Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Management of the Treatment-Experienced Patient

Virologic Failure and Suboptimal Immunologic Response (Last updated May 1, 2014; last reviewed May 1, 2014)

Panel's Recommendations

- Assessing and managing an antiretroviral (ARV)-experienced patient experiencing antiretroviral therapy (ART) failure is complex. Expert advice is critical and should be sought.
- Evaluation of virologic failure should include an assessment of adherence, drug-drug or drug-food interactions, drug tolerability, HIV RNA and CD4 T lymphocyte (CD4) cell count trends over time, treatment history, and prior and current drug-resistance testing results.
  - Drug-resistance testing should be performed while the patient is taking the failing ARV regimen **(AI)** or within 4 weeks of treatment discontinuation **(AII)**. Even if more than 4 weeks have elapsed since the ARVs were discontinued, resistance testing can still provide useful information to guide therapy, though it may not detect previously selected resistance mutations **(CIII)**.
- The goal of treatment for ARV-experienced patients with drug resistance who are experiencing virologic failure is to establish virologic suppression (i.e., HIV RNA below the lower limits of detection of currently used assays) **(AI)**.
- A new regimen should include at least two, preferably three, fully active agents **(AI)**. A fully active agent is one that is expected to have ARV activity on the basis of the patient's treatment history and drug-resistance testing results and/or the drug's novel mechanism of action.
- In general, adding a single fully active ARV agent to a virologically failing regimen is **not** recommended because of the risk of development of resistance to all drugs in the regimen **(BII)**.
- For some highly ARV-experienced patients, maximal virologic suppression is not possible. In this case, ART should be continued **(AI)** with regimens designed to minimize toxicity, preserve CD4 cell counts, and at least delay clinical progression.
- When no viable suppressive regimen can be constructed for a patient with multi-drug resistant HIV, the clinician should consider enrolling the patient in a clinical trial of investigational agents or contacting pharmaceutical sponsors that may have investigational agents available.
- Discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases the risk of clinical progression. Therefore, this strategy is **not** recommended **(AI)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

With use of antiretroviral therapy (ART) regimens currently recommended for initial therapy, HIV-infected patients have a high likelihood of achieving and maintaining plasma HIV RNA levels below the lower limits of detection (LLOD) of currently used assays (see What to Start). Patients on ART who do not achieve this treatment goal or who experience virologic rebound often develop resistance mutations to one or more components of their regimens, depending upon the regimen initiated. It is estimated that nearly 25% of those receiving ART are not virologically suppressed.[1,2] Many patients with detectable viral loads are non-adherent to treatment. Depending on their treatment histories, some of these patients may have minimal or no drug resistance; others may have extensive resistance. Managing patients with extensive resistance is complex and usually requires consultation with an HIV expert. This section of the guidelines defines virologic failure in patients on ART and discusses strategies to manage these individuals.

Virologic Definitions

Virologic Suppression: A confirmed HIV RNA level below the LLOD of available assay.

Virologic Failure: The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL.

Incomplete Virologic Response: Two consecutive plasma HIV RNA levels ≥200 copies/mL after 24 weeks on an ARV regimen. Baseline HIV RNA may affect the time course of response; some regimens will take longer than others to suppress HIV RNA levels.

Virologic Rebound: Confirmed HIV RNA ≥200 copies/mL after virologic suppression.

Virologic Blip: After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

Goal of ART Treatment and Virologic Responses

The goal of ART is to suppress HIV replication to a level below which drug-resistance mutations do not emerge. Although the evidence is not conclusive, it is generally believed that selection of drug resistance mutations does not occur in patients with HIV RNA levels persistently suppressed to below the LLOD of current assays.[3]

