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

Laboratory Monitoring for Adverse Effects of ART

Guideline Information

Intended users	Clinicians providing ambulatory care for patients with HIV
Last reviewed and updated	June 8, 2021
Lead author	Noga Shelev, MD
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Writing group	Joseph P. McGowan, MD, FACP, FIDSA; Steven M. Fine, MD, PhD; Rona Vail, MD; Samuel T. Merrick, MD; Asa Radix, MD, MPH, PhD; Christopher J. Hoffmann, MD, MPH; Charles J. Gonzalez, MD
Committee	Medical Care Criteria Committee
Developer and funding	New York State Department of Health AIDS Institute (NYSDOH AI)
Development	See Supplement: Guideline Development and Recommendation Ratings

Updates

June 8, 2021	**Noga Shelev, MD, with the MCCC:** Updated Table 1: Minimum Laboratory Monitoring Frequency With Initiation of or Change in ART for Patients <50 Years Old and Without Chronic Comorbidities to recommend laboratory monitoring of renal function in patients taking tenofovir alafenamide (TAF) at the same frequency as for patients taking tenofovir disoproxil fumarate (TDF).

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Contents

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 Comprehensive Primary Care for Adults With HIV 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 (ART) as detailed in Table 1: Minimum Laboratory Monitoring Frequency With Initiation of or Change in ART for Patients <50 Years Old and Without Chronic Comorbidities. (A3)
- Recommendations in Table 1 represent the minimum frequency of monitoring in healthy patients receiving ART. Patients with comorbidities, polypharmacy, baseline laboratory abnormalities, or symptoms suggestive of antiretroviral toxicity may require more frequent testing. (A3)

This guideline summarizes the recommended minimum frequency of routine laboratory monitoring in healthy patients receiving 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 Comprehensive Primary Care for Adults With HIV). 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 [DHHS 2022b; 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 guideline section 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 Laboratory Monitoring Frequency With Initiation of or Change in ART for Patients <50 Years Old and Without Chronic Comorbidities [a] (Rating: A3)

	Year 1 of ART (initiation or change)			After 1 Year on ART Regimen	
Laboratory Test	**Baseline**	**3 Months**	**12 Months**	**Every 6 Months**	**Annual**
Hepatic panel (AST, ALT, alkaline phosphates, total bilirubin)	All	All	All	—	All
Random blood glucose	All	All	All	—	—
Complete blood count [b]	All	With ZDV	With ZDV	With ZDV	—
eGFR [c]	All	All	With TAF or TDF	—	With TAF or TDF
Test for proteinuria (urinalysis or protein-to-creatinine ratio), glucosuria, serum phosphorus	With TAF or TDF	—	With TAF or TDF	—	With TAF or TDF

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

Notes:

a. More frequent monitoring may be required for patients >50 years old and patients with chronic comorbidities.
b. See the NYSDOH AI guideline Comprehensive Primary Care for Adults With HIV.
c. Patients with decreased eGFR at baseline or those taking concomitant nephrotoxic drugs may need more frequent monitoring of renal function. See the guideline section Screening for Organ-Specific Adverse Events > Nephrotoxicity for more information.

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 (ARVs). Various guidelines recommend screening for ART-induced nephrotoxicity [DHHS 2022a; Gorriz, et al. 2014; Holt, et al. 2014; Lucas, et al. 2014]. 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 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 fumarate (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 Laboratory Monitoring Frequency With Initiation of or Change in ART for Patients <50 Years Old and Without Chronic Comorbidities.

Plasma concentrations of tenofovir are approximately 4-fold lower with use of TAF than with TDF, and while nephrotoxicity due to TAF is rare, cases of acute renal failure, proximal renal tubulopathy, and Fanconi Syndrome have

been reported in clinical use. Therefore, Table 1 provides recommendations for frequency of monitoring of renal function in patients taking tenofovir prodrugs (TDF and TAF) that does not distinguish formulation used.

Either of the MDRD or CKD-EPI equations can be used to measure estimated glomerular filtration rates (GFRs, 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 ARVs 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 ARVs have the potential to cause idiopathic abnormalities in liver function, especially in patients with preexisting liver disease. As a class, non-nucleoside 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, there is no recommended 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 nucleoside reverse transcriptase inhibitors (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 [Freiberg, et al. 2013; Currier, et al. 2003] (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 [Ryom, et al. 2018; Friis-Moller, et al. 2007].

Table 1: Minimum Laboratory Monitoring Frequency With Initiation of or Change in ART for Patients <50 Years Old and Without Chronic Comorbidities does not provide specific recommendations for lipid profile testing in patients on ART. In most patients, screening should follow recommendations for the general population [Siu 2015; Goff, et al. 2014]. 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.

All Recommendations

☑ ALL RECOMMENDATIONS

Frequency of Laboratory Monitoring During ART

- Clinicians should screen patients for asymptomatic adverse events associated with antiretroviral therapy (ART) as detailed in Table 1: Minimum Laboratory Monitoring Frequency With Initiation of or Change in ART for Patients <50 Years Old and Without Chronic Comorbidities. (A3)
- Recommendations in Table 1 represent the minimum frequency of monitoring in healthy patients receiving ART. Patients with comorbidities, polypharmacy, baseline laboratory abnormalities, or symptoms suggestive of antiretroviral toxicity may require more frequent testing. (A3)

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Supplement: Guideline Development and Recommendation Ratings

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding Source	NYSDOH AI
Program Manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff.
Mission	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
Expert Committees	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout NYS to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of NYS, all relevant clinical practice settings, key NYS agencies, and community service organizations. See Expert Committees.
Committee Structure	• Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor • Contributing members • Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Conflicts of Interest Disclosure and Management	• Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation. • The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member.
Evidence Collection and Review	• Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. • A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.
Recommendation Development	• The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee's expert opinion. • The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Review and Approval Process	• Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. • Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations when required. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External Reviewers	• External peer reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback. • Peer reviewers may include nationally known experts from outside of New York State.
Update Process	• JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations. • If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates. • All contributing committee members review and approve substantive changes to, additions to, or deletions of recommendations; JHU editorial staff track, summarize, and publish ongoing guideline changes.

Table S2: Recommendation Ratings and Definitions		
Strength	**Quality of Evidence**	
A: Strong B: Moderate C: Optional	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
	*	Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial.
	2	Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes.
	2†	Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline.
	3	Based on committee expert opinion, with rationale provided in the guideline text.