified in the history or physical examination.
- Make follow-up appointment with health care provider.
- Answer the patient's questions.

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Initial and Interim Laboratory and Other Tests

Background

This chapter discusses the laboratory tests and other monitoring that should be performed for HIV-infected individuals. This involves testing for staging HIV infection, screening for comorbidities, establishing baselines before treatment with antiretroviral (ARV) medications, and monitoring responses to ARV therapy (ART).

Note that documentation of HIV infection by laboratory testing is essential for each patient, and it should be included in the patient's chart.

HRSA HAB Performance Measures

Percentage of patients, aged 6 months and older with a diagnosis of HIV/AIDS, with at least two **CD4 cell counts or percentages** performed during the measurement year at least 3 months apart

(All-Age measure)

Percentage of patients, regardless of age, with a diagnosis of HIV who had an **HIV drug resistance test** performed before initiation of HIV antiretroviral therapy if therapy started during the measurement year

(All-Age measure)

Percentage of patients, regardless of age, with a diagnosis of HIV with a **viral load test** performed at least every 6 months during the measurement year

(All-Age measure)

Percentage of patients aged 3 months and older with a diagnosis of HIV/AIDS, for whom there was documentation that a **tuberculosis screening** test was performed and results interpreted (for tuberculin skin tests) at lease once since the diagnosis of HIV infection

(All-Age measure)

Percentage of patients for whom **hepatitis C screening** was performed at least once since the diagnosis of HIV

(Adult and Adolescent measure)

Percentage of patients, regardless of age, for whom **hepatitis B screening** was performed at least once since the diagnosis of HIV/AIDS or for whom there is documented infection or immunity

(Adult and Adolescent measure)

Percentage of patients, regardless of age, with a diagnosis of HIV who were prescribed HIV antiretroviral therapy and who had a fasting **lipid panel** during the measurement year

(All-Age measure)

Percentage of adult patients with a diagnosis of HIV who had a **test for syphilis** performed within the measurement year

(Adult and Adolescent measure)

Percentage of patients with a diagnosis of HIV at risk of sexually transmitted infections who had a **test for gonorrhea** within the measurement year

(Adult and Adolescent measure)

Percentage of female patients with a diagnosis of HIV who have a **Pap screening** in the measurement year

(Adult and Adolescent measure)

O: Objective

Table 1. Laboratory Evaluations for HIV-Infected Patients

Test	Rationale	Result	Frequency and Comments
HIV Confirmation, Staging and ART Monitoring			
HIV Antibody	• Confirm diagnosis, if not documented previously		• At entry to care
CD4 Count	• For HIV staging and prognosis • Helps guide urgency of ART initiation • Indicates risk of opportunistic illnesses and guides initiation of prophylaxis against opportunistic infections • Used to monitor immune reconstitution during ART	• Reported in cells/µL	• Perform at baseline (twice). • Repeat every 3-6 months for stable patients on or off ART; may repeat every 6-12 months if stable and suppressed viral load. • Repeat if results are inconsistent with the clinical picture or with previous trends. • See chapter *CD4 and Viral Load Monitoring*.
CD4 Percentage	• Used in addition to the absolute CD4 count for monitoring trends; may be discrepant with absolute CD4 • *Pneumocystis* pneumonia prophylaxis is indicated for CD4 percentage <14% regardless of absolute count	**CD4 Count (cells/µL)** / **Expected CD4 Percentage** >500 / >29% 200-500 / 14%-28% <200 / <14%	• Usually obtained with absolute CD4 count.
Quantitative Plasma HIV RNA (HIV Viral Load)	• Estimates level of HIV replication • Used to monitor effect of ART • May be used to identify acute HIV infection; has high sensitivity in setting of acute infection, when antibody may be negative	• Reported in copies/mL • In untreated patients, detectable (with rare exceptions) and measured to the upper limit of detection (usually >500,000 copies/mL) • For patients taking ART, ideally suppressed to undetectable levels (usually <40 or <75 copies/mL)	• Perform at baseline (twice). • For patients on new or modified ART regimen: perform 2-8 weeks after initiation or change in ART, then every 4-8 weeks until viral load is suppressed. • For patients on stable ART: perform every 3-4 months (if stable and viral load suppressed >2-3 years, consider every 6 months). • For patients not taking ART: perform every 3-6 months; more frequently if CD4 count is low. *Factors that may temporarily increase viral load:* • Immunizations • Active infections

Test	Rationale	Result	Frequency and Comments
Predicting Safety and Efficacy of ARVs			
Drug Resistance Testing (Genotype, Phenotype)	• To assess whether the patient's HIV virus is likely to be resistant to specific ARV medications	• Genotype: detects specific mutations to ARV medications • Phenotype: measures HIV viral replication in the presence of ARVs	• Genotype is recommended for all ARV-naive patients. For greatest accuracy, should be done as early as possible in the course of HIV infection. • Acute or primary infection: recommended (genotype). • Chronic infection and treatment naive: recommended before initiation of ART. (genotype). If resistance test was performed at entry, consider repeat testing. • Pregnancy: recommended before initiation of ART (repeat if done earlier) or for patients with detectable HIV RNA while taking ART. • Virologic failure: recommended. • Obtain genotype for integrase mutations if integrase inhibitor resistance is a concern. (See chapter *Resistance Testing* for more information.)
Coreceptor Tropism Test	• Determine coreceptor tropism	• If CXCR4-tropic (or dual/mixed tropic) virus is detected, CCR5 antagonist is not likely to be effective and should not be used	• Test before making decision to treat with CCR5 antagonist, or if virologic failure occurs while on a CCR5 antagonist (phenotypic assay preferred). • For standard assay, HIV RNA must be >1,000 copies/mL (a proviral DNA test is available for samples with HIV RNA below limits of detection; has not been clinically validated).
HLA-B*5701	• Establish risk of hypersensitivity reaction to abacavir	• If positive, high risk of abacavir hypersensitivity reaction; abacavir should not be used	• Test before starting treatment with abacavir.

Test	Rationale	Result	Frequency and Comments
Baseline and Subsequent Hematologic, Renal, Hepatic, and Metabolic Screening			
Complete Blood Count (CBC) with Differential and Platelets	• Detects anemia, thrombocytopenia, leukopenia	• Normal	• Perform at baseline. • Repeat every 3-6 months.
		• Abnormal	• Requires follow-up evaluation as indicated; may influence choice of ARVs. • Repeat more frequently if the patient's results are abnormal or if the patient is taking bone marrow suppressive drugs (including zidovudine).
Chemistry Profile **Electrolytes, Creatinine, eGFR (Estimated Glomerular Filtration Rate), Blood Urea Nitrogen** **Liver Transaminases, Bilirubin (Total and Direct)**	• Detects electrolyte abnormalities, kidney disease, liver disease	• Normal/abnormal	• Perform at baseline; before starting ART. • Repeat 2-8 weeks after starting or modifying ART, then every 3-6 months if stable. • May influence ARV selection. • May be useful in monitoring drug toxicities. • Abnormalities should prompt evaluation of cause.
Urinalysis with Urine Protein and Creatinine	• Used to screen for kidney disease	• Normal/abnormal	Screen at baseline and before initiation or change of ART regimen. Repeat every 12 months. Repeat every 6 months for patients on tenofovir, more frequently if indicated. Abnormalities should prompt evaluation of cause. See chapter *Renal Disease*.

Test	Rationale	Result	Frequency and Comments
Baseline and Subsequent Hematologic, Renal, Hepatic, and Metabolic Screening (continued)			
Lipid Profile (Total Cholesterol, LDL, HDL, Triglycerides); fasting	• Detects dyslipidemia, identifies risk factors for cardiovascular disease	• Normal/abnormal	• Baseline; before starting ART. • Consider repeating 4-8 weeks months after starting or changing ART. • Repeat annually if normal (on or off ART), or more frequently (e.g., every 6 months) if abnormal or risk of cardiovascular disease. • May influence ARV selection. • May be useful in monitoring drug toxicities. See chapter *Dyslipidemia*.
Glucose (preferably fasting) or hemoglobin A1C	• Detects diabetes and hyperglycemia	• Normal/abnormal	• Baseline; before starting ART. • Repeat every 3-6 months if abnormal, every 6 months if normal on ART; every 12 months if normal and not on ART. • May influence ARV selection. • May be useful in monitoring drug toxicities. See chapter *Insulin Resistance, Hyperglycemia, and Diabetes on Antiretroviral Therapy*.
Hepatitis A, B, and C Screening			
Hepatitis A Serology			
Hepatitis A Antibody (HAV IgG)	• Screen for immunity to hepatitis A; vaccinate those not immune	• Negative	• Offer hepatitis A vaccine if indicated. (See chapter *Immunizations for HIV-Infected Adults and Adolescents*.)
		• Positive	• Immune; no vaccine necessary.

Test	Rationale	Result	Frequency and Comments
Hepatitis A, B, and C Screening (continued)			
Hepatitis B Serology (See chapter *Hepatitis B Infection*.)			
Hepatitis B Surface Antigen (HBsAg)	• Indicates active hepatitis B	• sAg negative	• Most likely, no chronic infection (may be falsely negative). • Vaccinate if HBsAb negative (not immune).
		• sAg positive	• Indicates chronic or acute hepatitis B infection; requires further evaluation (check HBV DNA). (See chapter *Hepatitis B Infection*.)
Hepatitis B Core Antibody (Anti-HBc, IgG)	• Indicates past infection or ongoing infection	• Anti-HBc negative	• The patient most likely has not been infected with hepatitis B; consider vaccination if HBsAb negative and HBsAg negative.
		• Anti-HBc positive	• The patient most likely has been infected with hepatitis B; this test alone does not distinguish past exposure and active infection. • In rare cases, may be falsely negative in some patients with chronic infection. • If sAb negative and sAg negative, check HBV DNA to rule out active infection; vaccinate if HBV DNA is not detected. • If sAb is positive, patient is immune.
Hepatitis B Surface Antibody (Anti-HBs)	• Indicates immunity status	• Anti-HBs negative	• The patient is not immune to hepatitis B; consider vaccination, unless patient has active hepatitis (sAg positive or HBV DNA positive).
		• Anti-HBs positive	• The patient is immune to hepatitis B either by previous infection or by immunization; may be negative in acute hepatitis B infection.