There is controversy regarding the clinical implications of HIV RNA levels between the LLOD and <200 copies/mL in patients on ART. In addition, viremia at this threshold appears to occur more frequently because newer real-time PCR assays are more sensitive than PCR-based viral load platforms used in the past.[4-6] Findings from a large retrospective analysis showed that an HIV RNA threshold for virologic failure of <200 copies/mL had the same predictive value for virologic rebound to >200 copies/mL as a threshold of <50 copies/mL.[7] However, some studies have suggested that viremia at this low level (i.e., <200 copies/mL) can be predictive of progressive viral rebound[8,9] and can be associated with the evolution of drug resistance.[10] In contrast to in individuals with higher levels of HIV RNA, a substantial amount of circulating virus in those with low level of HIV RNA (<50 copies/mL) is believed to result from the release of HIV from long-lived latently infected cells and does not signify ongoing viral replication with the potential emergence of drug-resistant virus.[11]

Persistent HIV RNA levels ≥200 copies/mL are often associated with evidence of viral evolution and accumulation of drug-resistance mutation.[12] This association is particularly common when HIV RNA levels are >500 copies/mL.[13] Therefore, persistent plasma HIV RNA levels ≥200 copies/mL should be considered virologic failure.

Viremia blips (e.g., viral suppression followed by a detectable HIV RNA level and subsequent return to undetectable levels) are not usually associated with subsequent virologic failure.[14]

Causes of Virologic Failure

Virologic failure can occur in a patient for many reasons. Data from patient cohorts in the earlier era of combination ART suggested that suboptimal adherence and drug intolerance/toxicity accounted for 28% to 40% of virologic failure and regimen discontinuations.[15,16] More recent data suggest that most virologic failure on first-line regimens occurs because of either pre-existing (transmitted) drug resistance or suboptimal adherence.[17] Virologic failure is associated with both patient- and regimen-related factors.

Patient-Related Factors:

- Higher pretreatment or baseline HIV RNA level (depending on the specific regimen used)
- Lower pretreatment or nadir CD4 T-cell count (depending on the specific regimen used)
- Comorbidities (e.g., active substance abuse, psychiatric disease, neurocognitive deficits)
- Presence of drug-resistant virus, either transmitted or acquired
- Prior treatment failure
- Incomplete medication adherence and missed clinic appointments

- Interruption of or intermittent access to ART

ARV Regimen-Related Factors:

- Drug adverse effects and toxicities
- Suboptimal pharmacokinetics (variable absorption, metabolism, or, theoretically, penetration into reservoirs)
- Suboptimal virologic potency
- Prior exposure to suboptimal regimens (e.g., functional monotherapy)
- Food requirements
- High pill burden and/or dosing frequency
- Adverse drug-drug interactions with concomitant medications
- Prescription errors

Management of Patients with Virologic Failure

Assessment of Virologic Failure

If virologic failure is suspected or confirmed, a thorough work-up that includes consideration of the factors listed in the Causes of Virologic Failure section above is indicated. In many cases, the cause(s) of virologic failure can be identified. In some cases, however, no obvious cause(s) may be found. It is important to distinguish among the causes for virologic failure because the approaches to subsequent therapy differ. The following potential causes of virologic failure should be explored in depth.

- **Incomplete Adherence.** Assess the patient's adherence to the regimen. Identify and address the underlying cause(s) for incomplete adherence (e.g., drug intolerance, difficulty accessing medications, depression, active substance abuse) and, if possible, simplify the regimen (e.g., decrease pill count or dosing frequency) (see Adherence).
- **Medication Intolerance.** Assess the patient's tolerance of the current regimen and the severity and duration of side effects, keeping in mind that even minor side effects can affect adherence. Management strategies to address intolerance in the absence of drug resistance may include:
  - Using symptomatic treatment (e.g., antiemetics, antidiarrheals)
  - Changing one ARV in a regimen to another agent in the same drug class (see Adverse Effects section)
  - Changing from one drug class to another class (e.g., from a Non-Nucleoside Reverse Transcriptor Inhibitor [NNRTI] to a protease inhibitor [PI] or an integrase strand transfer inhibitor [INSTI]) if necessary (see Adverse Effects section).
- **Pharmacokinetic Issues.**
  - Review food requirement for each medication, and assess whether the patient adheres to the requirement.
  - Review recent history of gastrointestinal symptoms such as vomiting or diarrhea that may result in short-term malabsorption.
  - Review concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult Drug Interactions section and tables for common interactions) and make appropriate substitutions for ARV agents and/or concomitant medications, if possible.
  - Consider therapeutic drug monitoring (TDM) if pharmacokinetic drug-drug interactions or impaired drug absorption leading to decreased ARV exposure is suspected (see also Exposure-Response Relationship and Therapeutic Drug Monitoring).

