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

Laboratory Monitoring for Adverse Effects of ART

Updates, Authorship, and Related Guidelines

Date of current publication	November 22, 2024
Highlights of changes, additions, and updates in the November 22, 2024 edition	• Updated to include long-acting injectable forms of ART • Added discussion of weight gain and diabetes mellitus risk associated with certain ART regimens • Updated citations and references throughout the guideline
Intended users	Clinicians providing ambulatory care for patients with HIV
Lead author	Shauna Gunaratne, MD, MPH, DTM&H
Writing group	Rona M. Vail, MD, AAHIVS; Sanjiv S. Shah, MD, MPH, AAHIVS; Steven M. Fine, MD, PhD; Joseph P. McGowan, MD, FACP, FIDSA, AAHIVS; Samuel T. Merrick, MD, FIDSA; Asa E. Radix, MD, MPH, PhD, FACP, AAHIVS; Anne K. Monroe, MD, MSPH; Jessica Rodrigues, MPH, MS; Christopher J. Hoffmann, MD, MPH, MSc, FACP; Brianna L. Norton, DO, MPH; Charles J. Gonzalez, MD
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Committee	Medical Care Criteria Committee
Developer and funder	New York State Department of Health AIDS Institute (NYSDOH AI)
Development process	See Supplement: Guideline Development and Recommendation Ratings
Related NYSDOH AI guideline	Primary Care for Adults With HIV

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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 taking oral and long-acting injectable 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.

The guideline aims to achieve the following goals:

- Assist clinicians in determining the frequency of routine laboratory monitoring for adverse effects of ART.
- Inform clinicians about the range of adverse effects and toxicities associated with ART.

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

Frequency of Laboratory Monitoring During ART

☑ RECOMMENDATION

Frequency of Laboratory Monitoring During ART

- Clinicians should screen patients for asymptomatic adverse effects associated with oral and long-acting injectable antiretroviral therapy (ART) as detailed in Table 1: Minimum Laboratory Monitoring Frequency With Initiation of or Change in ART for Patients Aged <50 Years and Without Chronic Comorbidities [a]. (A3)

Note:

a. 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.

This guideline summarizes the recommended minimum frequency of routine laboratory monitoring in healthy patients receiving ART. Patients with HIV should also be monitored for relevant age- and sex-specific health problems [Thompson, et al. 2021]. Patients with comorbidities, or who take or start additional medications, or who have baseline laboratory abnormalities may require more frequent or additional evaluation. 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.

This committee's recommendations diverge from those of other published guidelines in that they suggest less frequent monitoring for ART-related adverse effects [UpToDate 2023; DHHS 2022]. 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]. This guideline applies to both oral and long-acting injectable formulations of ART.

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 Oral and Long-Acting Injectable ART for Patients Aged <50 Years 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 [b]**	**12 Months**	**Every 6 Months**	**Annual**
Hepatic panel (AST, ALT, alkaline phosphatase, total bilirubin)	All	All	All	—	All
Random blood glucose	All	All	All	—	With INSTIs or PIs
Complete blood count [c]	All	With ZDV	With ZDV	With ZDV	—
eGFR [d]	All	All	With TAF or TDF	—	With TAF or TDF [a]
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; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

Notes:

a. More frequent monitoring may be required for patients aged ≥50 years and patients with chronic comorbidities.
b. Monitoring for patients using long-acting injectable ART may occur every 3 or 4 months to align with injection appointments to minimize healthcare visits.
c. See NYSDOH AI guideline Primary Care for Adults With HIV.
d. Patients with decreased eGFR at baseline or those taking concomitant nephrotoxic drugs may need more frequent monitoring of renal function (see guideline section Screening for Organ-Specific Adverse Effects > 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 2024; Cervantes and Atta 2023; Gillis, et al. 2015]. 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 (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 [Cervantes and Atta 2023], 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 Aged <50 Years 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 possible Fanconi Syndrome have been reported in clinical use [Bahr and Yarlagadda 2019; Novick, et al. 2017]. 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 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]. 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 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. Current evidence does not show associations between specific ARTs and abnormal liver enzymes in patients on long-term ART [Chew, et al. 2023].

Dyslipidemia, insulin resistance, and diabetes mellitus: ART has been associated with weight gain, dyslipidemia, metabolic syndrome, insulin resistance, and new-onset diabetes mellitus (see NYSDOH AI guideline Primary Care for Adults With HIV > HIV-Specific Primary Care > Metabolic changes). A range of untoward lipid effects has been observed with a variety of ARVs, including PIs, NNRTIs, and certain nucleoside reverse transcriptase inhibitors (NRTIs) [Kalra, et al. 2023]. In general, such changes are small and do not result in pharmacologic changes to lipid management.

Emerging evidence has shown weight gain associated with switching from TDF to TAF and switching from NNRTI-based regimens to integrase strand transfer inhibitor (INSTI)-based regimens, especially when the switches occur together [Erlandson, et al. 2021; Mallon, et al. 2021; Surial, et al. 2021; van Wyk, et al. 2021; Bourgi, et al. 2020; Lake, et al. 2020; Venter, et al. 2020]. The observed effect of weight gain may be due to cessation of weight suppression caused by TDF and, possibly, NNRTI-based regimens. This information may help care providers more accurately frame the discussion with patients on observed weight gain with ARV switches [Bosch, et al. 2023; Bourgi, et al. 2023].

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 [Hirsch, et al. 2024; Grinspoon, et al. 2023; Freiberg, et al. 2013; Currier, et al. 2003] (see 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary 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]. Current or prior abacavir use has also been associated with an elevated risk of cardiovascular events and myocardial infarction in persons with HIV, as seen in multiple large cohort studies [Fichtenbaum, et al. 2024; Jaschinski, et al. 2023; Elion, et al. 2018]. INSTI-based regimens have been associated with a higher risk of development of diabetes mellitus than non-INSTI-based regimens [O'Halloran, et al. 2022; Rebeiro, et al. 2021].

Table 1: Minimum Laboratory Monitoring Frequency With Initiation of or Change in ART for Patients Aged <50 Years 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 patients without HIV [Avgousti and Feinstein 2023; Grinspoon, et al. 2023; Feinstein, et al. 2019]. However, clinicians may opt to perform more frequent lipid testing in patients with underlying cardiovascular comorbidities and those taking a PI-based therapy. Clinicians may also opt to perform diabetes mellitus screening in patients with weight gain after initiating ART and those on INSTI-based regimens.

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: LABORATORY MONITORING FOR ADVERSE EFFECTS OF ART

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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 New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations.
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
Disclosure and management of conflicts of interest	• 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. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External reviews	• External review of each guideline is invited at the developer's discretion. • External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.
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 and will invite full committee review as indicated.

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.