Test	Rationale	Result	Frequency and Comments
Hepatitis A, B, and C Screening (continued)			
Hepatitis C Serology (See chapter *Hepatitis C Infection*.)			
Hepatitis C Antibody (HCV IgG)	• Hepatitis C status	• HCV negative	• Patient is not infected with hepatitis C. • Screen at baseline; consider annual screening for high-risk patients, and if clinically indicated.
		• HCV positive	• Patient has chronic hepatitis C infection or past infection with spontaneous clearance (no protective immunity); confirm positive results with HCV RNA.
Other Opportunistic Infection Screening Tests			
***Toxoplasma gondii* IgG**	• Detects past exposure; if positive, patient has increased risk of developing CNS toxoplasmosis if CD4 count <100 cells/µL	• Negative	• Repeat if patient becomes symptomatic or when CD4 count drops to ≤100 cells/µL.
		• Positive	• Note as baseline information. • Start toxoplasmosis prophylaxis if CD4 count drops to ≤100 cells/µL.
Tuberculosis (TB) Screening **TST (Tuberculin Skin Test) or IGRA (Interferon-Gamma Release Assay) (if no history of TB or positive TB screening test in the past)**	• Detects latent TB infection (LTBI)	• Normal	• Repeat every 12 months if high risk of repeated or ongoing exposure. • Repeat if CD4 count was <200 cells/µL on initial test but increases to >200 cells/µL on ART.
		• Abnormal (TST induration ≥5 mm or positive IGRA)	• Evaluate for active TB. (See chapter *Latent Tuberculosis Infection*.)
Chest X-Ray (if pulmonary symptoms are present or positive LTBI test)	• Detects latent or active diseases	• Normal	• Repeat as indicated for pulmonary symptoms or positive LTBI test.
		• Abnormal	• Evaluate for TB, PCP, or other pathology.

Test	Rationale	Result	Frequency and Comments
Other Opportunistic Infection Screening Tests (continued)			
Papanicolaou Test (cervical for women; consider anal for women and men)	• Detects abnormal cell changes, dysplasia	• Normal	• Cervical: Repeat in 6 months, then annually if negative on two tests and no ongoing risk factors. • Anal: No national guidelines; consider screen at baseline. Follow-up interval has not been determined; consider same as in cervical Pap screening.
		• Abnormal	• Perform workup, treat (see chapters *Cervical Dysplasia* and *Anal Dysplasia*) and follow up as indicated by condition.
Pregnancy Screening			
Pregnancy Test	• Indicates pregnancy status	• Positive/negative	• Perform before starting efavirenz (given risk of teratogenicity). • If positive, consider ART initiation; avoid efavirenz in first trimester (see chapters *Reducing Perinatal HIV Transmission* and *Care of HIV-Infected Pregnant Women*).
Sexually Transmitted Disease Testing			
Serum VDRL (Venereal Disease Research Laboratory) or RPR (Rapid Plasma Reagin) (some centers screen using a treponemal test)	• Screen for syphilis at least annually in sexually active persons who are at risk; for men who have sex with men (MSM) with multiple partners: every 3-6 months	• Negative/nonreactive	• Counsel about safer sex and avoiding STDs. • Repeat every 3-12 months, depending on risk factors.
		• Positive/reactive: confirm with treponemal test	• Treat patient; refer partner(s) for evaluation and treatment; counsel about safer sex. (See chapter *Syphilis*.) • Perform serial testing if monitoring active disease. (See chapter *Syphilis*.)

Test	Rationale	Result	Frequency and Comments
Women			
Gonorrhea (GC) and Chlamydia (CT) Testing	Screen for STDs in sexually active women at risk according to CDC and USPSTF guidelines; screen all ≤25 years of age at baseline and at least annually; more frequently if risk factors Screen all sites of possible exposures: • Pharynx (recommended for GC screening) • Cervix/vagina • Rectum	• Negative	• Counsel about safer sex and avoiding STDs. • Repeat every 6-12 months; more frequently if at high risk (e.g., adolescents).
		• Positive	• Treat patient; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex. • Retest at 3 months.
Trichomoniasis Testing	• Wet mount (insensitive), culture or nucleic acid amplification test (NAAT) of vaginal secretions • Screen HIV-infected women annually	• Negative	• Counsel about safer sex and avoiding STDs. • Repeat every 12 months.
		• Positive	• Treat patient; refer partner(s) for evaluation and treatment; counsel about safer sex. • Retest at 3 months.
Men			

Gonorrhea (GC) and Chlamydia (CT) Testing	• Screen for STDs in sexually active men who are at risk according to CDC guidelines, especially MSM
	• Screen all MSM at baseline and at least annually; frequency of subsequent testing depends on risk factors
	• Screen sites of possible exposures:
	  • Pharynx, if receptive oral sex (recommended for GC screening)
	  • Rectum, if receptive anal sex
	  • Urethra for MSM, if insertive oral or anal sex
		• Negative	• Counsel about safer sex and avoiding STDs.
			• Retest every 3-12 months, depending on risk factors.

		• Positive	• Treat; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex. • Retest at 3 months.

Test	Rationale	Result	Frequency and Comments
Consider/Optional			
G6PD Level	• Prevent hemolytic reactions to certain medications by screening higher-risk patients (African, Mediterranean, Asian, Sephardic Jewish descent); some would recommend screening all patients	• Normal range	• No intervention is necessary beyond documentation.
		• Abnormal range	• Avoid oxidant drugs such as dapsone, primaquine, and sulfonamides, if possible.
Cytomegalovirus (CMV) Antibody (anti-CMV IgG) (for those at low risk of CMV, especially those who are not MSM or injection drug users)	• Detects exposure; may reveal future disease risk	• Negative	• Avoid exposure by practicing safer sex. • If blood transfusion is required, use CMV-negative or leukocyte-reduced blood.
		• Positive	• Be aware of disease risk in advanced HIV infection, when CD4 count is <50 cells/µL.
Varicella zoster (Varicella IgG) (for those without history of chickenpox or shingles)	• Detects exposure	• Negative	• Consider vaccination, if CD4 count is >200 cells/µL.
		• Positive	• No intervention is necessary.
Dilated Retinal Examination	• Detects CMV, ophthalmic toxoplasmosis, or HIV retinopathy	• Normal	• If CD4 count is >100 cells/µL, repeat annually. • If CD4 count is <50 cells/µL or symptoms of retinal changes are present, repeat every 6 months.
		• Abnormal	• Follow up immediately with ophthalmologist.

Patient Education

- Discuss safer sex (review specifics appropriate to the patient's sexual practices and infections) to prevent the patient's exposure to herpes, hepatitis B, hepatitis C, and other STDs, and to prevent the patient from exposing others to HIV or other pathogens. In addition, remind the patient that safer sex practices will limit the risk of reinfection with HIV. (See chapters *Preventing HIV Transmission/Prevention with Positives* and *Preventing Exposure to Opportunistic and Other Infections*.)
- If *Toxoplasma* IgG test result is negative, see chapter *Preventing Exposure to Opportunistic and Other Infections*.
- If CMV test result is negative, counsel the patient that CMV is shed in semen, vaginal and cervical secretions, saliva, and urine of infected people. Latex condoms will help reduce risk. For women considering childbearing, CMV should be avoided to prevent severe disease and even death of the neonate. (See chapter *Preventing Exposure to Opportunistic and Other Infections*.)
- For patients who are hepatitis C negative and are using injection drugs, offer referral to a drug treatment program or a clean needle exchange program. (See chapters *Preventing HIV Transmission/Prevention with Positives* and *Preventing Exposure to Opportunistic and Other Infections*.)

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Interim History and Physical Examination

Background

This chapter shows the suggested frequency and follow-up intervals of the history and physical examination for monitoring HIV-infected patients, as well as specific areas to assess in an ongoing manner. With this information, the clinician can track disease progression and formulate and maintain an appropriate care plan. Note that information gathered in the history or physical examination may indicate a need for additional directed explorations.

It is important to document new or ongoing symptoms and functional limitations at each visit. This information is particularly useful when outside agencies must determine the patient's disability status. (See chapter *Karnofsky Performance Scale*.)

See chapter *Initial and Interim Laboratory and Other Tests* for recommended screening tests.

HRSA HAB Performance Measures

Percentage of patients, regardless of age, with a diagnosis of HIV who had at least **one medical visit in each 6-month period** of the 24-month measurement period with a minimum of 60 days between medical visits

(Core measure)

Percentage of female patients with a diagnosis of HIV who have a **Pap screening** in the measurement yearr

(Adult and Adolescent measure)

Percentage of patients with a diagnosis of HIV who received **HIV risk counseling** in the measurement year

(Adult and Adolescent measure)

Percentage of new patients with a diagnosis of HIV who have been **screened for substance use** (alcohol and drugs) in the measurement year

(Adult and Adolescent measure)

Percentage of patients aged 12 years and older **screened for clinical depression** on the date of the encounter using an age-appropriate standardized depression screening tool AND, if positive, a follow-up plan is documented on the date of the positive screen

(Adult and Adolescent measure)

Table 1. History and Physical Examinations

History	Physical Examination
Every visit (at least every 3-4 months)	

• New symptoms
• Medications
  • HIV-related medications
  • Medications for other conditions
  • Over-the-counter medications
  • Herbs or vitamins
• Adherence to medications and clinical care visits
• Antiretroviral (ARV) doses missed in the past 3 days, in the past month
• Knowledge of HIV regimen
• HIV transmission risk behaviors and risk reduction methods
• Sexual history (risk factors for STDs)
• Mood
• Alcohol and recreational drug use
• Tobacco use
• Allergies
• Pain
• Social supports
• Housing
• Insurance
• Intimate partner violence
	• Vital signs (temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation)
	• Weight
	• General appearance and body habitus (including evaluation for lipodystrophy)
	• Skin
	• Oropharynx
	• Lymph nodes
	• Heart and lungs
	• Abdomen
	• Neurologic
	• Psychiatric (e.g., mood, affect, and attention)

Every 6 months	
As above	As above, plus: • Vision and funduscopic examination (if CD4 count <100 cells/µL) • Ears/nose
Every 6 months (twice), and, if both are normal, annually thereafter (see chapters *Cervical Dysplasia* and *Anal Dysplasia*)	
As above	• Women: pelvic examination; cervical Papanicolaou (Pap) test; consider anorectal examination, anal Pap test • Men: consider anal examination, anal Pap test
Annually	
Update initial history: HIV-related symptoms, hospitalizations, major illnesses, and family history	Complete physical to include: • Genitorectal examination • Testicular examination • Prostate examination • Breast examination

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HIV Classification: CDC and WHO Staging Systems

Background

HIV disease staging and classification systems are critical tools for tracking and monitoring the HIV epidemic and for providing clinicians and patients with important information about HIV disease stage and clinical management. Two major classification systems currently are in use: the U.S. Centers for Disease Control and Prevention (CDC) classification system and the World Health Organization (WHO) Clinical Staging and Disease Classification System.

