Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring

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HIV RNA (viral load) and CD4 T lymphocyte cell (CD4) count are the two surrogate markers of antiretroviral therapy (ART) responses and HIV disease progression that have been used for decades to manage and monitor HIV infection.

Viral load is a marker of response to ART. A patient's pre-ART viral load level and the magnitude of viral load decline after initiation of ART provide prognostic information about the probability of disease progression.[1] The key goal of ART is to achieve and maintain durable viral suppression. Thus, the most important use of the viral load is to monitor the effectiveness of therapy after initiation of ART.

CD4 count provides information on the overall immune function of a person with HIV. Measurement of CD4 count is particularly useful **before** initiation of ART to establish the need for the initiation of opportunistic infection (OI) prophylaxis and to assess the urgency to initiate ART; and **after** initiation of ART to assess immunologic response and to establish the need for discontinuation of OI prophylaxis.

The management of patients with HIV has changed substantially with the availability of newer, more potent, and less toxic antiretroviral (ARV) agents. ART is now recommended for all patients with HIV regardless of their viral load or CD4 count **(AI)** (see the Initiation of Antiretroviral Therapy section). In the past, the clinical practice supported by treatment guidelines was generally to monitor both CD4 count and viral load concurrently. However, because most patients with HIV in care now receive ART, the rationale for frequent CD4 count monitoring is weaker. The roles and usefulness of these two tests in clinical practice are discussed in the following sections.

Plasma HIV-1 RNA (Viral Load) Monitoring

Viral load is the most important indicator of initial and sustained response to ART and should be measured in all patients with HIV at entry into care **(AI),** at initiation of therapy **(AI),** and on a regular basis thereafter. For those patients who choose to delay therapy or remain untreated for whatever reason, repeat viral load testing while not on ART is optional **(CIII).** Pre-treatment viral load level is also an important factor in the selection of an initial ARV regimen, because several currently approved ARV drugs or regimens have been associated with poorer responses in patients with high baseline viral load (see the What to Start section). Commercially available HIV-1 RNA assays do not detect HIV-2 viral load. For further discussion on HIV-2 RNA monitoring in patients with HIV-1/HIV-2 coinfection or HIV-2 mono-infection, see the HIV-2 Infection section.

Several systematic reviews of data from clinical trials involving thousands of participants have established that decreases in viral load following initiation of ART are associated with reduced risk of progression to AIDS or death.[1-3] Thus, viral load testing is an established surrogate marker for treatment response.[4] The minimal change in viral load considered to be statistically significant (2 standard deviations) is a three-fold change (equivalent to a 0.5 $\log_{10}$ copies/mL change). Optimal viral suppression is defined as a confirmed HIV RNA level below the lower limit of detection of available assays (generally <20 copies/mL, depending on the assay used). After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression, known as a "blip," may occur in successfully treated patients and is not usually predictive of virologic failure.[5] Furthermore, the data on the association between persistently low level but quantifiable viremia (HIV RNA <200 copies/mL) and virologic failure is conflicting. One study showed an increased risk of subsequent failure at this level of viremia; however, the association was not observed in other studies.[6-9] These guidelines and the AIDS Clinical Trials Group (ACTG) now define

virologic failure as the inability to achieve or maintain suppression of viral replication to HIV RNA level <200 copies/mL—a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability[10] (see the Virologic Failure section).

Individuals who are adherent to their ARV regimens and do not harbor resistance mutations to the component drugs can generally achieve viral suppression 8 to 12 weeks after ART initiation or after modification due to virologic failure; rarely, it may take longer in some patients. Recommendations on the frequency of viral load monitoring are summarized below:

- **After initiation of ART.** Plasma viral load should be measured before initiation of ART and within 4 to 8 weeks after treatment initiation **(AIII).** The purpose of the measurements is to confirm an adequate virologic response to ART, indicating appropriate regimen selection and patient adherence to therapy. Repeat viral load measurement should be performed at 4- to 8-week intervals until the level falls below the assay's limit of detection **(BIII).**
- **In patients with viral suppression, with ART modification because of drug toxicity or for regimen simplification.** Viral load measurement should be performed within 4 to 8 weeks after changing therapy **(AIII).** The purpose of viral load monitoring at this point is to confirm the effectiveness of the new regimen.
- **In patients on a stable, suppressive ARV regimen.** Viral load measurement should be repeated every 3 to 4 months **(AIII)** or as clinically indicated to confirm continuous viral suppression. Clinicians may extend the interval to 6 months for adherent patients whose viral load has been suppressed for more than a year, whose clinical and immunologic status is stable, and who are not at risk for inadequate adherence **(AIII).**
- **In patients with virologic failure who require a change in ARV regimen.** Plasma viral load should be measured before ART change and within 4 to 8 weeks after treatment modification **(AIII).** The purpose of the measurements is to confirm an adequate virologic response to the new regimen. Repeat viral load measurement should be performed at 4- to 8-week intervals until the level falls below the assay's limit of detection **(BIII).** If viral suppression is not possible, repeat viral load measurement every 3 months or more frequently if indicated **(AIII).**
- **In patients with suboptimal response.** The frequency of viral load monitoring will depend on clinical circumstances, such as adherence and availability of further treatment options. In addition to viral load monitoring, several other factors—such as patient adherence to prescribed medications, suboptimal drug exposure, or drug interactions—should be assessed. Patients who fail to achieve viral suppression should undergo drug-resistance testing to aid in the selection of an alternative ARV regimen (see the Drug-Resistance Testing and Virologic Failure sections).

