Laboratory Monitoring for Adverse Effects of ART

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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**

- Clinicians should screen patients for asymptomatic adverse events associated with antiretroviral therapy as detailed in Table 1: Minimum Laboratory Monitoring Frequency With Initiation of or Change in Antiretroviral Therapy for Patients <50 Years Old and Without Chronic Comorbidities. (A3)
- Recommendations in Table 1 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. (A3)

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 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 [Sax 2018; Clinical Info HIV.gov 2019]. 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 third 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 Laboratory Monitoring Frequency With Initiation of or Change in Antiretroviral Therapy for Patients <50 Years Old and Without Chronic Comorbidities [a] (Rating: A3)

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Year 1 of ART (initiation or change)</th>
<th>After 1 Year on ART Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 Months</td>
</tr>
<tr>
<td>Hepatic panel (AST, ALT, alkaline phosphates, total bilirubin)</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Random blood glucose</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Complete blood count [b]</td>
<td>All</td>
<td>With ZDV</td>
</tr>
<tr>
<td>eGFR [c]</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Test for proteinuria (urinalysis or protein-to-creatinine ratio), glucosuria, serum phosphorus</td>
<td>With TAF or TDF</td>
<td>—</td>
</tr>
</tbody>
</table>

**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 section on 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 [Gorriz, et al. 2014; Holt, et al. 2014; Lucas, et al. 2014; Clinical Info HIV.gov 2021]. 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 Antiretroviral Therapy 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 [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].

*Table 1: Minimum Laboratory Monitoring Frequency With Initiation of or Change in Antiretroviral Therapy 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 [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.
All Recommendations

All RECOMMENDATIONS: LABORATORY MONITORING FOR ADVERSE EFFECTS OF ART

Frequency of Laboratory Monitoring During ART

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References