The CDC disease staging system (most recently revised in 1993) assesses the severity of HIV disease by CD4 cell counts and by the presence of specific HIV-related conditions. The definition of AIDS includes all HIV-infected individuals with CD4 counts of <200 cells/μL (or CD4 percentage <14%) as well as those with certain HIV-related conditions and symptoms. Although the fine points of the classification system rarely are used in the routine clinical management of HIV-infected patients, a working knowledge of the staging criteria (in particular, the definition of AIDS) is useful in patient care. In addition, the CDC system is used in clinical and epidemiologic research.

In contrast to the CDC system, the WHO Clinical Staging and Disease Classification System (revised in 2007) can be used readily in resource-constrained settings without access to CD4 cell count measurements or other diagnostic and laboratory testing methods. The WHO system classifies HIV disease on the basis of clinical manifestations that can be recognized and treated by clinicians in diverse settings, including resource-constrained settings, and by clinicians with varying levels of HIV expertise and training.

S: Subjective

When a patient presents with a diagnosis of HIV infection, review the patient's history to elicit and document any HIV-related illnesses or symptoms (see chapter *Initial History*).

O: Objective

Perform a complete physical examination and appropriate laboratory studies (see chapters *Initial Physical Examination* and *Initial and Interim Laboratory and Other Tests*).

A: Assessment

Confirm HIV infection and perform staging.

P: Plan

Evaluate symptoms, history, physical examination results, and laboratory results, and make a staging classification according to the CDC or WHO criteria (see below).

CDC Classification System for HIV Infection

The CDC categorization of HIV/AIDS is based on the lowest documented CD4 cell count and on previously diagnosed HIV-related conditions (see Table 1). For example, if a patient had a condition that once met the criteria for category B but now is asymptomatic, the patient would remain in category B. Additionally, categorization is based on specific conditions, as indicated below. Patients in categories A3, B3, and C1-C3 are considered to have AIDS.

Table 1. CDC Classification System for HIV-Infected Adults and Adolescents

CD4 Cell Count Categories	Clinical Categories		
	A Asymptomatic, Acute HIV, or PGL	B* Symptomatic Conditions, not A or C	C# AIDS-Indicator Conditions
(1) ≥500 cells/μL	A1	B1	C1
(2) 200-499 cells/μL	A2	B2	C2
(3) <200 cells/μL	A3	B3	C3

Abbreviations: PGL = persistent generalized lymphadenopathy

* Category B Symptomatic Conditions

Category B symptomatic conditions are defined as symptomatic conditions occurring in an HIV-infected adolescent or adult that meet at least one of the following criteria:

- They are attributed to HIV infection or indicate a defect in cell-mediated immunity.
- They are considered to have a clinical course or management that is complicated by HIV infection.

Examples include, but are not limited to, the following:

- Bacillary angiomatosis
- Oropharyngeal candidiasis (thrush)
- Vulvovaginal candidiasis, persistent or resistant
- Pelvic inflammatory disease (PID)
- Cervical dysplasia (moderate or severe)/ cervical carcinoma in situ
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving two or more episodes or at least one dermatome
- Idiopathic thrombocytopenic purpura
- Constitutional symptoms, such as fever (>38.5°C) or diarrhea lasting >1 month
- Peripheral neuropathy

Category C AIDS-Indicator Conditions

- Bacterial pneumonia, recurrent (two or more episodes in 12 months)
- Candidiasis of the bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month in duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month in duration), or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1-month in duration)
- Kaposi sarcoma
- Lymphoma, Burkitt, immunoblastic, or primary central nervous system
- *Mycobacterium avium* complex (MAC) or *Mycobacterium kansasii*, disseminated or extrapulmonary

- *Mycobacterium tuberculosis*, pulmonary or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP)
- Progressive multifocal leukoencephalopathy (PML)
- *Salmonella* septicemia, recurrent (nontyphoid)
- Toxoplasmosis of brain
- Wasting syndrome caused by HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (two or more loose stools per day for ≥1 month) or chronic weakness and documented fever for ≥1 month

WHO Clinical Staging of HIV/AIDS and Case Definition

The clinical staging and case definition of HIV for resource-constrained settings were developed by the WHO in 1990 and revised in 2007. Staging is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS, and it does not require a CD4 cell count. This staging system is used in many countries to determine eligibility for antiretroviral therapy, particularly in settings in which CD4 testing is not available. Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS (see Table 2). These stages are defined by specific clinical conditions or symptoms. For the purpose of the WHO staging system, adolescents and adults are defined as individuals aged ≥15 years.

Table 2. WHO Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV Infection	
• Asymptomatic	• Acute retroviral syndrome
Clinical Stage 1	
• Asymptomatic	• Persistent generalized lymphadenopathy
Clinical Stage 2	
• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) • Herpes zoster	• Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruptions • Seborrheic dermatitis • Fungal nail infections
Clinical Stage 3	
• Unexplained severe weight loss (>10% of presumed or measured body weight) • Unexplained chronic diarrhea for >1 month • Unexplained persistent fever for >1 month (>37.6ºC, intermittent or constant) • Persistent oral candidiasis (thrush) • Oral hairy leukoplakia • Pulmonary tuberculosis (current)	• Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) • Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis • Unexplained anemia (hemoglobin <8 g/dL) • Neutropenia (neutrophils <500 cells/µL) • Chronic thrombocytopenia (platelets <50,000 cells/µL)

Clinical Stage 4	
• HIV wasting syndrome, as defined by the CDC (see Table 1, above) • *Pneumocystis* pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) • Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) • Extrapulmonary tuberculosis • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis • HIV encephalopathy • Cryptococcosis, extrapulmonary (including meningitis)	• Disseminated nontuberculosis mycobacteria infection • Progressive multifocal leukoencephalopathy • Candida of the trachea, bronchi, or lungs • Chronic cryptosporidiosis (with diarrhea) • Chronic isosporiasis • Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis) • Recurrent nontyphoidal *Salmonella* bacteremia • Lymphoma (cerebral or B-cell non-Hodgkin) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis • Symptomatic HIV-associated nephropathy • Symptomatic HIV-associated cardiomyopathy • Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

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CD4 and Viral Load Monitoring

Background

The CD4 cell count and HIV viral load (RNA level) are closely linked to HIV-related illness and mortality. They give prognostic information on HIV progression and on response to therapy.

HRSA HAB Performance Measures

Percentage of patients, aged 6 months and older with a diagnosis of HIV/AIDS, with at least two **CD4 cell counts or percentages** performed during the measurement year at least 3 months apart

(All-Age measure)

Percentage of patients, regardless of age, with a diagnosis of HIV with a **viral load test** performed at least every 6 months during the measurement year

(All-Age measure)

CD4 Monitoring

CD4 lymphocyte cells (also called T-cells or T-helper cells) are the primary targets of HIV. The CD4 count and the CD4 percentage mark the degree of immunocompromise. The CD4 count is the number of CD4 cells per microliter (μL) of blood. It is used to stage the patient's disease, determine the risk of opportunistic illnesses, assess prognosis, and guide decisions about the urgency of starting antiretroviral therapy (ART) (see chapters *Risk of HIV Progression/Indications for ART* and *Antiretroviral Therapy*). The CD4 percentage is the percentage of the lymphocyte population that is CD4+; it is measured directly by flow cytometry. A CD4 percentage of <14% is considered to correspond to the same degree of immunosuppression as an absolute CD4 count of <200 cells/μL. The absolute CD4 count is calculated from the CD4 cell percentage and the total white blood cell count.

The normal values for CD4 count vary considerably among different laboratories. The mean normal value for most laboratories is approximately 500-1,300 cells/μL. This calculated value is subject to more fluctuations than the CD4 cell percentage. Illness, vaccination, diurnal variation, laboratory error, and some medications can result in transient CD4 cell count changes, whereas the CD4 percentage remains more stable. Because CD4 counts may vary, treatment decisions generally should not be made on the basis of a single CD4 value. When results are inconsistent with previous trends, tests should be repeated, and treatment decisions usually should be based on two or more similar values. A change between two test results is considered significant if it is a 30% change in absolute CD4 count or 3 percentage point change in CD4 percentage.

In persons with untreated HIV infection, the CD4 count declines by approximately 50-80 cells/μL per year, on average. The pattern of decline may be slow and steady, or the CD4 count may level off for an extended period of time (as in long-term nonprogressors) and then decrease. Although it takes an average of 10 years for a newly infected person to progress to AIDS, there is great variation among patients. For some patients, disease progression occurs within a year or two. For others, it takes more than 20 years, and a small number of patients appear to maintain high CD4 counts and undetectable HIV RNA levels without ART (aviremic or "elite" controllers).

Among asymptomatic individuals, the CD4 count until recent years was the major factor that guided the decision to initiate therapy, and it remains so in resource-limited areas of

the world. Current United States guidelines recommend treatment for all HIV-infected individuals regardless of CD4 count. The CD4 count, though, can help clinicians and patients decide how quickly to start therapy. Clinical status, viral load, pregnancy, comorbidities, patient adherence to medications, and risk of HIV transmission are among the other factors that should be taken into consideration (see chapters *Risk of HIV Progression/Indications for ART* and *Antiretroviral Therapy*).

Prophylaxis against opportunistic infections is based on CD4 count, and sometimes on CD4 percentage. For example, a CD4 count of <200 cells/μL or a CD4 percentage of <14% is an indication for prophylaxis against *Pneumocystis jiroveci* pneumonia; a CD4 count of <50 cells/μL is an indication for prophylaxis against *Mycobacterium avium* complex. (See chapters *Opportunistic Infection Prophylaxis* and *Risk of HIV Progression/ Indications for ART*.) The CD4 count also guides decision making in determining when to stop prophylaxis against opportunistic infections with patients whose CD4 counts rise in response to ART.

Effective ART typically results in CD4 count increases of >50 cells/μL within weeks after viral suppression, and increases of 50-100 cells/μL per year thereafter. For some patients, CD4 counts may not increase that quickly or steadily, even with durable viral load suppression. Patients who are older (age >50) and those with lower baseline CD4 cell counts are more likely to have blunted CD4 count responses. For monitoring purposes, the CD4 count should be repeated approximately every 3-6 months both in stable untreated patients and in patients on ART. For patients on ART with persistently suppressed HIV RNA and CD4 counts solidly above thresholds for opportunistic infection risk, current guidelines suggest monitoring every 6-12 months, and some data demonstrate that even less frequent CD4 checks in such patients is safe. The CD4 count should be checked more often if clinically indicated (e.g., switching therapy, ART failure, rapidly declining CD4 count) (see Table 1).

Viral Load Monitoring

The HIV-1 viral load measurement indicates the number of copies of HIV-1 RNA per milliliter of plasma. Although HIV ultimately resides within cells, the plasma measurement is an accurate reflection of the burden of infection and the magnitude of viral replication. It is used to assess the risk of disease progression and can help guide initiation of therapy. It is critical in monitoring virologic response to ART.