- **Suspected Drug Resistance.** Perform resistance testing while the patient is still taking the failing regimen or within 4 weeks after the regimen is discontinued if the patient's plasma HIV RNA level is >1000 copies/mL **(AI)**, and possibly even if between 500 to 1000 copies/mL **(BII)** (see Drug-Resistance Testing). In some patients, resistance testing should be considered even after treatment interruptions of more than 4 weeks—recognizing that the lack of evidence of resistance in this setting does not exclude the possibility that resistance mutations may be present at low levels **(CIII)**. Evaluate the extent of drug resistance, taking into account the patient's past treatment history and prior resistance test results. Drug resistance is cumulative; thus, all prior treatment history and resistance test results should be considered when evaluating resistance. Routine genotypic or phenotypic testing provides information relevant for selecting nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, and PIs. Additional drug-resistance tests for patients experiencing failure on INSTIs and/or a fusion inhibitor **(AII)**, and viral tropism tests for patients experiencing failure on a CCR5 antagonist **(BIII)** are also available. Typically, these tests must be ordered separately from tests for resistance to NRTIs, NNRTIs, and PIs. (See Drug-Resistance Testing.)

Managing Virologic Failure

Once virologic failure is confirmed, every effort should be made to assess if poor adherence and drug-drug or drug-food interactions may be contributing to the inadequate virologic response to ART. In general, if virologic failure persists after these issues have been adequately addressed, the regimen should be changed as soon as possible to avoid progressive accumulation of resistance mutations.[18] In addition, several studies have shown that virologic responses to new regimens are greater in individuals with lower HIV RNA levels[8,19] and/or higher CD4 cell counts at the time of regimen changes.[8,19] Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases the risk of clinical progression.[20,21] Therefore, this strategy is **not** recommended **(AI)** (see Discontinuation or Interruption of Antiretroviral Therapy).

Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs whose expected activity is based on the patient's drug treatment history, resistance testing, or the mechanistic action of a new drug class **(AI)**.[8,22-31] Despite drug resistance, some ARV drugs (e.g., NRTIs) may contribute partial ARV activity to a regimen[21], but other agents (e.g., enfuvirtide [T-20], NNRTIs, raltegravir [RAL]) likely will not.[32-34] Using a "new" drug that a patient has not previously taken does not ensure that the drug will be fully active; there is still the potential for drug-class cross-resistance that reduces drug activity. In addition, archived drug-resistance mutations may not be detected by standard drug-resistance tests, particularly if testing is performed when the patient is not taking the drug in question. This illustrates the importance of considering both treatment history and prior and current drug-resistance test results when designing a new regimen. Drug potency and viral susceptibility are more important factors to consider than the number of component drugs.

In general, patients who receive at least three active drugs selected on the basis of past and present drug resistance test results and treatment history, experience better and more sustained virologic responses than those receiving regimens with fewer active drugs. However, in select cases, adding a fully active ritonavir-boosted [RTV] PI (PI/r) to a single active drug may result in a regimen that is as effective as a regimen that includes more active agents.[23,24,26,27,35,36] Active ARV drugs are those with activity against drug-resistant viral strains. These include newer members of existing drug classes that are active against HIV that are resistant to older drugs in the same classes (e.g., ETR, DRV and tipranavir [TPV], and dolutegravir [DTG])[8,31] and drugs with unique mechanisms of action (e.g., the fusion inhibitor T-20, the CCR5 antagonist maraviroc [MVC] in patients with no detectable CXCR4-using virus). In the presence of certain drug resistance mutations, the recommended doses of select ARVs, such as DRV/r and DTG need to be given twice daily instead of once daily to achieve higher drug concentrations.[37,38] Drug-resistance tests for patients experiencing failure on a FI and/or INSTIs, and viral tropism tests for patients experiencing failure on a CCR5 antagonist are also available, although these assays must be performed independent of routine drug resistance testing (see Drug-Resistance Testing).

