Chapter 10:

Abnormal Laboratory Values in HIV Disease

David H. Spach, MD
John G. Bartlett, MD

Common Abnormalities

What are some common abnormalities found when screening asymptomatic patients?

Some disease processes associated with HIV can be first identified in laboratory screening tests while patients are still asymptomatic. The primary care provider plays an essential role in monitoring for laboratory abnormalities, whether these abnormalities result from diseases or from antiretroviral therapy (ART). Table 10-1 lists screening tests that assist in promptly identifying and managing medical problems in asymptomatic patients. Abnormal laboratory tests occur more frequently in HIV-infected persons because 1) HIV is a multi-system disease, 2) HIV causes immune suppression that may result in opportunistic infections and tumors that involve multiple systems, 3) the drugs used routinely in management can cause adverse reactions that affect multiple systems, and 4) patients at high risk for HIV are often at high risk for other medical conditions.

What constitutes a positive PPD in HIV disease?

Induration of 5mm or more at 48-72 hours constitutes a positive PPD test for tuberculosis in a person with HIV. A PPD should be done at baseline and repeated annually if the initial test was negative and the patient is in a high-risk category for tuberculosis. The test has a relatively high rate of false-negative results in patients with a CD4 cell count of $< 200/mm^3$. Therefore, if the initial test was done when the CD4 cell count was low, it should be repeated when the CD4 cell count increases to $> 200/mm^3$ following ART. Patients with a positive PPD test need a chest x-ray and evaluation for active disease before isoniazid (INH) prophylaxis is initiated.

What is the role of a baseline chest x-ray?

A chest x-ray is recommended for detection of latent or active tuberculosis and other lung diseases and as a baseline for patients who are at high risk for pulmonary disease, especially bacterial pneumonia, *Pneumocystis* pneumonia, and tuberculosis. The x-ray is particularly important for any patients with a positive PPD skin test.

What do you do when a patient has a positive VDRL or RPR?

The standard screening tests for syphilis in sexually active patients are the nontreponemal tests, the VDRL or RPR. Any positive screening test should be confirmed with a fluorescent treponemal antibody absorbed test (FTA-ABS). Confirmation is particularly important because for biologic false-positive tests are more common with injection drug use, pregnancy and HIV infection. With a positive test, primary, secondary, and early latent syphilis (less than 1 year) should be treated with a single injection of benzathine penicillin (2.4 million units IM) once, late latent syphilis (more than 1 year or of unknown duration) should be treated with 3 doses at 1-week intervals of benzathine penicillin (2.4 million units IM with each dose), and neurosyphilis should be treated with aqueous penicillin G, 18-24 million units/day IV for 10-14 days. Patients who are not pregnant and do not have neurosyphilis who cannot receive penicillin may be treated with doxycycline (100 mg po bid) given for 14 days for primary, secondary, and early latent syphilis and for 28 days for late latent syphilis. Because the efficacy of doxycycline is not well established, patients who received doxycycline need extra followup. With penicillin allergy and neurosyphilis or pregnancy, there should be penicillin skin testing; if negative, penicillin is given, and if positive the patient should undergo penicillin desensitization followed by penicillin treatment. A lumbar puncture is recommended for any patient with neurologic signs or

Table 10-1. Abnormalities Identified in Screening Tests

Test	Implications of abnormal findings
CBC	Anemia – usually due to HIV or zidovudine Neutropenia – usually due to HIV or drugs, especially ganciclovir and zidovudine Thrombocytopenia – usually due to HIV
Alanine aminotransferase (ALT)	Usual causes of elevated levels are chronic hepatitis (HBV, HCV), alcoholic liver disease, or adverse drug reactions.
Creatinine	Usual causes of renal failure are common medical conditions in this population (hypertension, heroin use, diabetes, IgA nepropathy, etc), adverse reactions to drugs (including indinavir), or HIV nephropathy
Toxoplasma titer	Positive results in 10% of adults in US, higher in other countries. This indicates latent disease with possible activation if CD4 count <100/mm^3
VDRL or RPR	If positive, need confirmatory FTA-ABS
Screen for *N. gonorrhoeae* and *C. trachomatis*	Positive results indicate high-risk behavior and need for treatment
PPD	Induration ≥5mm indicates need for evaluation for active TB and, if negative, INH treatment
Chest x-ray	Ghon complex, adenopathy, or evidence of chronic lung disease
CD4 count	Barometer of immune function
Viral load	Indicates rate of progression of untreated HIV and response to HAART
Hepatitis panel	
Anti-HCV	Positive results ± confirmatory HCV RNA usually indicates chronic HCV infection
Anti-HBc or *Anti-HBs serology*	Positive results indicate prior antigenic experience with HBV
HBsAg	Indicates HBV; if positive >6 months indicates chronic HBV
Anti-HAV	Positive test indicates prior antigenic experience due to HAV infection or vaccination

