



CLINICAL GUIDELINES PROGRAM

NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV · HCV · SUBSTANCE USE · LGBT HEALTH

Laboratory Monitoring for Adverse Effects of ART

Lead Author: Noga Shalev, MD, with the Medical Care Criteria Committee, September 2019

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Laboratory Monitoring for Adverse Effects of ART

Purpose of This Guideline

This guideline was developed by the New York State Department of Health (NYSDOH) AIDS Institute (AI) to establish an evidence-based approach to routine laboratory monitoring of antiretroviral toxicity. Data are lacking regarding the need for and frequency of routine laboratory monitoring in patients receiving antiretroviral therapy (ART). To date, no randomized controlled studies have assessed the optimal type and frequency of monitoring. The data available are based on short-term randomized clinical trials of ART strategies, observational cohort data, and long-term epidemiologic data.

Refer to the NYSDOH AI guideline *Primary Care Approach* for information on other routine laboratory monitoring for patients with HIV.

Frequency of Laboratory Monitoring During ART

RECOMMENDATIONS: FREQUENCY OF LABORATORY MONITORING DURING ART

- Clinicians should screen patients for asymptomatic adverse events associated with antiretroviral therapy as detailed in *Table 1: Frequency of Laboratory Monitoring During Year 1 of Antiretroviral Therapy or at Regimen Change* and *Table 2: Frequency of Laboratory Monitoring After Year 1 of Antiretroviral Therapy*. (A3)
- Recommendations in the tables represent the minimum frequency of monitoring in healthy patients receiving antiretroviral therapy. Patients with comorbidities, polypharmacy, baseline laboratory abnormalities, or symptoms suggestive of antiretroviral toxicity may require more frequent testing (see *Tables 1 and 2* for ratings).

This guideline summarizes the recommended minimum frequency of routine laboratory monitoring in healthy patients receiving antiretroviral therapy (ART). Patients with comorbidities, or who take or start additional medications, or who have baseline laboratory abnormalities may require more frequent or additional evaluation. Patients with HIV should also be monitored for relevant age- and sex-specific health problems as per recommendations for the general population [Aberg, et al. 2014] (see the NYSDOH AI guideline *Primary Care Approach*). NYSDOH AI recommendations apply to resource-rich settings; [World Health Organization guidelines](#) do not require access to laboratory monitoring as a condition for initiation or continuation of ART [WHO 2016].

This Committee's recommendations diverge from those of other published guidelines in that they suggest less frequent monitoring for ART-related adverse effects [AIDSinfo 2017; Sax 2018]. The reduced frequency of testing reflects the notably reduced toxicities associated with [contemporary antiretroviral regimens](#), earlier initiation of ART, and the absence of data to support more frequent testing. This guideline also suggests less frequent monitoring after the first year of ART or at regimen change, based on the observation that most laboratory-detected toxicities occur in the first year of therapy [Gudina, et al. 2017].

The second section of this guideline, which addresses *Screening for Organ-Specific Adverse Effects*, discusses the range of adverse effects and toxicities associated with ART. Patients rarely present with symptoms suggestive of antiretroviral toxicity; frequent laboratory monitoring may be needed in such cases.

Table 1: Minimum Frequency of Laboratory Monitoring During Year 1 of Antiretroviral Therapy or at Regimen Change (Rating: A3)

Laboratory Test		Entry to Care or ART Initiation	At 4 Weeks	At 3 Months	At 6 Months	At 12 Months
Hepatic panel [a]		X		X		X
Random blood glucose		X		X		X
eGFR [b]	With TDF	X	X	X	X	X
	Without TDF [c]	X			X	X
Proteinuria [d]	With TDF	X		X		X
	Without TDF	X				X
Complete blood count	With ZDV	X	X	X	X	X
	Without ZDV	X				

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

Notes:

- a. AST, ALT, alkaline phosphates, and total bilirubin.
- b. Patients with decreased eGFR at baseline or those taking concomitant nephrotoxic drugs may need more frequent monitoring of renal function.
- c. Including TAF-containing regimens. See the section on *Screening for Organ-Specific Adverse Events > Nephrotoxicity* for more information.
- d. Urinalysis or urine protein-to-creatinine ratio.