There are several commercially available HIV-1 viral load assays and numerous institution-specific assays. The range of detectable virus differs somewhat with each test, but the lowest level of detection generally is 20-75 copies/mL. A viral load below this "undetectable" level indicates the inability of the assay to detect HIV in the plasma, but does not indicate absence or clearance of the virus from the body. The highest levels of detection of the viral load assays typically are between 500,000 copies/mL and 750,000 copies/mL. Viral loads higher than these levels are reported, for example, as >500,000 copies/mL. Note that commercially available assays may not detect HIV-2, and they do not accurately quantify it.

After initial infection with HIV, the viral load quickly peaks to very high levels, usually >100,000 copies/mL (see chapter *Early HIV Infection*). During the period of acute infection, when HIV antibody testing may indicate negative results, the viral load test may be used to detect HIV infection. Generally, 3-6 months after primary infection, the viral load declines and then levels off, remaining in a steady state. Among patients who are not taking ARV medications, a small number maintain a low or even undetectable viral load (aviremic or "elite" controllers), but the vast majority of those patients have relatively high HIV RNA levels.

Higher plasma viral loads are associated with more rapid declines in CD4 cells and with increased risk of progression to symptomatic disease and AIDS; they also are associated with higher risk of HIV transmission (see chapter *Risk of HIV Progression/Indications for ART*). In untreated persons, the CD4 cell count is more useful in determining the urgency of ART initiation, but once a patient has started ART, the viral load is used to monitor the response to therapy. A key goal of ART is to achieve a viral load that is below the level of quantitation (e.g., <40 copies/mL). Because CD4 and clinical responses may lag behind changes in viral load, viral load testing is essential for detecting virologic failure in a timely manner. With an effective ARV regimen, a decline of at least 10-fold (1 logarithm) is expected within the first month, and suppression to undetectable levels should be achieved within 3-6 months after initiation of therapy. Isolated low-level elevations (typically <400 copies/mL) in viral load may occur in patients on ART; these "blips" generally do not predict subsequent virologic failure. (Additionally, some viral load assays appear to produce low-level positive results [<200 copies/mL] more commonly than others; as with blips, these do not in general appear to increase the risk of virologic failure.) To avoid confusing virologic failure with blips or test variability, current guidelines define virologic failure as repeated HIV RNA levels >200 copies/mL. If the viral load does not reduce to an undetectable level (or at least <200 copies/mL), or if it rebounds after suppression, virologic failure has occurred, and possible causes should be investigated (e.g., poor ARV adherence, resistance to ARVs, or reduced drug exposure).

The HIV viral load should be checked at least twice at baseline, before the patient starts an ART regimen. Follow-up viral load measurement should be performed at regular intervals, depending on the patient's clinical situation (see Table 1). For stable patients, viral load usually should be monitored every 3-4 months; for highly adherent and stable patients with suppressed viral loads for at least several years, monitoring every 6 months is adequate. With new therapy or changes in therapy, significant change in viral load or CD4 count, or declining clinical status, the viral load should be measured at more frequent intervals.

Table 1. CD4 and HIV Viral Load Monitoring Schedule

	Baseline	Follow-Up Before ART Initiation	At ART Initiation or Switch	After ART Initiation or Switch	Follow-Up on Effective ART	Treatment Failure or Clinical Indications
CD4 Count	√	Every 3-6 months	√	3-6 months	Every 3-6 months*	√
HIV Viral Load	√	Every 3-6 months	√	2-8 weeks, then every 4-8 weeks until HIV RNA is undetectable	Every 3-4 months**	√

* Clinically stable patients on ART with sustained viral suppression and CD4 counts above threshold for opportunistic infection risk: may monitor every 6-12 months.

**Adherent patients on stable ART with viral suppression and stable immunologic status for >2-3 years: can consider monitoring every 6 months.

Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. Available at aidsinfo.nih.gov/guidelines. Accessed December 1, 2013.

Viral loads, like CD4 counts, are affected by laboratory variation, assay fluctuations, and patient variables such as acute illness and recent vaccinations. Variations of <0.5 $\log_{10}$ copies/mL (threefold) usually are not clinically significant. Viral load results that are inconsistent with previous trends should be repeated, and treatment decisions usually should be based on two or more similar values. Recent illnesses or vaccinations can transiently increase viral load. If a patient has had a recent illness or vaccination, the viral load measurement should be deferred for 4 weeks, if possible.

Patient Education

- The CD4 cell count is the best indicator for gauging the strength of the immune system and for determining whether a person is at risk of infection with certain organisms. The higher the CD4 count, the stronger the immune system.
- CD4 counts are variable. Caution patients not to pin emotions and hopes to a single laboratory result. A change of <30% may not be significant.
- The HIV viral load is the best indicator of the level of HIV activity in the patient's body.
- The CD4 count and HIV viral load may be used to help determine how urgently therapy is needed (note, though, that current guidelines recommend ART for all persons with HIV infection, regardless of CD4 or viral load).
- A key goal of therapy is to suppress the viral load to below the level of detectability by laboratory tests. An undetectable viral load does not mean HIV has been completely eradicated or that the patient is not infectious to others.
- For most patients on effective ART, the CD4 count will rise as the virus is suppressed. This indicates an improvement in the immune system.
- In stable patients on ART, the CD4 count and HIV viral load usually should be monitored every 3-6 months.

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Risk of HIV Progression/ Indications for ART

Background

The CD4 cell count and HIV viral load (RNA level) are closely linked to HIV-related illness and mortality, and are the laboratory measures that are followed in clinical practice. They are the primary markers that give prognostic information on disease progression and on response to antiretroviral therapy (ART) (see chapter *CD4 and Viral Load Monitoring*). However, it is increasingly recognized that a number of other factors are involved in HIV disease progression. These include individual HIV-specific immune responses, immune activation, viral factors, host genetics, and age. The role of these factors and their interplay is complex and incompletely understood.

CD4 Count

The CD4 count (and CD4 percentage) marks the degree of immunocompromise. The CD4 count is used to stage the patient's disease progression, determine the risk of opportunistic illnesses, and assess prognosis (see chapter *CD4 and Viral Load Monitoring*). The CD4 count also helps to determine the urgency and the timing of ART initiation, and the need for prophylaxis against opportunistic infections. It also helps in formulating differential diagnoses for symptomatic patients (see Table 1, Figure 1, and chapters *CD4 and Viral Load Monitoring* and *Opportunistic Infection Prophylaxis*).

Persons with HIV infection are at increased risk of complications at lower CD4 counts. A CD4 count of <200 cells/μL (or CD4 percentage of <14%) indicates severe immunosuppression, and is an AIDS-defining condition. Persons with CD4 counts below this level are at greater risk of a number of opportunistic illnesses and death, increasingly so at lower CD4 counts (see Table 1).

Table 1. Correlation Between CD4 Cell Counts and Complications of HIV Infection

CD4 Count* (cells/μL)	Infectious Complications	Noninfectious Complications#
>500	• Acute retroviral syndrome • Candidal vaginitis	• Persistent generalized lymphadenopathy (PGL) • Guillain-Barré syndrome • Myopathy • Aseptic meningitis
200-500	• Pneumococcal and other bacterial pneumonias • Pulmonary tuberculosis • Herpes zoster • Oropharyngeal candidiasis (thrush) • Cryptosporidiosis (self-limited) • Kaposi sarcoma (cutaneous) • Oral hairy leukoplakia • Herpes simplex (oral/genital)	• Cervical intraepithelial neoplasia • Cervical cancer • B-cell lymphoma • Anemia • Mononeuropathy multiplex • Idiopathic thrombocytopenic purpura • Hodgkin lymphoma • Lymphocytic interstitial pneumonitis • Fatigue
<200	• *Pneumocystis jiroveci* pneumonia (PCP) • Disseminated histoplasmosis and coccidioidomycosis • Miliary/extrapulmonary tuberculosis • Progressive multifocal leukoencephalopathy (PML)	• Wasting • Peripheral neuropathy • HIV-associated dementia • Cardiomyopathy • Vacuolar myelopathy • Progressive polyradiculopathy • Non-Hodgkin lymphoma
<100	• Disseminated herpes simplex virus • Toxoplasmosis • Cryptococcosis • Cryptosporidiosis, chronic • Microsporidiosis • Candidal esophagitis • Kaposi sarcoma (visceral/pulmonary)	
<50	• Disseminated cytomegalovirus (CMV) • Disseminated *Mycobacterium avium* complex (MAC)	• Central nervous system (CNS) lymphoma

* Most complications occur with increasing frequency at lower CD4 cell counts.

\# Some conditions listed as "noninfectious" are associated with transmissible microbes. Examples include lymphoma (Epstein-Barr virus) and anal and cervical cancers (human papillomavirus).

Adapted from Bartlett JG, Gallant JE, Pham P. *2012 Medical Management of HIV Infection.* Baltimore: Johns Hopkins University School of Medicine; 2012. Used with permission.

Increasing evidence suggests that the risk of complications from HIV infection occurs across a broad spectrum of CD4 counts, and that patients with relatively high counts (those with counts of >350 cells/μL and even those with counts of >500 cells/μL) also have increased rates of morbidities compared with HIV-uninfected persons. The complications in persons with higher CD4 counts typically are not the classic AIDS-related opportunistic illnesses but are "non-AIDS" illnesses such as cardiovascular disease, neurocognitive decline, and non-AIDS-associated cancers.

In asymptomatic individuals, CD4 count has been used as the main indicator of need for ART. It is well established that ART is extremely effective

at reducing HIV-related illness in persons with lower CD4 counts. In recent years, accumulating data have suggested that ART also is beneficial for persons with high pretreatment CD4 counts.

Randomized trials have shown that starting ART for asymptomatic patients with pretreatment CD4 counts of 200-350 cells/μL results in decreased morbidity and mortality compared with starting therapy for persons with CD4 counts of <200 cells/μL. For patients with pretreatment CD4 counts of >350 cells/μL, data from several randomized controlled studies and cohort studies have found decreased rates of complications and death among persons who initiated ART at CD4 counts of ≥350 cells/μL, compared with persons who initiated treatment at lower CD4 counts. Additionally, some (though not all) observational evidence suggests a mortality benefit of ART even among persons with pretreatment CD4 counts of >500 cells/μL. These cohort studies are complemented by a number of investigations that demonstrate ongoing and adverse effects of HIV and associated inflammation on various organ systems. A randomized controlled trial to evaluate the strategy of starting treatment at CD4 counts >500 cells/μL is under way.

These lines of evidence, along with studies showing a substantial impact of ART in decreasing HIV transmission, and the availability of ARVs that generally are safe, tolerable, and effective, support the rationale for earlier initiation of treatment. The current U.S. Department of Health and Human Services (HHS) adult and adolescent treatment guidelines recommend starting ART for all HIV-infected persons regardless of CD4 count, both to enhance the health of the infected individual and to prevent transmission of HIV. The strength of this recommendation is greater if the CD4 count is lower or the clinical status is poorer, and according to transmission risk groups (see Table 2 and chapter *Antiretroviral Therapy*).