symptoms, patients with therapeutic failure (persistent clinical evidence of syphilis or a sustained 4-fold increase in titer), and all patients with latent syphilis, which includes latent syphilis of unknown duration. Some experts have recommended performing lumbar puncture for all HIV-infected persons with syphilis, regardless of the stage of syphilis. With respect to followup, the nontreponemal test should be done at 3, 6, 9, 12, and 24 months.

Hematologic Complications

What are the common causes of anemia?

Anemia, which is common in HIV disease, is usually caused by 1) late-stage HIV, presumably due to viral infection of progenitor cells, 2) associated complications that infiltrate the marrow, 3) nutritional deficiency, 4) adverse drug reactions, or 5) iron deficiency. The findings and management are summarized in Table 10-2.

What causes thrombocytopenia?

Most cases are attributed to HIV infection of the multi-lineage hematopoietic progenitor cells in the marrow. This HIV-associated thrombyocytopenia can occur in relatively early HIV, but is more common with late-stage disease. Although zidovudine (AZT) may cause anemia or neutropenia, early studies showed that it reverses thrombocytopenia. For patients not receiving ART, the preferred treatment for HIV-associated thrombocytopenia is to promptly initiate ART. The decision to intervene with intravenous immune globulin (IVIG) or corticosteroids is driven by signs or symptoms of active bleeding, the need to do an invasive procedure, or a lack of response to ART.

What causes neutropenia?

Neutropenia is most commonly related to drug therapy, especially with zidovudine (AZT), ganciclovir, or valganciclovir, but it can also be caused by late-stage HIV or marrow-infiltrate disease. With absolute neutrophil counts of $<500/mm^3$ it is important to monitor for infection and intervene with empiric antibiotics rapidly when appropriate. Address neutropenia by discontinuing the implicated agent or by providing cytokine therapy using G-CSF or GM-CSF.

Table 10-2. Causes of Anemia in HIV

Cause	Cells	Reticulocyte count	Other tests	Treatment
HIV disease	Normal	Low	Low erythropoietin level	ART Recombinant human erythropoietin (rHU EPO)
Tumors and infectious diseases	Normal	Low	Positive identification of underlying disease (eg, lymphoma, KS, MAC, TB, CMV, histoplasmosis)	Treatment of underlying disease
Parvovirus	Normal	0	Positive serology & PCR for parvovirus	IVIG
Nutritional deficiency	MCV > 100 (but not with AZT or d4T)	Low	Low B12/folate level	Folic acid or cobalamin
Iron deficiency	MCV low	Low	Blood loss, low Fe, transferrin	Treatment of cause Iron therapy
Drug (toxicity)	Normal	Normal	Identify offending drug (zidovudine, ganciclovir, TMP-SMX, etc.)	Stop implicated agent
Drug (hemolysis)	Normal	Increased	Identify offending drug (dapsone, ribavirin); increased LDH, indirect bilirubin/low haptoglobin	RBC therapy Stop drug

LIVER DISEASE

What are the common causes of abnormal liver function tests?

Abnormal screening liver function tests reflect associated conditions (hepatitis B or C viral infection as discussed below), adverse drug reactions, alcoholic hepatitis, and HIV-related complications, including Kaposi sarcoma, lymphoma, *Mycobacterium avium* complex (MAC), tuberculosis, cytomegalovirus (CMV), or histoplasmosis. Start by defining the process as cholangiopathic or hepatocellular based on results of liver function tests (LFTs).

- AIDS cholangiopathy typically presents with right upper quadrant pain, high alkaline phosphatase, characteristic duct dilatation on ultrasound, and a CD4 cell count of $< 100/mm^3$. The usual causes are infection (microsporidia, cytomegalovirus, or cryptosporidia) or idiopathic. Most cases respond temporarily to endoscopic biliary sphincterotomy.
- Hepatocellular injury is much more common and is caused by diverse conditions, including 1) hepatitis viruses, 2) alcoholic hepatitis, 3) cirrhosis, and 4) adverse drug reactions. All antiretroviral drugs are potentially hepatotoxic, but the indications for intervention vary depending on the mechanism and severity (see Table 10-3).

When should you stop antiretroviral drugs because of hepatotoxicity?

