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

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HIV RNA (viral load) and CD4 T lymphocyte (CD4) cell 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 person'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.[1-4] The key goal of ART is to achieve and maintain durable viral suppression. Thus, an important use of the viral load is to monitor the effectiveness of therapy after initiation of ART. The use of viral load testing to confirm the attainment and maintenance of viral suppression is instrumental in the operationalization of Undetectable = Untransmittable (or U=U)/Treatment as Prevention (see the Antiretroviral Therapy to Prevent Sexual Transmission of HIV [Treatment as Prevention] section).

It should be noted that commercially available HIV-1 RNA assays do not detect HIV-2 viral load. For further discussion on HIV-2 RNA monitoring in people with HIV-1/HIV-2 coinfection or HIV-2 mono-infection, see the HIV-2 Infection section.

CD4 count provides information on the overall immune function of a person with HIV. Measurement of CD4 count at entry into care and **before** initiation of ART is particularly useful in establishing the need to initiate opportunistic infection (OI) prophylaxis. Monitoring **after** initiation of ART is important for assessing immunologic response and establishing the need to discontinue OI prophylaxis.

The management of people with HIV has changed substantially with the availability of newer, more potent, easier-to-use, and less toxic antiretroviral (ARV) drugs. ART is recommended for all people with HIV regardless of their viral load or CD4 count **(AI)** (see the Initiation of Antiretroviral Therapy section). Because almost all people with HIV in care now receive ART and achieve good immunologic responses, the rationale for frequent CD4 count monitoring is weaker. The roles and usefulness of these two tests in clinical practice are discussed below.

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 people with HIV at entry into care **(AI),** at initiation of therapy (if treatment is delayed) **(AI),** and on a regular basis thereafter. For those people in whom therapy is delayed, repeat viral load testing is recommended approximately every 3 to 6 months **(BIII),** aligning with CD4 count testing. Repeating viral load testing at these intervals provides an opportunity for discussions about the benefits of ART, both for the treatment of HIV and prevention of HIV transmission. Pre-treatment viral load level is also an important factor in the selection of an initial ARV regimen because some ARV drugs or regimens have been associated with poorer responses in people with high baseline viral load (see the What to Start section).

Several systematic reviews of data from clinical trials involving thousands of participants in the early era of potent ART have established that decreases in viral load following initiation of ART are associated with reduced risk of progression to AIDS or death.[1-4] Thus, viral load testing is an established surrogate marker for treatment response. The minimal change in viral load considered to be statistically significant (2 standard deviations) is a threefold 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 people 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. Several studies showed an increased risk of subsequent failure, drug resistance, morbidity, and mortality at this level of viremia[6-12]; however, the association was not observed in other studies.[10,11,13-17] These guidelines now define virologic failure as the inability to achieve or maintain suppression of viral replication to HIV RNA levels of <200 copies/mL—a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability[18] (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 people. Recommendations on the frequency of viral load monitoring are summarized below:

- **After initiation of ART:** Plasma viral load should be measured when ART is initiated **(AI)** and within 4 to 8 weeks after treatment initiation **(AIII).** The purpose of these measurements is to confirm an adequate virologic response to ART, indicating appropriate regimen selection and individual adherence to therapy. Repeat viral load measurement should be performed every 4 to 8 weeks until the level falls below the assay's limit of detection **(BIII).**
- **In people with viral suppression, with ART modification because of regimen simplification or drug toxicity:** 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 people 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 people 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 people 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 every 4 to 8 weeks 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 people 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 individual adherence to prescribed medications, suboptimal drug exposure, or drug interactions—should be assessed. People 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 people with HIV. Low pre-treatment CD4 count is the strongest predictor of disease progression and mortality according to findings from clinical trials and cohort studies.[4,19] 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 three percentage points. Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) **is not recommended (BIII)** because it has not been proven to be clinically useful and is more expensive than monitoring CD4 count alone.

Use of CD4 Count for Initial Assessment

CD4 count should be measured in all people with HIV 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)[20] and the urgency to initiate ART **(AI),** even though ART is recommended for all people with HIV, regardless of CD4 count **(AI)** (see the Initiation of Antiretroviral Therapy section). Although most OIs occur in people with CD4 counts <200 cells/mm^3, some OIs can occur in people with higher CD4 counts.[21]

Use of CD4 Count for Monitoring Response to ART

The CD4 count is used to assess a person'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).[20] For most people, 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.[22] People who initiate therapy with a low CD4 count[23,24] or at an older age[25] may have a blunted increase in their counts despite virologic suppression.

Frequency of CD4 Count Monitoring

ART is recommended for all people with HIV. For people with HIV and pre-treatment CD4 count <300 cells/mm^3, repeating CD4 count 3 months after ART initiation will provide information regarding the magnitude of immune reconstitution **(AIII).** This repeat measurement is most important in people who initiate ART with more advanced disease and require OI prophylaxis or treatment. In these individuals, 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. After ART initiation, CD4 count should be repeated every 3 to 4 months for the first 1 to 2 years of suppressive ART for those with CD4 counts <300 cells/mm^3 **(BII)** and every 6 months if CD4 count is ≥300 cells/mm^3 with viral suppression **(BIII).** After 1 to 2 years of suppressive ART, reducing CD4 count monitoring to every 6 months may be considered for some people whose CD4 counts remain at <300 cells/mm^3 **(BIII);** for those with CD4 counts ≥300 cells/mm^3, CD4 count monitoring is optional unless clinically indicated **(BIII).**

The CD4 count response to ART varies widely, but a poor CD4 response in a person with viral suppression is rarely an indication for modifying an ARV regimen (see the Suboptimal CD4 Recovery section). In people with consistently suppressed viral loads who have already experienced ART-related immune reconstitution (i.e., CD4 count ≥300 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 people with viral suppression and CD4 counts >300 cells/mm^3.[26] Similarly, the ARTEMIS trial found that CD4 count monitoring had no clinical benefit in people who had suppressed viral loads and CD4 counts >200 cells/mm^3 after 48 weeks of therapy.[27] Furthermore, the risk of *Pneumocystis jirovecii* pneumonia is extremely low in people on suppressive ART who have CD4 counts between 100 cells/mm^3 and 200 cells/mm^3.[28] Although uncommon, CD4 count declines can occur in a small percentage of virologically suppressed people and may be associated with adverse clinical outcomes, such as cardiovascular disease, malignancy, and death.[29,30]

An analysis of costs associated with CD4 count monitoring in the United States estimated that reducing CD4 count monitoring in treated people from every 6 months to every 12 months could result in annual savings of approximately $10 million.[31]

CD4 count should be monitored more frequently, as clinically indicated, when there are changes in a person'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 people who do not maintain viral suppression while on ART, CD4 count monitoring should be done every 3 to 6 months **(AIII).**

In people who remain untreated for whatever reason, CD4 count should be monitored every 3 to 6 months to monitor for disease progression and assess the urgency of ART initiation and the need for OI prophylaxis **(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[32,33] or coinfection with human T-lymphotropic virus type I[34] may cause misleadingly elevated CD4 counts. In all these settings, CD4 percentage remains stable and may be a more appropriate parameter to assess a person's immune function.[35]

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