Table 2: Minimum Frequency of Laboratory Monitoring After Year 1 of Antiretroviral Therapy (Rating: A3)

Laboratory Test		Every 6 Months	Every 1 Year
Hepatic panel [a]			X
Random blood glucose		X	
eGFR	With TDF	X	
	Without TDF [b]		X
Proteinuria [c]	With TDF		X
Complete blood count	With ZDV	X	
	Without ZDV	See the NYSDOH AI guideline <i>Primary Care Approach</i>	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

Notes:

- a. AST, ALT, alkaline phosphates, and total bilirubin.
- b. See the section on *Screening for Organ-Specific Adverse Events > Nephrotoxicity* for more information.
- c. Urinalysis or urine protein-to-creatinine ratio.

Screening for Organ-Specific Adverse Effects

Nephrotoxicity

Antiretroviral therapy (ART) has been associated with a range of renal complications that may lead to renal insufficiency or failure [Hall, et al. 2011]. Furthermore, renal impairment requires dose adjustment or discontinuation of several antiretroviral agents. Various guidelines recommend screening for ART-induced nephrotoxicity [Gorriz, et al. 2014; Holt, et al. 2014; Lucas, et al. 2014; AIDSinfo 2018]. Data to support screening strategies and frequency are most robust for the detection of ART-associated kidney dysfunction than other organ-specific toxicities. Nevertheless, many recommendations continue to rely on expert opinion and consensus. Patients with reduced baseline renal function and those taking concomitant nephrotoxic medications may require more frequent renal monitoring, as clinically indicated.

A number of antiretroviral agents (ARVs) have been implicated in kidney dysfunction. However, only medications that contain tenofovir prodrugs are considered directly nephrotoxic to the renal tubules and glomeruli. Tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are both prodrugs of tenofovir and are widely used components of antiretroviral regimens in the United States. Because various forms of renal impairment have been reported in patients receiving tenofovir prodrugs [Laprise, et al. 2013; Zaidan, et al. 2013], specific recommendations regarding frequency of laboratory monitoring for regimens that include these agents have been made in *Table 1: Minimum Frequency of Laboratory Monitoring During Year 1 of Antiretroviral Therapy or at Regimen Change* and *Table 2: Minimum Frequency of Laboratory Monitoring After Year 1 of Antiretroviral Therapy*.

Plasma concentrations of tenofovir are approximately 4-fold lower with use of TAF than with TDF, and nephrotoxicity due to TAF is rarely reported in individuals with a creatinine clearance rate of >30 mL/min. The tables provide recommendations for more frequent monitoring of renal function in patients taking TDF but not TAF. However, in a variety of clinical scenarios, such as when TAF is used in patients with low estimated glomerular filtration rates (eGFRs), or in patients with concomitant use of other nephrotoxic agents, or when a pharmaco-enhancer is added to ARV combination regimens containing the higher-dose (25 mg) TAF formulations, frequency of monitoring for TAF-induced nephrotoxicity may be increased to mirror the suggestions for TDF-containing regimens.

Either of the **MDRD** or **CKD-EPI** equations can be used to measure eGFRs (see the National Institute of Diabetes and Digestive and Kidney Diseases Health Information Center *Glomerular Filtration Rate Calculators*). Using the same method of estimation over time is recommended. Certain antiretroviral agents have been associated with decreased glomerular secretion of creatinine, leading to a small rise in serum creatinine levels without concomitant decline in GFR. These agents include rilpivirine, dolutegravir, bictegravir, and the pharmaco-enhancer cobicistat. A recent consensus statement from Australia recommends that serum creatinine levels be checked 1 month after initiation of these agents to establish a new “baseline” measurement [Holt, et al. 2014]. However, no data suggest this approach alters clinical management. Estimation of GFR with a serum cystatin C measurement may provide a more accurate assessment in patients taking agents that affect creatinine secretion and is increasingly utilized in clinical practice [Galizzi, et al. 2018; Yukawa, et al. 2018].

