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Defining Treatment Failure in Resource-Rich Settings

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Abstract

Purpose of review—To define treatment failure in resource-rich settings; summarizing current guidelines, assays, the significance of detectable viremia, and definitions of treatment failure in clinical and research settings.

Recent findings—The goal of treatment should be full viral suppression, even in highly treatment experienced patients.

Summary—Treatment failure is defined as repeated HIV RNA values above the lower limit of detection of a sensitive assay (usually 50 copies per mL). This is based on evidence that the maximum clinical benefit of antiretroviral therapy is derived by keeping the viral load as low as possible. Full viral suppression should be achievable in all patients, both treatment naïve and experienced. Transient, low-detectable viremia (“blips”) may not predict virologic breakthrough. However, consecutive or higher-level transient viremia is associated with risk of treatment failure. Defining failure by a confirmed HIV RNA >50 copies/mL is the most conservative approach, but the use of such low limits of detection in clinical trials may lead to a high false positive “failure” rate, thus a definition of 200 copies/ mL may be preferable. Variation in clinical trial endpoint definitions creates a challenge for comparing results between studies. For example, using a composite endpoint to define treatment failure may result in a high proportion of “failures” that are not related to poor virologic response.

Keywords

Virologic failure; Treatment failure; Viral load; HIV RNA; Blips

INTRODUCTION

There is no standard definition of antiretroviral treatment failure: failure can be defined by clinical, immunologic, or virologic measures. However, since the effect of antiretroviral therapy is to reduce viral load, the success of antiretroviral treatment is defined most specifically by viral suppression. Although no trials have clearly established the exact viral load threshold necessary to achieve sustained clinical benefit, current consensus opinion and clinical evidence suggest that the goal of an HIV RNA level below the limit of detection

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(generally <50 copies/mL) should be the standard of care, even for highly treatment experienced patients.

This review will discuss the definition of treatment failure in resource-rich settings. It will cover the use of the viral load as a surrogate for HIV disease progression, current treatment guidelines, currently available assays, low-level viremia despite ARV therapy, monitoring for treatment failure in the clinic, and the use of different criteria for virologic failure in clinical trials.

WHY DEFINE FAILURE?

Detection of virologic failure is important for preventing disease progression and avoiding the development of antiretroviral resistance [1,2]. As such, a clear endpoint for failure needs to be established at the initiation of therapy. In the clinical setting, this facilitates communication between patient and physician regarding clinical response, and to help guide decisions on when to perform resistance testing or when to change medications. In the research setting, failure definitions establish measurable endpoints for comparison of study results. In either case, definitions of virologic failure need to be both sensitive and specific; neglecting significant viremia can lead to resistance and poorer clinical outcomes [3,4], but too stringent a definition of treatment failure may lead to unnecessary treatment changes [5,6*].

DEFINING FAILURE BY THE VIROLOGIC RESPONSE TO THERAPY

Since the late 1990s, when studies demonstrated that a decrease in HIV viral load correlated with decreased clinical disease progression [7–9*], periodic measurement of the viral load has been the standard of care for monitoring response to treatment in resource-rich settings. The validation of viral load as a clear surrogate for disease progression- correlating with both CD4 count and survival- allowed HIV RNA to become a marker for monitoring patients clinically. It also became a primary study endpoint in the approval of new antiretrovirals, obviating the need for clinical endpoint studies.

After the establishment of HIV RNA as a disease surrogate, subsequent research confirmed the benefit of frequent viral load monitoring [10], which is now recommended every 3–6 months. Similarly, viral load targets have evolved over the years, dropping to the current goal of <50 copies/mL. This has occurred despite the fact that relatively few studies have directly compared the risks and benefits of using different virologic thresholds to define treatment failure. However, the movement towards lower standards for acceptable viremia is reasonable based on a) the early (and continued) evidence that high viral load predicts CD4 decline and AIDS progression, b) the finding that persistently detectable viremia while on antiretrovirals risks the development of resistance mutations (albeit slowly if the viral load is low) [2,11–13], and c) research showing the negative effects of viremia, independent of CD4 count [14**].

Immunologic and clinical endpoints can also be incorporated into definitions of treatment failure, and it is of course clinically relevant to consider these factors in evaluating the overall picture of “treatment failure”. However, although CD4 count is a better short-term predictor of progression to AIDS or death, the maintenance of viral suppression is the best method to ensure long term success of therapy. Hence the strong focus on evaluating *virologic* failure in resource rich settings.