Clinical Scenarios of Virologic Failure

- **HIV RNA above the LLOD and <200 copies/mL.** Confirm that levels remain above the LLOD and assess adherence and drug-drug interactions (including those with over the counter products and supplements) and drug-food interactions. Patients with HIV RNA typically below the LLOD with transient increases in HIV RNA (i.e., blips) do not require a change in treatment **(AII)**.[5] Although there is no consensus on how to manage patients with persistent HIV RNA levels above the LLOD and <200 copies/mL, the risk of emerging resistance is believed to be relatively low. Therefore, these patients should be followed on their current regimens with HIV RNA levels monitored at least every 3 months to assess the need for changes in ART in the future **(AIII)**.

- **HIV RNA ≥200 and <1000 copies/mL.** Confirm that levels remain in this range, assess adherence, drug-drug interactions (including those with over the counter products and supplements), and drug-food interactions. In contrast to patients with HIV RNA levels persistently <200 copies/mL, those with persistent HIV RNA levels ≥200 copies/mL often develop drug resistance, particularly when their HIV RNA levels are >500 copies/mL. Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should be considered as virologic failure and resistance testing should be attempted if the HIV RNA level is >500 copies/mL. For individuals with sufficient therapeutic options, consider treatment change **(BIII)**.

- **HIV RNA >1000 copies/mL and NO drug resistance identified.** This scenario is almost always associated with non-adherence. Conduct a thorough assessment to determine the level of adherence and identify any drug-drug and drug-food interactions. Consider the timing of the drug-resistance test (e.g., Was the patient off ART for more than 4 weeks and/or nonadherent with the regimen at the time testing was performed?). Consider resuming the same regimen or starting a new regimen. Two to four weeks after treatment is resumed repeat viral load testing and—if viral load remains >500 copies/mL—perform genotypic testing to determine whether a resistant viral strain emerges **(CIII)**.

- **HIV RNA >1000 copies/mL and drug resistance identified.** The goals in this situation are to suppress HIV RNA levels maximally (i.e., to below the LLOD) and to prevent further selection of resistance mutations. With the availability of several newer ARVs, including some with new mechanisms of action, it is now possible to achieve these goals in many patients, including in those with extensive treatment experience and drug resistance. In the case of virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. In a patient with ongoing viremia and evidence of resistance, some drugs in a regimen (e.g., NNRTIs, T-20, or INSTIs) should be discontinued promptly to decrease the risk of selection of additional drug-resistance mutations and to preserve the activity of these drug classes in future regimens. A new regimen should include at least two, and preferably three, fully active agents **(AII)**. If only two active drugs can be identified, whenever possible, an active ritonavir-boosted PI (PI/r) should be prescribed as part of the regimen because of its higher genetic barrier for resistance. In a new regimen, it is the number of active agents and not necessarily the drug class that is most important. This principle was demonstrated in the OPTIONS study; virologic outcomes in those taking at least 2 fully active drugs were equal, whether or not the regimen was supplemented with NRTIs.[39]

Patients who fail a first-line, NNRTI-based regimen often have resistance to the NNRTI, as well as the cytosine analog components of the regimen (e.g., lamivudine [3TC] and emtricitabine [FTC]). The optimal management strategy for these patients is not known, but a number of studies have now demonstrated the activity of a fully active ritonavir-boosted PI (PI/r) alone[40] or with another fully active drug or even with an agent that has only partial activity. Three of these trials were head-to-head comparisons in this patient population.[41-43] Despite evidence of NRTI resistance in many of these patients, two of the studies found that regimens consisting of a PI/r combined with NRTIs were as active as the PI/r combined with RAL,[41,43] two other studies showed that the PI/r plus NRTIs combination was more active than the PI/r alone.[42,43] Resistance testing should be used to

guide therapy; however, on the basis of these studies, even those with NRTI resistance can be treated with a PI/r plus 2 to 3 NRTIs or RAL **(AI)**. Although data are limited, the second generation NNRTI ETR or the new INSTI DTG combined with a PI/r may also be an option in this situation.