CD4 Count Monitoring

The CD4 count is the most important laboratory indicator of immune function in patients with HIV. It is also the strongest predictor of disease progression and survival according to findings from clinical trials and cohort studies.[11,12] CD4 counts are highly variable; a significant change (2 standard deviations) between two tests is approximately a 30% change in the absolute count, or an increase or decrease in CD4 percentage by 3 percentage points. Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful and is more expensive than monitoring CD4 count alone; therefore, it **is not recommended (BIII).**

Use of CD4 Count for Initial Assessment

CD4 count should be measured in all patients at entry into care **(AI).** It is the key factor in determining the need to initiate OI prophylaxis (see the Adult and Adolescent Opportunistic Infections Guidelines)[13] and the urgency to initiate ART **(AI)** (see the Initiation of Antiretroviral Therapy section). Although most OIs occur in patients with CD4 counts <200 cells/mm^3, some OIs can occur in patients with higher CD4 counts.[14]

Use of CD4 Count for Monitoring Therapeutic Response

The CD4 count is used to assess a patient's immunologic response to ART. It is also used to determine whether prophylaxis for OIs can be discontinued (see the Adult and Adolescent Opportunistic Infections Guidelines).[13] For most patients on therapy, an adequate response is defined as an increase in CD4 count in the range of 50 cells/mm^3 to 150 cells/mm^3 in the first year of ART, generally with an accelerated response in the first 3 months of treatment. Subsequent increases average approximately 50 cells/mm^3 to 100 cells/mm^3 per year until a steady state level is reached.[15] Patients who initiate therapy with a low CD4 count[16,17] or at an older age[18] may have a blunted increase in their counts despite virologic suppression.

Frequency of CD4 Count Monitoring

ART is now recommended for all patients with HIV. In patients who remain untreated for whatever reason, CD4 counts should be monitored every 3 to 6 months to assess the urgency of ART initiation and the need for OI prophylaxis **(AIII).**

A repeat CD4 count 3 months after ART initiation will provide information regarding the magnitude of immune reconstitution **(AIII).** This repeat measurement is most important in patients who initiate ART with more advanced disease and require OI prophylaxis or treatment. In these patients, the magnitude and duration of CD4 count increase can be used to determine whether to discontinue OI prophylaxis and/or treatment as recommended in the Adult and Adolescent Opportunistic Infections Guidelines.[13] For patients beginning ART, CD4 count should be repeated every 3 months for the first 2 years of suppressive ART for those with CD4 counts <300 cells/mm^3 and every 6 months if CD4 count is ≥300 cells/mm^3. After 2 years of suppressive ART, CD4 count monitoring can be reduced to every 6 months for patients whose CD4 counts remain at <300 cells/mm^3 and every year for patients with CD4 counts between 300 cells/mm^3 and 500 cells/mm^3, and is optional for those with CD4 counts >500 cells/mm^3 **(BII).**

The CD4 count response to ART varies widely, but a poor CD4 response in a patient with viral suppression is rarely an indication for modifying an ARV regimen. In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution (i.e., CD4 count >500 cells/mm^3), the CD4 count provides limited information. Frequent testing is unnecessary, because the results rarely lead to a change in clinical management. One retrospective study found that declines in CD4 count to <200 cells/mm^3 are rare in patients with viral suppression and CD4 counts >300 cells/mm^3.[19] Similarly, the ARTEMIS trial found that CD4 count monitoring had no clinical benefit in patients who had suppressed viral loads and CD4 counts >200 cells/mm^3 after 48 weeks of therapy.[20] Furthermore, the risk of *Pneumocystis jirovecii* pneumonia is extremely low in patients on suppressive ART who have CD4 counts between 100 cells/mm^3 and 200 cells/mm^3.[21] Although uncommon, CD4 count declines can occur in a small percentage of virologically suppressed patients and may be associated with adverse clinical outcomes, such as cardiovascular disease, malignancy, and death.[22] An analysis of costs associated with CD4 count monitoring in the United States estimated that reducing CD4 count monitoring in treated patients from every 6 months to every 12 months could result in annual savings of approximately $10 million.[23]