Table 2. HHS Recommendations on Initiation of Antiretroviral Therapy

The HHS guidelines state that, ***"Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression."*** The strength and evidence for this recommendation vary by pretreatment CD4 cell count, as follows:

CD4 Criteria	Strength of Recommendation*
• CD4 count <350 cells/μL	• Strongly recommended (AI)
• CD4 count 350-500 cells/μL	• Strongly recommended (AII)
• CD4 count >500 cells/μL	• Moderately recommended (BIII)

Additionally, the guidelines state that, ***"ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV."*** The strength and evidence for this recommendation vary by transmission risk, as follows:

Transmission Risk Group	Strength of Recommendation*
• Perinatal transmission	• Strongly recommended (AI)
• Heterosexual transmission	• Strongly recommended (AI)
• Other transmission risk groups	• Strongly recommended (AIII)

* **Rating of recommendation:** A = strong; B = moderate; C = optional
Rating of evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies; III = expert opinion

Considerations
Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. Available at aidsinfo. nih.gov/guidelines. Accessed December 1, 2013.

A number of factors and coexisting conditions signal the need for speedier initiation of therapy, if possible. According to the HHS guidelines, these include the following:

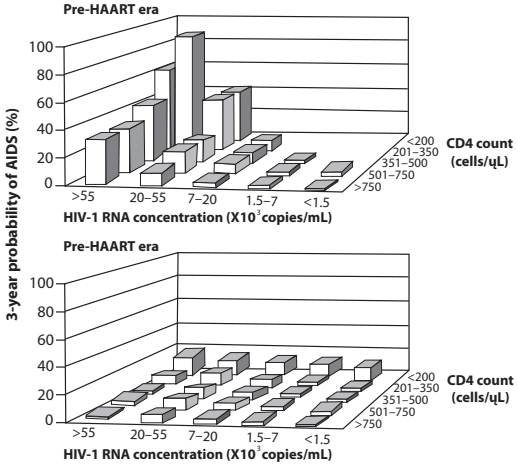
- Pregnancy
- History of AIDS-defining illness
- Acute opportunistic infection
- Lower CD4 cell count
- Acute/recent HIV infection
- HIV-associated nephropathy
- Hepatitis B coinfection
- Hepatitis C coinfection
- Rapidly declining CD4 counts (e.g., >100 cells/μL per year)
- Higher HIV RNA (e.g., >100,000 copies/mL)

HIV Viral Load

Whereas the CD4 count is an indicator of immune system function, the HIV viral load (RNA level) gives prognostic information on how quickly the CD4 count is likely to decline and, consequently, the risk of disease progression. Patients with high HIV viral loads generally demonstrate a faster decline in CD4 count and progression to AIDS-related illnesses; they also may have a higher rate of non-AIDS-related events even with relatively high CD4 counts (e.g., >350 cells/μL). Those with low viral loads usually have higher CD4 counts and remain asymptomatic for prolonged periods. A small percentage of persons with HIV infection may have very low or undetectable viral loads for extended periods of time.

By themselves, CD4 count and HIV viral load are useful, albeit rough, prognostic indicators. When considered together, they constitute a finer tool to estimate the risk of progression (see Figure 1).

Figure 1. Prognosis According to CD4 Cell Count and Viral Load in the Pre-ART and ART Eras: Kaplan-Meier Estimates of the Probability of AIDS at 3 Years



Abbreviations: HAART = highly active antiretroviral therapy
Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, Costagliola D, D'Arminio Monforte A, de Wolf F, Reiss P, Lundgren JD, Justice AC, Staszewski S, Leport C, Hogg RS, Sabin CA, Gill MJ, Salzberger B, Sterne JA; ART Cohort Collaboration. *Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies.* Lancet. 2002 Jul 13;360(9327):119-29. Reprinted with permission from Elsevier.

Other Factors Associated with HIV Progression

Although the CD4 count and HIV viral load are the most important predictors of HIV progression, it is increasingly recognized that a number of other factors, and likely others that remain unknown, contribute to disease progression in HIV infection.

Viral factors

Variations in the HIV genome have been associated with an altered rate of disease progression. For example, deletions in the *nef* gene have been associated with a slow rate of progression. On the other hand, virus that uses the CXCR4 protein as a coreceptor for entry (termed X4 virus or syncytia-inducing virus) has been associated with accelerated progression. As another example, drug-resistance mutations may

affect how efficiently the virus replicates (viral fitness). Patients who have virus with decreased fitness have slower immune deterioration than those with wild-type virus.

Host immune factors

Host genetic factors have been shown to alter the rate of HIV progression. Various human leukocyte antigen (HLA) alleles have been associated with faster or slower progression rates. Genetic polymorphisms also play a role. For example, CCR5 is a chemokine receptor that can serve as a coreceptor for HIV entry into the CD4 cell. A naturally occurring variant allele for CCR5 has a 32 base pair deletion. Individuals who are heterozygous for this allele have slower progression of HIV disease.

Increased immune activation and elevated markers of inflammation, such as IL-6 and D-dimer, also have been associated with risk of disease progression and death. They also may be involved in the ongoing damage seen in a number of end organs. Although T-cell activation and levels of inflammation decrease with ART, they often do not return to normal.

Age

Several studies have shown a higher risk of morbidity and mortality in older patients. When followed from seroconversion, older patients demonstrate faster disease progression compared with younger patients (see Table 3). Older patients also are found to have a less robust increase in the CD4 count in response to ART and may have a higher rate of non-AIDS-related morbidities.

Table 3. Median Survival and Time to AIDS by Age at Seroconversion

Age at Seroconversion (years)	Median (95% CI) Survival (years)	Median (95% CI) Time to AIDS (years)
15-24	12.5 (12.1-12.9)	11.0 (10.7-11.7)
25-34	10.9 (10.6-11.3)	9.8 (9.5-10.1)
35-44	9.1 (8.7-9.5)	8.6 (8.2-9.0)
45-54	7.9 (7.4-8.5)	7.7 (7.1-8.6)
55-64	6.1 (5.5-7.0)	6.3 (5.5-7.2)
≥65	4.0 (3.4-4.6)	5.0 (4.0-6.2)

Adapted from *Concerted Action on SeroConversion to AIDS and Death in Europe. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action*. Lancet. 2000 Apr 1;355(9210):1131-7.

Patient Education

- The CD4 cell count and HIV viral load are the two markers that provide information on the degree of current immunocompromise and the risk of disease progression.
- The lower the CD4 count, the higher the risk of AIDS-related illness.
- Current United States guidelines recommend ART for all HIV-infected individuals. In areas where treatment resources are limited, the CD4 count is the major indicator for initiation of ART.
- A low HIV viral load is associated with slower immune deterioration; a high viral load is associated with quicker immune deterioration.
- Older individuals may have a poorer response to therapy; earlier initiation of therapy may be considered for older patients.

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Early HIV Infection

Background

Acute HIV infection refers to the very early stages of HIV infection, or the interval from initial infection to the time that antibody to HIV is detectable; early HIV infection usually includes the first 6 months of infection. During the acute stage of HIV infection, patients typically have symptoms of acute retroviral illness, very high HIV RNA levels (>100,000 copies/mL) and detectable p24 antigen, and negative or indeterminate HIV antibody test results.

Diagnosing patients with acute HIV infection is a clinical challenge. The symptoms of acute HIV are nonspecific, and although many patients seek medical care for symptoms of acute retroviral syndrome, the diagnosis commonly is missed at initial presentation. The difficulties involve recognizing the clinical presentation of acute HIV infection and testing patients appropriately. In HIV treatment facilities, clinicians generally do not see patients with primary HIV infection unless they are referred with the diagnosis already established. In other health care settings, clinicians may not be familiar with the signs and symptoms of acute HIV infection and often do not consider this diagnosis. Despite the difficulties, recognizing early HIV infection in symptomatic patients is essential. Early diagnosis provides an opportunity for early linkage to HIV care and treatment and may decrease future HIV transmission by newly identified patients, who are particularly infectious during early untreated HIV infection.

After infection with HIV, it takes a median of about 25 days before the HIV antibodies are detectable in most people; in some individuals, it may be several months before seroconversion occurs. HIV RNA may be detectable within 10 days of infection and p24 antigen in about 15-20 days. Persons with known exposures to HIV, whether occupational or not, should be monitored closely beginning at about 3 weeks after exposure (routine monitoring at 6 weeks, 3 months, and 6 months after exposure to HIV is likely to result in delayed diagnosis of HIV infection). For information on postexposure prophylaxis, see chapters *Nonoccupational Postexposure Prophylaxis* and *Occupational Postexposure Prophylaxis*.

S: Subjective

Approximately two thirds of patients infected with HIV develop symptoms of acute HIV infection, a condition known as acute retroviral syndrome. Symptoms typically appear 2-6 weeks after exposure to HIV and generally include several of the following:

- Fever (present in 80-90%)
- Rash, often erythematous and maculopapular
- Fatigue
- Pharyngitis (with or without exudate)
- Generalized lymphadenopathy
- Urticaria
- Myalgia/arthralgia
- Anorexia
- Mucocutaneous ulceration
- Headache, retroorbital pain
- Neurologic symptoms (e.g., aseptic meningitis, radiculitis, myelitis, cranial nerve palsies)

This symptomatic phase usually persists for 2-4 weeks or less, although lymphadenopathy may last longer. Symptoms and signs are similar to those of many other illnesses, including other viral syndromes, influenza, and mononucleosis. However, generalized lymphadenopathy, rash, thrush, and mucosal ulceration are sufficiently uncommon in most adult febrile illnesses that, when present, they

should trigger suspicion of acute HIV infection. It is important to obtain a history of recent risk behaviors from all patients who present with symptoms consistent with acute HIV infection and to have a low threshold for testing for acute HIV infection. Common laboratory findings include leukopenia, thrombocytopenia, and mild transaminase elevations.

O: Objective

The 3rd-generation assays may detect HIV infection within 4 weeks, but new 4th-generation HIV antigen/antibody tests usually show positive results within 2-3 weeks after an infection occurs. During the symptomatic phase of HIV seroconversion, HIV antibody tests may still indicate negative or indeterminate serostatus. For patients who have negative or indeterminate antibody results but symptoms consistent with seroconversion illness and a recent risk history for HIV exposure, an HIV RNA (viral load) test should be performed. Patients with negative or indeterminate antibody test results but detectable HIV viral loads (particularly >10,000 copies/mL) can be considered to be infected with HIV, although the antibody test should be repeated later to confirm seroconversion. A low viral load (<10,000 copies/mL) may indicate a false-positive result, because viral loads typically run very high (i.e., >100,000 copies/mL and, often, millions of copies/mL) during the acute infection stage. For patients who have negative or indeterminate HIV antibody test results and low positive HIV viral loads, the HIV RNA test should be repeated on a different blood specimen.