- **Highly drug resistant HIV.** In recent years, use of currently available ARV drugs has resulted in a dramatic decline in the number of patients who have few treatment options because of multi-class drug resistance.[44] Despite this decline, there remains a subset of patients who have experienced toxicity and/or developed resistance to all or most currently available drugs such that design of a regimen with two or three fully active drugs is not possible. These patients may have started therapy before newer, more potent ARVs were available; thus, they developed resistance but had no options for salvage therapy. Standard genotypic testing for RT and PR mutations may be inadequate to identify fully active drugs to add to a new regimen. Additional testing for INSTI resistance, as well as genotypic and phenotypic testing for PR and RT mutations, may be necessary. A tropism assay can also help to determine whether MVC can be added to the new regimen.

If maximal virologic suppression cannot be achieved, the goals of ART are to preserve immunologic function and to prevent clinical progression, even in those with ongoing viremia. There is no consensus on the optimal management of these patients. It is reasonable to observe a patient on the same regimen, rather than changing the regimen, depending on the stage of HIV disease **(BII)**. Even partial virologic suppression of HIV RNA to >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefits.[45] Cohort studies provide evidence that continuing therapy, even in the presence of viremia and the absence of CD4 count increases, reduces the risk of disease progression.[46] Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained at <10,000 to 20,000 copies/mL.[47,48] However, these potential benefits all must be balanced with the ongoing risk of accumulating additional resistance mutations. The management of these patients always requires expert advice. In general, adding a single fully active ARV to the regimen is **not** recommended because of the risk of rapid development of resistance **(BII)**. However, in patients with a high likelihood of clinical progression (e.g., those with CD4 cell count <100 cells/mm^3) and limited drug options, adding a single drug to a regimen may reduce the risk of immediate clinical progression because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits **(CI)**. Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., ARV activity) of adding a single active drug to the regimen of a heavily ART-experienced patient is complicated and consultation with an expert is advised.

Patients with ongoing viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for research studies or expanded access programs or may qualify for single-patient access of an investigational new drug(s) (IND) as specified in Food and Drug Administration (FDA) regulations: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm163982.htm. Information about these programs may also be available from the sponsoring pharmaceutical manufacturer.

- **Previously treated patient with suspected drug resistance and in need of care but with limited information (i.e., incomplete or no self-reported history, medical records, or resistance data).** Every effort should be made to obtain the patient's medical records and prior drug-resistance testing results; however, this may not always be possible. One strategy is to restart the most recent ARV regimen and assess drug resistance in 2 to 4 weeks to guide selection of the next regimen. Another strategy is to start two or three drugs known to be active on the basis of the patient's treatment history (e.g., MVC if the patient has no detectable X4 virus and an INSTI if there is no prior history of treatment with drugs in this class).

In summary, the management of treatment-experienced patients with virologic failure often requires expert advice to achieve the goal of constructing virologically suppressive regimens. It is critical to carefully evaluate the cause of virologic failure including assessment of adherence, drug and food interactions, tolerability, HIV RNA and CD4 cell count changes over time, treatment history, and drug-resistance test

results before switching regimens. If HIV RNA suppression with use of currently approved agents is not possible, consider use of investigational agents that are available through clinical trials or expanded/single-patient access programs. If virologic suppression is still not achievable, the choice of regimens should focus on minimizing toxicity and preserving treatment options while maintaining CD4 cell counts to delay clinical progression.