For the patient on a suppressive ARV regimen whose CD4 count has consistently ranged between 300 cells/mm^3 and 500 cells/mm^3 for at least 2 years, the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends CD4 count monitoring on an annual basis **(BII).** Continued CD4 count monitoring for virologically suppressed patients whose CD4 counts have been consistently >500 cells/mm^3 for at least 2 years may be considered optional **(CIII).** The CD4 count should be monitored more frequently, as clinically indicated, when there are changes in a patient's clinical status that may decrease CD4 count and thus prompt OI prophylaxis. Examples of such changes include the appearance of new HIV-associated clinical symptoms or initiation of treatment known to reduce CD4 count (e.g., chronic corticosteroids, antineoplastic agents) **(AIII).** In patients who fail to maintain viral suppression while on ART, the Panel recommends CD4 count monitoring every 3 to 6 months **(AIII).**

Factors that Affect Absolute CD4 Count

The absolute CD4 count is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4 T lymphocytes. This absolute number may fluctuate in individuals or may be influenced by factors that may affect the total WBC count and lymphocyte percentages, such as use of bone marrow-suppressive medications, chronic corticosteroids, or the presence of acute infections. Splenectomy[24,25] or coinfection with human T-lymphotropic virus type I (HTLV-1)[26] may cause misleadingly elevated CD4 counts. In all these settings, CD4 percentage remains stable and may be a more appropriate parameter to assess a patient's immune function.[27]

Table 4. Recommendations on the Indications and Frequency of Viral Load and CD4 Count Monitoring[a]

Clinical Scenario	Viral Load Monitoring	CD4 Count Monitoring
Before initiating ART	At entry into care (AIII) If ART initiation is deferred, repeat before initiating ART (AIII). In patients not initiating ART, repeat testing is optional (CIII).	At entry into care (AI) If ART is deferred, every 3 to 6 months[a] (AIII)
After initiating ART	Preferably within 4 to 8 weeks after initiation of ART (AIII); thereafter, every 4 to 8 weeks until viral load is suppressed (BIII).	3 months after initiation of ART (AIII)
After modifying ART because of drug toxicities or for regimen simplification in a patient with viral suppression	4 to 8 weeks after modification of ART to confirm effectiveness of new regimen (AIII).	Monitor according to prior CD4 count and duration on ART, as outlined below.
After modifying ART because of virologic failure	Preferably within 4 to 8 weeks after modification (AIII); thereafter, every 4 to 8 weeks until viral load is suppressed (BIII). If viral suppression is not possible, repeat viral load testing every 3 months or more frequently if indicated (AIII).	Every 3 to 6 months (AI)
During the first 2 years of ART	Every 3 months (AIII)	Every 3 months if CD4 <300 cells/mm^3 (BII) Every 6 months if CD4 ≥300 cells/mm^3 (BII)
After 2 years of ART (VL consistently suppressed, CD4 remains <300 cells/mm^3)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years (AIII).	Every 6 months (BII)
After 2 years of ART (VL consistently suppressed, CD4 consistently 300–500 cells/mm^3)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years (AIII).	Every 12 months (BII)
After 2 years of ART (VL consistently suppressed, CD4 consistently >500 cells/mm^3)	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years (AIII).	Optional (CIII)
While on ART with detectable viremia (VL repeatedly >200 copies/mL)	Every 3 months (AIII) or more frequently if clinically indicated (see Virologic Failure).	Every 3 to 6 months (AIII)
Change in clinical status (e.g., new HIV clinical symptom or initiation of chronic systemic corticosteroids, or antineoplastic therapy)	Every 3 months (AIII)	Perform CD4 count and repeat as clinically indicated[b] (AIII)

[a] Some experts may repeat CD4 count measurement every 3 months in patients with low baseline CD4 counts (<200–300 cells/mm^3) before ART but every 6 months in those who initiated ART at higher CD4 counts (e.g., >300 cells/mm^3).

[b] The following are examples of clinically indicated scenarios: changes in a patient's clinical status that may decrease CD4 count and thus prompt initiation of prophylaxis for opportunistic infection, such as new HIV-associated symptoms, or initiation of treatment with medications that are known to reduce CD4 count.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; VL = viral load

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