The 4th-generation HIV tests do not distinguish between antigen positivity and antibody positivity. Patients with a positive result should be retested with an antibody test; if the result is negative or indeterminate and acute HIV is suspected, an HIV RNA test should be sent, as above (see chapter *Expedited HIV Testing*).

A/P: Assessment/Plan

Patients with early HIV infection will need additional medical evaluation, baseline laboratory testing, and intensive support, counseling, and education about HIV infection. See chapters *Initial History*, *Initial Physical Examination*, and *Initial and Interim Laboratory and Other Tests* for detailed information on the initial evaluation of HIV-infected patients.

Laboratory

The initial laboratory work should include the following:

- CD4 cell count and HIV viral load.
- A baseline HIV genotype test for all patients with early HIV infection, even those who do not choose to start antiretroviral treatment (ART). In some cities in the United States and Europe, 6-16% of infected individuals have acquired HIV virus strains with mutations that confer resistance to antiretroviral medications. These resistance mutations may be identified by early resistance testing, but may not be detectable later. (See chapter *Resistance Testing*.)
- Patients diagnosed on the basis of HIV RNA should have an HIV antibody test repeated in 3-6 months to document seroconversion.

Treatment

ART is recommended for all persons with HIV, including those with early HIV infection. Some limited evidence suggests that treatment initiated during primary HIV infection may have particular benefits, including preserving HIV-specific immune function that would otherwise be lost as the infection progresses, limiting the size of the HIV viral reservoir, and decreasing the loss of gastrointestinal lymphoid tissue. In addition, early treatment is expected to decrease rates of HIV transmission during a time of heightened infectiousness.

The potential advantages of ART for primary infection must be weighed against

the possibility of short- and long-term toxicities, the possibility of developing drug resistance, and the adherence challenges associated with starting ART quickly for newly diagnosed patients. Issues concerning the possible treatment of primary HIV infection are reviewed in the U.S. Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* (available at aidsinfo.nih.gov/guidelines).

For pregnant women with acute or recent HIV, the risk of perinatal HIV transmission is very high; thus, ART should be started as early as possible to try to prevent infection of the infant (see chapter *Reducing Perinatal HIV Transmission*).

For patients who opt to start therapy during primary HIV infection, the choice of agents and the recommendations for monitoring are the same as those for the treatment of patients with chronic HIV infection (see chapter *Antiretroviral Therapy*). The initial goal of therapy in primary HIV infection is to suppress the HIV viral load to undetectable levels.

Patient Education

- Patients with early HIV infection need support and counseling, as do all newly diagnosed patients.
- Intensive education about HIV infection, the course of disease progression, prognosis, and the benefits and risks of ART must be undertaken.
- Counseling patients about safer sex and drug injection techniques, as indicated, is especially important because these patients may have ongoing high-risk behaviors for HIV transmission and because they may be highly infectious during the primary infection period. (See chapter *Preventing HIV Transmission/Prevention with Positives* for more information about patient support and counseling in these areas.)

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Expedited HIV Testing

John Nelson, PhD, CPNP

Background

According to the U.S. Centers for Disease Control and Prevention (CDC), about 1.15 million people are living with HIV in the United States, and it has been estimated that about 18% of these individuals are unaware of their HIV serostatus. Additionally, it is estimated that 50,000 new HIV infections occur in the United States each year. It is important to identify persons who are infected with HIV as soon as possible after infection, in order both to link them to health care services and to reduce the risk that they will unknowingly transmit HIV to others.

In order to identify those with HIV infection, the CDC recommends routine voluntary HIV screening for all adults, adolescents, and pregnant women. Nevertheless, many people are reluctant to be tested, and many clinics do not offer routine testing. With expedited HIV testing, clients can be tested and receive their preliminary results during a single visit. The goals of expedited testing are to identify HIV infection as early as possible after initial infection and to do so in as little time as possible (negative results, indeterminate results, and confirmed positive test results are available during the same visit that testing is done). This makes it possible to link persons testing HIV positive to HIV medical care and other supports as quickly as possible. Expedited testing also allows for the efficient management of clients in need of urgent medical treatment (such as pregnant women) and situations requiring quick clinical decision making (such as assessment for postexposure prophylaxis).

Expedited HIV tests include both traditional nonlaboratory-performed rapid tests and antigen/antibody (Ag/Ab) laboratory-based tests. The Ag/Ab 4th-generation tests detect both HIV p24 antigen and anti-HIV antibodies (for HIV-1 and/or HIV-2). The 4th-generation tests are more sensitive during the acute phase of HIV infection than are the previous-generation screening immunoassay tests (including nonlaboratory-based rapid tests), so they are capable of diagnosing HIV infection at an earlier stage (as early as 2-3 weeks after infection). One laboratory-based 4th-generation test is capable of delivering the preliminary results within 1 hour.

Because of the greater sensitivity of 4th-generation laboratory-based immunoassays in identifying HIV at earlier stages of infection, it is now recommended that these tests be done whenever possible for HIV screening. Interestingly, 4th-generation testing is less expensive per test than the point-of-care (POC) rapid tests in the United States.

Clients and Settings for Expedited Testing

Expedited HIV testing is important in settings in which the availability of HIV test results would influence medical care immediately, or in routine screening in settings where HIV prevalence is high or clients are not likely to return for the test results. Settings in which the use of highly sensitive 4th-generation HIV Ag/Ab testing from a laboratory is preferable include labor and delivery facilities (where identification of HIV infection is critical in preventing perinatal transmission), prenatal care facilities, hospital emergency departments, urgent care and acute care clinics, sexually transmitted disease clinics, drug treatment clinics, hospitals, and other clinical care or testing sites in communities with a high prevalence of HIV. In high-risk jurisdiction settings such as jails and mobile health service vans, and in community outreach programs where access to an on-site laboratory does not exist, nonlaboratory-based rapid testing is still recommended.

Expedited HIV Tests

The U.S. Food and Drug Administration (FDA) has approved three 4th-generation HIV Ag/Ab tests for use in the United States (see Table 1). Federal regulations under the Clinical Laboratory Improvement Amendments (CLIA) program categorize tests as waived, moderate complexity, or high complexity. Many rapid tests are approved as CLIA-waived tests (see Table 2), meaning that they may be performed at the POC after appropriate staff training and with procedures in place to ensure quality control. These tests use whole blood or oral fluid and require a few simple steps to perform.

Other rapid tests are "nonwaived" tests and must be performed in laboratories. Results for rapid tests performed at the POC are available in less than 30 minutes; results for expedited tests done in a laboratory should be available within 1 hour.

As mentioned above, 4th-generation laboratory-based tests are recommended for HIV screening. In cases wherein laboratory-based 4th-generation HIV testing is not available, then 2nd- or 3rd-generation antibody POC rapid testing may be done with the knowledge that a person in seroconversion may test falsely negative.

Table 1. FDA-Approved 4th-Generation HIV Tests for Laboratory Use Only (CLIA Moderate- or High-Complexity Tests)

Test Name	Time to Test Result	Target Analyte (Test Generation)	Sensitivity for Established HIV-1 Infection & Sensitivity for HIV-2Infection (%) (95% Confidence Interval)	Specificity for Established HIV-1 Infection (%) (95% Confidence Interval)	Approved Specimen Types & Volume	Assay Format
Abbott Architect HIV Ag/Ab Combo Assay (fully automated CLIA moderate-complexity assay) **(Expedited)**	<30 min	HIV-1 p24 antigen and antibodies to HIV-1/2 **(4th generation)**	Plasma/Serum HIV-1 p24: 100 (94.3-100)/HIV-1: 100 (99.63-100) HIV-2: 100 (98.2-100)	Plasma/ Serum 99.8 (99.6-99.9)	Plasma/ Serum 150 µL	Chemi-luminescent micro-particle immuno-assay
Bio-Rad GS HIV Combo Ag/Ab EIA (manual or semi-automated CLIA high-complexity assay)	>3 hours	HIV-1 p24 antigen and antibodies to HIV-1/2 **(4th generation)**	Plasma/Serum HIV-1: 100 (99.7-100); HIV-2: 100 (98.1-100)	Plasma/ Serum 99.87 (99.76-99.93)	Plasma/ Serum 75 µL	Enzyme immuno-assay micro-well format
Alere Determine HIV-1/2 Ag/ Ab Combo	20 minutes	HIV p24 antigen and antibodies to HIV-1 and/or HIV-2 **(4th generation)**	Whole Blood 99.9 (99.4-100)	Whole Blood 99.6 (99.2-99.8)	Plasma/ Serum Whole Blood	Immuno-assay
MultiSpot HIV-1/HIV-2 Rapid Test	15 minutes	Antibodies to HIV-1 and HIV-2 (detection and differentiation) **(3rd generation)**	100% (99.9-100)	99.9% (99.8-100)	Plasma/ Serum	Immuno-assay

Adapted from U.S. Food and Drug Administration. *Complete List of Donor Screening Assays for Infectious Agents and HIV Diagnostic Assays.* September 17, 2013.

Table 2. FDA-Approved HIV Rapid Screening Assays for Point-of-Care Testing

Test Name	Time to Test Result	Target Analyte (Test Generation)	Sensitivity for Established HIV-1 Infection & Sensitivity for HIV-2 Infection (%) (95% Confidence Interval)	Specificity for Established HIV-1 Infection (%) (95% Confidence Interval)	Approved Specimen Types	Assay Format
SURE CHECK HIV 1/2 ASSAY (Clearview Complete HIV 1/2)	<15 minutes	Antibodies to HIV-1 and/or HIV-2; point-of-care test	99.7 (98.9-100)	99.9 (99.6-100)	Fingerstick & Whole Blood (Venipuncture, Fingerstick)	Rapid Immuno-assay
Clearview HIV 1/2 STAT-PAK ASSAY	15 minutes	Antibodies to HIV-1 and/or HIV-2; point-of-care test	99.7 (98.9-100)	99.9 (99.6-100)	Fingerstick & Whole Blood (Venipuncture, Fingerstick)	Rapid Immuno-assay
OraQuick ADVANCE Rapid HIV-1/2 Antibody Test	20 minutes	Antibodies to HIV-1 and/or HIV-2; point-of-care test	99.3 (98.4-99.7) Oral Fluid 99.6 (98.5-99.9) Whole Blood	99.8 (99.6-99.9) Oral Fluid 100 (99.7-100) Whole Blood	Oral Fluid, Whole Blood (Venipuncture, Fingerstick)	Rapid Immuno-assay
Chembio DPP HIV 1/2 Assay	<40 minutes	Antibodies to HIV-1 and/or HIV-2; point-of-care test	98.9 (98-99.4) Oral Fluid 99.8 (99.2-99.9) Fingerstick Whole Blood	99.9 (99.7-99.9) Oral Fluid 100 (99.8-100) Fingerstick Whole Blood	Oral Fluid, Whole Blood (Venipuncture, Fingerstick)	Rapid Immuno-chromato-graphic Assay
Uni-Gold Recombigen HIV-1/2	10 minutes	Antibodies to HIV-1 and/or HIV-2; point-of-care test	100 (99.5-100)	99.7 (99.0-100)	Whole Blood (Venipuncture, Fingerstick)	Rapid EIA
bioLytical INSTI HIV-1 Ab Test	60 seconds	Antibodies to HIV-1; point-of-care test	99.8 (99.3-99.9)	100 (99.7-100)	Whole Blood (Fingerstick)	Rapid Flow-Through Immuno-assay

Adapted from U.S. Food and Drug Administration. *Complete List of Donor Screening Assays for Infectious Agents and HIV Diagnostic Assays.* September 17, 2013.