There are 3 situations in which antiretroviral drugs should be stopped because of hepatotoxicity (see Table 10-3):

- **Hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms [DRESS])** The hypersensitivity reaction seen with abacavir (ABC) and nevirapine (NVP) is characterized by fever, eosinophilia, rash, and GI complaints, and usually occurs during the first 6 weeks of therapy. This situation should be urgently managed, and deaths have been reported.
- **Symptomatic lactic acidosis** This is ascribed to drugs in the NRTI class, which should be stopped.
- **Increased transaminase levels** This is ascribed to the PIs and the NNRTIs nevirapine (NVP) and efavirenz (EFV). The most serious reactions have occurred with nevirapine-associated hepatoxicity. The mechanism is unclear, and treatment interruption is often considered necessary only when clinical hepatitis occurs.

Do patients infected with HIV have increased rates of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, and does coinfection affect the natural progression of HIV?

HIV-infected patients have higher rates of chronic HBV infection after exposure to HBV. With HBV coinfection, there is a higher frequency of evidence for HBV replication (higher frequency of HBeAg and higher levels of HBV DNA) and higher rates of HBV-associated liver disease. It is not known if HBV alters the natural history of HIV, but coinfection is associated with increased frequency of hepatotoxicity with ART. The relationship with HCV is similar. HIV coinfection is relatively common, a frequency of about 30% in all HIV-infected patients and as many as 85% in those with injection drug use as the risk factor. HIV has an

Table 10-3. Antiretroviral Drugs That Cause Abnormal Liver Function

Drugs	Frequency of abnormal liver function	Comment
NRTIs		
stavudine (d4T) didanosine (ddI) zidovudine (AZT)	8%-16%	Mitochondrial toxicity; risk highest with stavudine and didanosine together; risk with zidovudine lower than stavudine
lamivudine (3TC) emtricitabine (FTC) abacavir (ABC) tenofovir (TDF)		Rare cause of mitochondrial toxicity
abacavir (ABC)	4%-6%	Hypersensitivity-DRESS syndrome
lamivudine (3TC) emtricitabine (FTC) tenofovir (TDF)		Withdrawal of these drugs may cause HBV exacerbation
NNRTIs		
nevirapine (NVP) efavirenz (EFV)	8%-16%	Mechanism not known
nevirapine (NVP)	Rare	Hypersensitivity – DRESS syndrome
PIs		
All PIs	4%-6%	Mechanism unknown
indinavir (IDV) atazanavir (ATV)	10%-20% 30%-50%	Elevated indirect bilirubin; usually asyptomatic

important effect on promoting more rapid progression of HCV, but it is not clear whether HCV adversely affects the rate of HIV progression. Many studies have shown that HCV coinfection is a poor prognostic factor in the ART era, but this may well reflect the influence of injection drug use rather than HCV-associated liver disease.

Who should you test for HBV and HCV, and what tests should you perform?

At entry into health care, all patients with HIV should be screened for antibodies to HBV and HCV, as well as HBV antigen (see Table 3-1 in Chapter 3). Knowledge of the HBV and HCV status can provide valuable information for those persons with abnormal LFTs. In addition, testing can identify patients who are seronegative for HBV who can receive HBV vaccination. Some patients with HIV have negative HBV surface antibody titers, negative HBV antigen, but positive core HBV antibody. If they have not recently acquired HBV, this serologic pattern suggests a low-level persistent immune response to HBV; these individuals probably have adequate protection to prevent reinfection, but no studies have been done to accurately evaluate their risk. Moreover, no formal recommendation exists to provide a booster HBV vaccine to those persons with negative HBV surface antibody titers but positive HBV core antibody. Serologic testing using an enzyme immunoassay for HCV is the preferred screening test for HCV, and those with positive tests should have a confirmatory test with either the RIBA assay or a test that detects HCV RNA. Several studies have shown that some persons coinfected with HIV and HCV, particularly those with severe advanced HIV disease, can have a negative HCV antibody test on the enzyme immunoassay, but a repeatable positive HCV RNA test. Thus, some experts would recommend doing an HCV RNA assay on a person with a negative HCV enzyme immunoassay if HCV infection is suspected (usually because of abnormal LFTs).

How should you treat HBV in persons coinfected with HIV?