Suboptimal Immunologic Response Despite Viral Suppression

After ART initiation, most patients experience improved immune function and maintain viral suppression; however, there remains a subset of patients who have suboptimal immunologic responses—defined as the failure to achieve and maintain an adequate CD4 response despite virologic suppression. In ARV-naive patients on initial ARV regimens, during the first year of ART, CD4 counts usually increase by approximately 150 cells/mm^3.[49] A CD4 count plateau may occur after 4 to 6 years of treatment with suppressed viremia.[50-54]

Although there is not an accepted specific definition for suboptimal immunologic response, some studies have focused on a failure to increase CD4 counts above a specific threshold (e.g., >350 or 500 cells/mm^3) over a specific period of time (e.g., 4 to 7 years). Others have focused on an inability to increase CD4 counts above pretherapy levels by a certain threshold (e.g., >50 or 100 cells/mm^3) over a given time period. The former criterion may be preferable because of data linking these thresholds with the risk of non-AIDS clinical events.[55]

The proportion of patients experiencing suboptimal immunologic response depends on how suboptimal response is defined, the observation period, and the CD4 count when treatment was started. In the longest study conducted to date, the percentage of patients with suppressed viremia who reached a CD4 count >500 cells/mm^3 through 6 years of treatment was 42% in those starting treatment with a CD4 count <200 cells/mm^3, 66% in those starting with a CD4 count 200 to 350 cells/mm^3, and 85% in those starting with a CD4 count >350 cells/mm^3.[56]

A persistently low CD4 count while on suppressive ART is associated with a small, but appreciable, risk of AIDS- and non-AIDS-related morbidity and mortality.[57,58] For example, in the FIRST study,[59] a low CD4 count on therapy was associated with an increased risk of AIDS-related complications (adjusted hazard ratio of 0.56 per 100 cells/mm^3 higher CD4 count). Similarly, a low CD4 count was associated with an increased risk of non-AIDS events, including cardiovascular, hepatic, and renal disease and cancer. Other studies support these associations.[60-63]

The following are some factors that have been associated with poor CD4 cell response:

- CD4 count <200/mm^3 at initiation of ART
- Older age
- Coinfection (e.g., hepatitis C virus [HCV], HIV-2, human T-cell leukemia virus type 1 [HTLV-1], HTLV-2)
- ARVs (e.g., zidovudine [ZDV],[64] tenofovir disoproxil fumarate [TDF] + didanosine [ddI][65-67]) and other medications
- Persistent immune activation
- Loss of regenerative potential of the immune system
- Concomitant medical conditions

Assessment of Patients with Suboptimal Immunologic Responses

CD4 count should be confirmed by repeat testing. Concomitant medications should be reviewed carefully, with a focus on those known to decrease white blood cells or, specifically, CD4 T-cells (e.g., cancer chemotherapy, interferon, prednisone, ZDV; combination of TDF and ddI), and consideration should be given to substituting or discontinuing these drugs, if possible. Untreated coinfections (e.g., HIV-2, HTLV-1,

HTLV-2) and serious medical conditions (e.g., malignancy) also should be considered. In many cases, no obvious cause for immunologic failure can be identified.

Management of Patients with Suboptimal Immunologic Response

There is no consensus with regards to when or how to manage patients with suboptimal immunologic response. Given the risk of clinical events, it is reasonable to focus on patients with CD4 counts <200 cells/mm^3 because patients with higher CD4 counts have a lower risk of clinical events. It is not clear that suboptimal immunologic response in the setting of virologic suppression should prompt a change in the ARV regimen. Because ongoing immune activation occurs in some patients with suppressed HIV RNA levels, some have suggested adding a drug to an existing regimen. However, this strategy does not result in clear virologic or immunologic benefit. Others suggest changing the regimen to another regimen (e.g., from NNRTI-based to PI-based, INSTI-based, or CCR5 antagonist-based regimens), but this strategy has not shown clear benefit.

In two large randomized studies, an immune-based therapy, interleukin-2, demonstrated CD4 count increases but no clinical benefit[68] and therefore is not recommended **(AI)**. Other immune-based therapies (e.g., gene therapies, growth hormone, cyclosporine, interleukin-7) are under investigation. Currently, immune-based therapies should not be used outside the context of a clinical trial **(AIII)**.

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