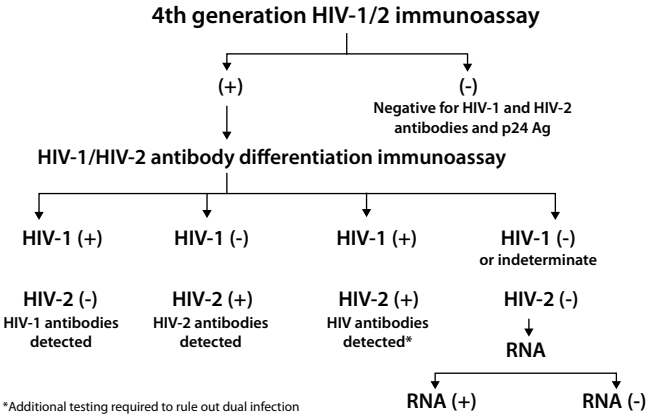
Interpreting Test Results

All FDA-approved tests are highly sensitive and specific. As previously mentioned, 4th-generation HIV Ag/Ab tests have significantly greater sensitivity to very recent (acute) HIV infection. The negative predictive value of all rapid and expedited HIV tests is close to 100%. That means a client who receives a negative rapid test result almost assuredly is not infected, barring recent exposures (e.g., sexual contact or needle sharing with an infected person within the past 1-3 months, depending on the test used).

For clients who test reactive (positive) on a rapid or expedited test, the result is considered preliminary and must be confirmed. Traditionally, confirmation has been done by use of either a Western blot (WB) or immunofluorescence assay (IFA). However, neither of these confirmatory tests is expedited, and neither is able to differentiate HIV-1 and HIV-2 infections simultaneously. The confirmatory test currently recommended by the CDC is one that is able to differentiate HIV-1 and HIV-2 antibodies and is expedited (e.g., MultiSpot HIV-1/HIV-2 Rapid Test). If the confirmatory test result is positive, the client is considered to be infected with HIV. If the confirmatory test result is negative (no HIV Ab bands with a WB test or no visible reaction on the MultiSpot in the HIV-1 and/or HIV-2 Ab areas) or indeterminate (with the WB test, greater than 0 bands but too few bands to be considered positive), then an HIV RNA-1 test should be done immediately to check for early infection (Figure 1). In this case, a detectable HIV RNA (unless very low) will indicate early HIV infection – the client is most likely HIV infected and is seroconverting from antibody negative to positive status. The HIV-1 RNA test should be done regardless of the original HIV screening test (4th-generation Ag/Ab or earlier-generation Ab). With detectable HIV RNA, the client should be considered infected, but an HIV confirmatory (WB or IFA) antibody test should be repeated in roughly 2-4 weeks to determine HIV antibody status. In the case of possible HIV-2 infection, consultation with an HIV specialist is recommended.

The positive predictive value of a single positive rapid or expedited HIV test result depends on the specificity of the test and the HIV prevalence in the community. The high specificity of the rapid or expedited tests means that, if a test result is positive, the likelihood that a client is truly HIV infected depends on the local HIV prevalence. In a population with a high HIV prevalence, a positive test result is likely a true positive, but in a population with a low HIV prevalence, that result has a greater chance of being a false positive.

Figure 3. 4th-Generation HIV Testing Algorithm



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Information for the Client

Educating the Client Before Testing

It is important to offer expedited HIV testing as part of a broader health screening, to educate clients about HIV infection and about the test, and to give them an opportunity to ask questions and to decline testing. The provider should emphasize that a second test is always performed in order to confirm a positive preliminary screening (laboratory or POC) test result. When possible, expedited or rapid testing should be made available during a regular visit so that clients do not face additional waiting time, and so that HIV infection can be detected as early as possible.

Giving Reactive (Preliminary Positive) Rapid Test Results

Example of simple language to use outside labor and delivery settings

The following wording is suggested when the client's rapid (nonconfirmed) test result is positive (or the expedited confirmatory testing is negative [and therefore the final result is "indeterminate"]):

> *"Your preliminary screening test result was positive, but we won't know for sure if you are infected with HIV until we get the results from your confirmatory test. In the meantime, you should take precautions to avoid transmitting the virus. This means protecting all sex partners from possible exposure (using condoms, for example), not sharing needles or syringes for any purpose, and not sharing razors."*

Emphasize the importance of a confirmatory test, arrange for the confirmatory test to be done immediately. If an expedited, confirmatory test is available (MultiSpot Rapid), the client should not leave until that test has been completed and the result given. If an expedited confirmatory test is not available, then schedule a return visit for the client to receive the test result. It is important to develop a plan for follow-up with this client during this waiting period (by phone or in-person) and to reinforce the importance of following up. (Be sure to have the client's contact information in case he or she does not return for confirmatory results.)

Example of language to use in labor and delivery settings

The following wording is suggested when the client's nonconfirmed expedited or rapid test result is positive:

> *"Your preliminary HIV screening result was positive. You may have HIV infection. We need to do confirmatory tests to verify this first result, but it is important to start medication immediately to reduce the risk of passing HIV to your baby while we wait for the result. It is important to delay breast-feeding until we have the confirmatory test results."*

Follow-Up for Results of Confirmatory Tests

Clinical sites that offer expedited or rapid HIV testing should have a protocol for conveying the results of preliminary and confirmatory positive HIV test results to clients. With rapid tests and expedited laboratory-based testing, the client may be given the confirmatory results on the same day tested. If expedited laboratory-based confirmatory testing (MultiSpot Rapid), is not available, blood for confirmatory WB or IFA must be collected. In this case, results generally will not be available the same day, but appropriate specimen collection and test ordering should be done before the client leaves on the day the preliminary positive result is given.

If the confirmatory result is negative or indeterminate (after a positive preliminary result), testing for HIV-1 RNA must be done.

Sites should either provide confirmatory notification services in-house or have mechanisms in place for notifying clients of

their test results. All clients with confirmed positive HIV test results should be referred immediately for HIV care, community-based HIV services, or health department disease intervention specialists (who are trained to link people to care). Testing sites should establish reliable referral pathways to qualified HIV care providers with follow-up policies and procedures in place to make sure that linkage to care actually occurred.

Client Education

In general settings and in situations not involving labor and delivery, advise clients of the following:

- Expedited laboratory and rapid nonlaboratory HIV testing is an important component of health screening. Learning early that they have HIV infection can help clients better maintain their health.
- Knowing that they have HIV infection can help clients start treatment as soon as possible, and to take precautions to prevent transmission of HIV to others.
- Clients can refuse an HIV test, and it will not affect the care they receive.
- The results from expedited or rapid tests are available at the same visit, usually in less than 1 hour.
- The expedited 4th-generation Ag/Ab tests are very accurate and are better at identifying newly infected persons than the 2nd- and 3rd-generation rapid and laboratory screening tests.
- If the expedited or rapid test result is positive, a second, confirmatory test always is done in order to provide assurance that the screening test result was accurate; and, if the confirmatory test is either negative or indeterminate, a third test (HIV viral load) needs to be done to determine whether the client is infected.
- It is important that clients return for the results of all confirmatory tests.
- If a client's expedited or rapid test result is negative, that client is most likely not infected with HIV, *unless* the infection occurred within the past month – the test may not detect very recent infection.
- Test results are kept confidential. However, if a confirmatory test result is positive, most state laws require that information to be reported to the health department.
- There are clinics and other resources to help clients obtain more information as well as counseling, care, or treatment. The provider should provide specific referrals to these as well as assist the client in linkage to the referral site as soon as possible.

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Resistance Testing

Background

Genotype and phenotype testing for resistance currently is commercially available for all nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitors that have been approved by the U.S. Food and Drug Administration (FDA). In addition, standardized genotype testing is commercially available for enfuvirtide (a fusion inhibitor).

HRSA HAB Performance Measures

Percentage Percentage of patients, regardless of age, with a diagnosis of HIV who had an **HIV drug resistance test** performed before initiation of HIV antiretroviral therapy if therapy started during the measurement year

(All-Age measure)

Neither genotype nor phenotype predicts which antiretroviral (ARV) drugs will be active in a particular patient, only ARVs that are not likely to be active. Nevertheless, studies comparing the use of resistance testing with expert opinion alone have shown that resistance testing can improve virologic control of HIV. Resistance testing is used to guide subsequent treatment for patients whose antiretroviral therapy (ART) is failing and for those whose viral load is not completely suppressed after starting therapy. It also is used to select an initial regimen that is likely to be effective for patients who have never been treated, and it is recommended for all patients with HIV infection (both acute and chronic) upon entry into care, whether or not ART is to be initiated. In addition, resistance testing is recommended for pregnant women who are not on ART and for those who are on ART but have a detectable HIV viral load.

Genotype Tests

Genotype testing works by amplifying and sequencing HIV taken from a patient to look for mutations in the HIV reverse transcriptase, protease, integrase, or envelope genes that are known to correlate with clinical resistance to ARV drugs. Genotype tests generally can detect mutations in plasma samples with HIV RNA levels of >1,000 copies/mL, but sometimes are successful with viral loads of 500-1,000 copies/mL. Species representing 20% or more of the amplified product usually can be detected by current techniques, but minor species may not be detected. Resistance mutations that developed in the past during treatment with certain ARV medications may be archived as minor species and become invisible to genotype testing (as early as 4-6 weeks) after the drug is discontinued. These resistance mutations may reemerge and cause drug failure, however, if the previous drug is used again. By contrast, mutations acquired at the time of infection (from a transmitted virus that was already resistant) appear to persist for years, although the duration is not known precisely and may vary by mutation.