All coinfected patients should be considered for HBV therapy. Recommendations are somewhat arbitrary, but most recommend therapy with an alanine aminotransferase (ALT) at least 2 times the upper limit of normal (ULN), evidence of active HBV replication (e antigen or HBV DNA level of $> 10^5$c/mL), and preferably with histologic evidence of moderate disease activity or fibrosis. There are 2 major forms of treatment and neither is "preferred." One form is interferon-alfa-2a or alfa-2b given subcutaneously 3 times a week or once a day for 24-48 weeks. Many authorities now

recommend pegylated interferon with subcutaneous injections once a week, although there are few published studies with this formulation for treatment of HBV. The second form of therapy is nucleosides and nucleotides with activity against HBV. This gets tricky because many of these agents are active against HIV as well, and there are variable rates of HBV resistance. Lamivudine (3TC) is highly active against HBV but is associated with high rates of HBV resistance, up to 90% at 4 years. The same applies to emtricitabine (FTC). Alternatives are adefovir dipivoxil (trade name Hepsera), which is used in a dose that is probably not active against HIV but is highly active against HBV, has good activity against lamivudine-resistant strains, and has low rates of resistance by HBV during treatment. Tenofovir (TDF) has the same attributes as adefovir but is also highly active against HIV. It should be emphasized that the rationale for treating HBV is to reduce viral replication and hepatic disease progression but that cure is rarely achieved. Other standard components of therapy in patients coinfected with HBV are 1) advising them to avoid or limit alcohol consumption, 2) teaching them appropriate precautions to prevent transmission of both viruses, and 3) administering hepatitis A vaccine if they are susceptible.

Who should receive HBV vaccine?

All HIV-infected persons with no evidence of HBV infection should receive this vaccine, although the response rates are related to age (decreased with increasing age) and with CD4 cell counts (responses decrease with lower counts). The standard is 3 doses followed by a measurement of HBs antibody levels about 1 month after the third dose. If the level is < 10 IU/mL the 3-dose series should be repeated. If the patient does not respond to the second series, no further vaccinations are currently recommended and the patient is considered a "non-responder."

How do you treat patients with HCV coinfection?

Patients coinfected with HIV and HCV should be 1) advised to avoid or limit alcohol consumption, 2) counseled to use appropriate precautions to prevent transmission of both viruses, and 3) given hepatitis A and B vaccine if they are susceptible. The prevention message should emphasize that the major route of transmission is by shared needles; the risk of transmission of HCV perinatally or with sexual contact is substantially less than that for HIV or HBV.

With regard to treatment of HCV, the goal is for cure, something that cannot be achieved with HIV or, to a large extent, with HBV. All patients with HCV should be evaluated for HCV therapy. Standard indications in the absence of HIV infection are chronic HCV, detectable HCV-RNA, and a liver biopsy showing bridging or portal fibrosis. The ALT levels may be elevated, but this finding is variable and does not indicate the severity of HCV-associated liver disease and is considered nonspecific. The liver biopsy is important for HCV therapeutic decisionmaking, but it is indicated only if the patient is considered a candidate for treatment based on multiple variables including the severity and stability of HIV, other comorbidities, probability of adherence, and contraindications for interferon. The standard treatment is pegylated interferon plus ribavirin for 48 weeks, regardless of the genotype. There is limited long-term experience with this treatment in patients with HIV coinfection, but it appears that the rate of a sustained virologic response as indicated by negative HCV DNA levels at 6 months post-therapy are significantly lower compared to those who are seronegative for HIV. This particularly applies to genotype 1, which accounts for the majority of cases. It also appears that the optimal response occurs when patients have relatively high CD4 cell counts, so this treatment is often preferred for those in early stage disease and for those who have responded to ART.

What HCV therapy should you use for persons coinfected with HIV and HCV?

Currently, there are limited published data regarding various HCV treatment regimens for persons coinfected with HIV. Trials have generally shown relatively poor responses to interferon monotherapy. Based on rapidly accumulating data from trials that have not included HIV-infected persons, pegylated interferon (pegylated interferon-alpha-2a or pegylated interferon-alpha-2b) plus ribavirin is now the standard of care. (For treatment guidelines, refer to Suggested Resources.) In addition, several series involving persons coinfected with HIV and HCV have suggested better sustained viral response rates with pegylated interferon plus ribavirin than with older regimens. For persons not infected with HIV, recent guidelines have recommended that those with genotypes 2 or 3 receive 24 weeks of therapy and those with genotypes 1 and 4 receive 48 weeks of therapy. The optimal duration of therapy for persons coinfected with HIV and HCV remains unknown, but most trials have used 48 weeks, regardless of genotype.

Are there special considerations regarding adverse effects of HCV therapy in persons coinfected with HIV?