Finally, a number of protease inhibitors (PIs), including indinavir and atazanavir, have been shown to cause crystal-induced nephropathy.

→ KEY POINT

- Testing of serum creatinine levels 1 month after initiation of cobicistat, bictegravir, dolutegravir, and rilpivirine establishes a new “baseline.” These drugs are associated with decreased secretion of creatinine, leading to higher serum creatinine levels without a concomitant decline in GFR.

Hepatotoxicity

Most antiretroviral agents have the potential to cause idiopathic abnormalities in liver function, especially in patients with preexisting liver disease. As a class, nonnucleoside reverse transcriptase inhibitors (NNRTIs) show the highest rates of hepatotoxicity, most notably with the first-generation NNRTI nevirapine and, to a lesser extent, efavirenz. Because drug-induced hepatotoxicity of any kind generally occurs within the first 6 to 12 weeks of treatment, *Tables 1* and *2* make no distinction in terms of frequency of monitoring based on the ART regimen.

Dyslipidemia, Insulin Resistance, and Diabetes Mellitus

ART has been associated with weight gain, dyslipidemia, metabolic syndrome, insulin resistance and new-onset diabetes mellitus. A range of untoward lipid effects has been observed with a variety of ARVs, including PIs, NNRTIs, and certain NRTIs. In general, such changes are small and do not result in pharmacologic changes to lipid management. The traditional risk factors for metabolic disorders—such as age, weight, and diet—are stronger risk factors for metabolic disease than ART toxicity. Nevertheless, in several studies, patients with HIV had a higher rate of cardiovascular disease than controls without HIV [Currier, et al. 2003; Freiberg, et al. 2013] (see *2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease*). The use of certain ritonavir-boosted PIs has been associated with an increased risk of myocardial infarction in long-term observational studies [Friis-Moller, et al. 2007; Ryom, et al. 2018].

The tables do not provide specific recommendations for lipid profile testing in patients on ART. In most patients, screening should follow recommendations for the general population [Goff, et al. 2014; Siu 2015]. However, clinicians may opt to perform more frequent lipid testing in patients with underlying cardiovascular comorbidities and those taking a PI-based therapy.

Cytopenias

Bone marrow suppression as a consequence of ART is rare and most often associated with the use of zidovudine. The most common cytopenia caused by zidovudine is a macrocytic anemia. In resource-rich settings, early treatment and newer regimens have made cytopenias an extremely rare complication of ART. Only patients receiving zidovudine as part of their antiretroviral regimen require monitoring of blood counts.

Pancreatitis and Lactic Acidosis

In the early era of ART, the NRTIs stavudine and didanosine were associated with a significantly increased risk of both pancreatitis and lactic acidosis. However, pancreatitis and lactic acidosis are exceedingly rare complications with current ART regimens. Therefore, routine laboratory monitoring of serum lipase and lactic acid to detect these abnormalities is not recommended with contemporary ART regimens.

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All Recommendations

All RECOMMENDATIONS: LABORATORY MONITORING FOR ADVERSE EFFECTS OF ART

Frequency of Laboratory Monitoring During ART

- Clinicians should screen patients for asymptomatic adverse events associated with antiretroviral therapy as detailed in *Table 1: Frequency of Laboratory Monitoring During Year 1 of Antiretroviral Therapy or at Regimen Change* and *Table 2: Frequency of Laboratory Monitoring After Year 1 of Antiretroviral Therapy*. (A3)
- Recommendations in the tables represent the minimum frequency of monitoring in healthy patients receiving antiretroviral therapy. Patients with comorbidities, polypharmacy, baseline laboratory abnormalities, or symptoms suggestive of antiretroviral toxicity may require more frequent testing (see *Tables 1* and *2* for ratings).