A genotype test takes 1-2 weeks to complete. The results are reported as a list of the mutations detected; most reports also include an interpretation that indicates the drug resistance likely to be conferred by those mutations (see "Limits of Resistance Testing," below).

Note that the standard genotype tests detect only mutations that may affect reverse transcriptase inhibitors and PIs; a specific genotype for the integrase inhibitor (or fusion inhibitor) class must be ordered if there is concern for resistance to this class. Resistance to CCR5 antagonists is uncommon; a change in coreceptor tropism is a more likely cause of virologic failure for patients taking maraviroc. For such patients, a coreceptor tropism assay should be obtained. Afterwards, if resistance to CCR5 antagonists is still suspected, a resistance test can be obtained.

Genotype results must be interpreted carefully. Because mutations can become invisible to the genotype testing process when the selective pressure of a drug is removed, a thorough ARV history, a review of any past resistance tests, and expert clinical assessment are necessary to put the results of a genotype test in proper perspective and to identify options for further treatment (see "Limits of Resistance Testing," below). A compilation of the most common HIV mutations selected by the three classes of antiretroviral agents is available at www.hiv.lanl.gov/content/index. Other resources useful in understanding resistance testing and interpreting test results include the information complied by the International Antiviral Society-USA and the Stanford University HIV Drug Resistance Database (hivdb.stanford.edu).

A "virtual phenotype" is a genotype that is compared with a databank of patient samples that have been analyzed by paired genotype and phenotype testing. The patient's genotype is matched to a banked genotype, and the patient's phenotype is then predicted on the basis of the phenotypes paired to the banked genotype. A virtual phenotype can be completed in the same amount of time as a genotype. Results are reported as a genotype (listing the mutations detected) as well as a predicted fold change in the 50% inhibitory concentration (IC50) of each drug to the patient's virus (see "Phenotype Tests," below). The predicted susceptibility of the patient's virus to each drug is then reported, based on biologic and clinical cutoffs.

Phenotype Tests

Phenotype testing works by splicing the HIV reverse transcriptase and HIV protease genes from a patient's virus into a standardized laboratory strain, which is then grown in the presence of escalating concentrations of ARV drugs. The test measures the IC50 of each drug against the virus in vitro. Results are reported as fold change in IC50, as compared with a drug-susceptible control strain or with a previous test of the same patient's blood. The predicted susceptibility of the patient's virus to each drug is then reported, based on what is known about the correlation between fold change in IC50 of that drug and clinical resistance. As with genotype testing, the phenotype may not be able to detect resistance if the HIV RNA level is low (<1,000 copies/mL) and may not detect minor species. Therefore, a thorough history of ARV use and resistance tests, as well as expert interpretation, are essential for determining the significance of the results (see "Limits of Resistance Testing," below). A phenotype takes 2-3 weeks to complete.

Choosing Between Genotype and Phenotype

Genotype testing is faster and cheaper than phenotype testing, and it can detect emerging resistance, that is, virus with a mixture of strains of which some may be sensitive and some may be resistant to a given drug, as long as they are present in sufficient quantity. It is therefore generally recommended (including by the U.S. Department of Health and Human Services [HHS]) for ART-naive patients and for patients whose first or second ART regimens are failing. Additionally, in some instances it is very important to know the exact viral mutation pattern in order to predict the virus's response to subsequent therapy, particularly in patients with virologic failure on a regimen containing an NNRTI or integrase inhibitor. HHS recommends phenotype testing when patients are suspected of having complicated or multidrug resistance patterns (for example, in the setting of extensive prior ART), or when patients are found to have such patterns on genotype testing (especially resistance to PIs).

Using Genotype and Phenotype Tests at the Same Time

Genotype and phenotype tests have a few complementary properties that may, in some circumstances, make it desirable to use both tests at the same time. This strategy is especially advantageous when trying to devise a regimen for patients who have been exposed to many ARV agents and have few remaining treatment options, and for whom the development of additional resistance could be particularly dangerous. For example, early mutations may appear on a genotype before increases in inhibitory concentrations are detectable on a phenotype. Phenotype testing can detect loss or gain of drug efficacy caused by complex interactions of mutations that, by themselves, would not be predictive. In some cases, results of the genotype and the phenotype may be discordant; in these cases, consultation with an expert is recommended.

Recommendations for Resistance Testing

An overview of when genotype and phenotype testing is and is not recommended is presented in Table 1.

Table 1. Resistance Testing Recommendations

Clinical Setting/Recommendation	Rationale
Recommended	
Acute HIV infection • Genotype	• Determine whether drug-resistant virus was transmitted, to help design an initial regimen or to change a regimen accordingly. • If ART is deferred, consider repeating genotype at the time of ART initiation.
Chronic HIV infection before starting ART • Genotype • Coreceptor tropism assay	• Determine whether drug-resistant virus was transmitted to help design an initial regimen. • Perform upon entry to care (as close to the time of infection as possible), because transmitted drug-resistant virus is more likely to be detected earlier in the course of HIV infection. • If ART is deferred, consider repeating genotype at the time of ART initiation. • Consider integrase genotypic resistance assay if integrase inhibitor resistance is a concern. • Perform coreceptor tropism assay if use of a CCR5 antagonist is being considered.
Virologic failure during ART • Genotype if failure of 1st or 2nd regimen • Both phenotype and genotype if multiple prior regimens, suspicion of mutations to multiple ARVs (especially PIs), or evidence of such mutations on genotype • Coreceptor tropism assay	• Determine the role of resistance in drug failure and optimize the selection of active drugs for the new regimen, if indicated. • Perform while patient is taking ARVs, or ≤4 weeks after discontinuing ARVs. • If virologic failure on integrase inhibitor or fusion inhibitor, obtain specific genotypic testing for resistance to these to determine whether to continue them. • Perform coreceptor tropism assay if use of a CCR5 antagonist is being considered.
Suboptimal suppression or viral load • Genotype or phenotype, depending on clinical situation (as above)	• Determine role of resistance: identify active drugs for new regimen.
Pregnant women • Genotype or phenotype, depending on treatment history (as above)	• Perform before initiation of ART or prophylaxis. • Perform for all on ART with detectable HIV RNA levels. • Optimize the selection of active drugs for ARV regimen.
Not Usually Recommended	
After discontinuation (>4 weeks) of ARVs	• Assist in selecting optimal regimen to achieve maximal viral suppression. • Drug-resistance mutations may decrease in number and become undetectable on assays.
Plasma viral load <500 HIV RNA copies/mL	• Resistance assays are likely to be unsuccessful in patients with HIV RNA <500 copies/mL, because of the low number of RNA copies. In those with levels >500 but <1,000 copies/mL, testing may fail but can be considered.

Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. Available at aidsinfo.nih.gov/guidelines. Accessed December 1, 2013.

Antiretroviral-Naive Patients

With treatment-naive patients, resistance testing may reveal resistance mutations that were acquired at the time of infection, through infection with a strain of HIV that had already developed ARV resistance. Current guidelines recommend genotype testing for recently infected patients and for ARV-naive, chronically infected patients before initiation of therapy. It is important to test as early as possible in the course of HIV infection, to increase the likelihood of detecting transmitted mutations. The rationale for resistance testing in ARV-naive patients is twofold: 1) The prevalence of primary resistance is substantial, particularly in locations with a high prevalence of persons taking ART; and 2) Unknowingly starting a patient on ARV medications to which his or her virus is already resistant may risk failure of the initial regimen, rapid acquisition of additional resistance mutations, and curtailment of future treatment options.

Limits of Resistance Testing

As discussed above, drug-resistant HIV evolves in response to selective pressure applied by the ARV drugs in the patient's system. Specific resistance mutations develop in response to the pressure exerted by specific drugs (M184V, for example, evolves in response to lamivudine or emtricitabine). The presence of viral resistance suggests that a particular drug (and drugs with similar resistance patterns, or cross-resistance) is unlikely to be successful in suppressing viral replication.

In contrast, the absence of resistance to a drug on a genotype or phenotype test does not necessarily indicate that the drug will be effective, particularly if that drug (or drugs sharing cross-resistance) has been used previously. If a particular drug is discontinued, the viral strains harboring the mutations that confer resistance to that drug may decrease below the threshold of detection by the resistance assay, so the resistance test may not reveal certain resistance mutations. In such situations, minority populations of resistant viruses may exist in reservoirs and may emerge rapidly under selective pressure if that drug is restarted, or if drugs with similar or overlapping resistance patterns are used. The implications of archived mutations are twofold: 1) Resistance tests are most reliable when the patient is still taking the failing regimen; and 2) Resistance testing should be interpreted in the context of both the drugs that the patient was taking at the time of the test and the drugs that the patient had been exposed to previously (i.e., the patient's ARV history). In addition, it is important to review any previous resistance tests, which may show resistance mutations that were not revealed on subsequent testing.

Resistance Testing in Patients with Virologic Failure

As discussed in the chapter *Antiretroviral Therapy*, factors other than resistance may cause failure of ART; these include nonadherence, drug-drug interactions, and malabsorption. Therefore, before assuming drug failure, it is important to assess the causes of ARV regimen failure. If resistance is suspected, resistance testing should be done while the patient is taking the failing regimen, for the reasons noted above.

Patient Education

Advise patients of the following:

- Resistance testing can improve the likelihood of virologic control of HIV.
- Most treatment guidelines recommend resistance testing in certain circumstances.
- Both genotype and phenotype testing can detect resistance only if it exists in at least 20% of the viral species present in a patient (known as the dominant species). Minor species may harbor resistance that remains undetected by either test.
- In general, a patient's viral load must be at least 1,000 copies/mL for either test to be reliable, although samples with >500 copies/mL sometimes can be analyzed.
- Resistance tests are most reliable when performed while a patient is still taking a failing regimen, or within 4 weeks after stopping.
- Neither test predicts which drugs will be active in a particular patient, only drugs that are not likely to be active.

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Karnofsky Performance Scale

Background

The Karnofsky Performance Scale is an assessment tool intended to assist clinicians and caretakers in gauging a patient's functional status and ability to carry out activities of daily living.

It is important to assess a patient's performance on a regular basis, especially as the effects of HIV progress. Documentation of Karnofsky scores over time may be very useful in following a patient's course of illness, and can help a disabled patient in his/her application for disability benefits. It also is used for some research applications.

The Karnofsky Performance Scale

Description	Percent (%)
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor signs or symptoms of disease	90
Normal activity with effort; some signs or symptoms of disease	80
Cares for self; unable to carry on normal activity or do work	70
Requires occasional assistance, but is able to care for most personal needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special care and assistance	40
Severely disabled; hospitalization indicated although death not imminent	30
Very sick; hospitalization necessary; requires active support treatment	20
Moribund; fatal processes progressing rapidly	10
Dead	0