Treatment with interferon (or pegylated interferon) and ribavirin has significant possible adverse effects, including reactions at injection sites, bone marrow suppression, thyroid dysfunction, neuropsychiatric symptoms, and birth defects. Because interferon may cause significant leukopenia, CD4 cell counts should be monitored, and patients should be warned that CD4 counts might transiently decline while they are receiving interferon. Persons coinfected with HCV and HIV may suffer drug interactions and toxicities. Ribavirin causes anemia; because this complication occurs more frequently when ribavirin is combined with AZT, either this combination should be avoided or more frequent use of erythtopoetin should be anticipated. Ribavirin may enhance intracellular didanosine (ddI) levels and augment toxicity of the drug resulting with higher rates of pancreatitis and lactic acidosis; didanosine should not be given with ribavirin.

Is liver transplantation an option for HIV-infected persons?

Liver transplantation is an option in some transplant centers that combine expertise in HIV management with the transplant service. In a study at 5 institutions of 24 HIV-infected patients survival rates were similar to rates in patients without HIV infection (Ragni et al, 2003). Nevertheless, management is complicated by problems of drug interactions between ART and the standard immunosuppressive agents, poor tolerance of ART after liver transplantation, and relatively high frequency of acute graft rejection. As in patients without HIV infection, the prognosis with liver transplantion is poorer when liver disease is caused by HCV. The recommendation at present is to give the highest priority in patients with HIV infection to those without HCV and to those receiving and tolerating ART who have achieved HIV virologic control and immune reconstitution.

Renal Disease

What are the possible causes of abnormal renal function tests?

Renal function is important to monitor because abnormal renal function may require altering drug dosage regimens, and it is important to know the cause of the abnormality. In general, renal dysfunction in patients with HIV infection can be caused by adverse drug reactions, HIV-associated nephropathy, and non-HIV-related conditions. The multitude of conditions that are not necessarily complications of HIV infection or its treatment include hypertension, glomerulonephritis, and heroin use.

For the patient on ART, what drugs are most likely to cause renal disease?

Adverse drug reactions that cause renal disease are most commonly associated with aminoglycosides, amphotericin, foscarnet, and cidofovir. The antiretroviral agent that is most frequently implicated is indinavir (IDV), which may cause indinavir crystals in the collection system, resulting in nephrolithiasis. The presentation may be renal colic, or it may be asymptomatic with evidence of crystals on urinalysis. In addition, indinavir can cause a crystal-induced nephropathy. On rare occasions, tenofovir (TDF) may cause renal insufficiency.

What are the cause and implications of HIV-associated nephropathy?

HIV-associated nephropathy, which is apparently the result of HIV infection of the kidney, presents as large, echogenic kidneys on ultrasound, nephrotic-range proteinuria, and rapidly progressing renal failure. This may occur at any stage of HIV but is most common as a late complication. Pre-ART studies show benefit from treatment with ACE inhibitors and possibly with corticosteroids; more recent studies show anecdotal evidence of a sometimes dramatic response to ART, but data from controlled trials are not available. Renal biopsy is necessary to establish the diagnosis. For patients with end-stage renal disease, there is increasing interest in and experience with renal transplantation. The usual criteria are irreversible renal failure combined with HIV response to ART resulting in virologic control and a CD4 cell count of $> 200 mm^3$.

KEY POINTS

Laboratory tests are frequently abnormal in HIV disease because 1) HIV is a multi-system disease, 2) HIV causes immune suppression that may result in opportunistic infections and tumors, 3) treatment has many potential adverse reactions affecting multiple systems, and 4) patients with HIV are often at high risk for other medical conditions.

Hematologic complications include anemia, neutropenia, and thrombocytopenia. The most common causes of anemia and neutropenia are either drug toxicity or the direct effect of HIV on progenitor cells; the cause of thrombocytopenia is most commonly a direct effect of HIV.

Liver disease is common because of high rates of concurrent viral hepatitis, especially HCV, and because all antiretrovirals are potentially hepatotoxic.

Abnormal renal function is usually a direct effect of HIV infection of the kidneys resulting in a rapid progression with nephrosis and end-stage renal disease; abnormal renal function from any cause is important to know about because it requires altering dose regimens for nucleosides.

SUGGESTED RESOURCES

Kimmel PL, Barisoni L, Kopp JB. Pathogenesis and treatment of HIV-associated renal diseases. *Ann Intern Med.* 2003;139:214-226.

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SUGGESTED RESOURCES

(CONTINUED)

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WEBSITES

CDC National Center for Infectious Diseases: http://www.cdc.gov/ncidod/diseases/hepatitis/ Accessed 2/04.

Hepatitis B Foundation: http://www.hepb.org Accessed 2/04.

HIV and Hepatitis: http://www.hivandhepatitis.com Accessed 2/04.

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