GUIDELINES FOR DEFINING TREATMENT FAILURE

Several panels provide guidelines for determining if a patient is failing to respond to ARV therapy (Table 1) [15–17]. All give a timeline of 24 weeks after starting therapy for achieving

virologic suppression at <50 copies/mL (allowing a longer timeline if the pretreatment viral load is high), and a goal to keep viral load undetectable thereafter. Viral rebound is defined as a *confirmed* viremia greater than the limit of detection. A genotype at baseline and at time of confirmed treatment failure is recommended.

It should be noted that these guidelines differ significantly from guidelines for defining treatment failure in developing nations [18].

ASSAYS

The methods most commonly used clinically for quantifying HIV-1 RNA levels (viral loads) are reverse transcription-polymerase chain reaction (RT-PCR) (Roche Amplicor HIV-1 Monitor v1.5), Nucleic Acid Sequence-based Amplification (NASBA) (bioMérieux NucliSens), Branched Chain DNA (bDNA) (Bayer Versant HIV RNA 3.0), and quantitative real-time PCR assays (Abbott RealTime HIV-1 and Roche Taqman HIV-1). There are also assays available that estimate viral load via RT activity (Cavidi ExaVir Load) and p24 antigen levels (Up24). These are less expensive (but less sensitive) and are currently under evaluation for use in resource-limited settings [19,20].

The lower limit of detection for the currently used ultrasensitive assays varies slightly by assay but the most common definition for “undetectable” in the literature is <50 copies per ml (based on the lower limit of detection of the widely used Roche Amplicor Monitor assay). Although the newer assays may report numeric values lower than 50 copies per ml, the majority of published data is based on thresholds of <50. Since there may be variation among assays near the lower limits of detection, there are currently no recommendations on how to use values <50 copies/mL to guide clinical decision-making.

A number of factors such as biological variation around the patient’s steady state, differences in handling of samples, or selection of a different assay can cause the same patient to go from “undetectable” to “detectable” without any change in that patient’s risk for success or failure [21–25]. A recent “outbreak” of detectable viremia in previously suppressed patients illustrates this point. With the introduction of a new viral load assay, one HIV treatment center found that 77% of previously undetectable patients developed detectable HIV RNA. An investigation found this to be due to a change in the recommended handling of plasma samples rather than due to patient factors or a difference in sensitivity between the two assays [25]. However, sensitivity differences may also exist between the assays, particularly near the lower limits of detection. For example, Lima and colleagues recently reported that a change from Roche Amplicor Monitor to the Roche Taqman assay resulted in a higher proportion of patients reported as >50 copies/mL [26]. Their study found poor correlation between the two assays near the lower limit of detection (other reports have also found some variability at the lower ranges but with a more acceptable degree of correlation [27–29]). Furthermore, there are differences in sensitivity by sub-type. A recent comparison of the real-time PCR assays found that the Roche Taqman appeared to have lower sensitivity for non-B subtypes (and it does not detect group O) [28].

Thus, in both clinical and research settings, the clinician should be aware of the specific assay in use and of any changes in assay or sample processing. Attention must be paid to the sensitivity of an assay for the predominant sub-type in the clinical or study population. When possible, the same lab and viral load detection methodology should be used within a clinic or throughout a study to minimize intra-assay and intra-laboratory variation; or, if a change must occur, concomitant testing should be done to establish new patient baselines [22,30].

DEFINING TREATMENT FAILURE IN CLINICAL SETTINGS

The clinical goal for all patients is suppression on a fully active, tolerable, and sustainable regimen, thus avoiding the development of resistance mutations and achieving maximal clinical benefit. Until recently, acceptance of virologic failure was considered if the patient was clinically and immunologically stable, especially in a highly treatment-experienced patient where viral suppression may not have been possible. However, recent availability of newer ARV agents makes the goal of suppression potentially achievable for all patients [31–35**].

Predictors of treatment failure

Patient characteristics, clinical factors and HIV RNA responses can predict treatment response. A number of studies have shown an association between early response after initiation of therapy and future virologic suppression; finding lowest failure risk in patients with lower HIV RNA nadir (even down to <20 copies/mL) [36] and increased risk of failure in patients who do not drop 1 log₁₀ by week 4 [15,37] or have viral load >1000 copies/mL at 4 weeks [38]. However, patients with high pre-therapy viral load may take longer to reach these targets [39]. Other factors associated with an increased risk of treatment failure include: history of extensive treatment experience, prior AIDS diagnosis, low CD4, prior treatment failure, medication intolerances, pharmacokinetic interactions, low medication adherence, missed appointments, younger age and non-white race [4,15,40–43]. Attention paid to these factors at treatment initiation may allow the clinician to maximize a given patient's chances for success.

Rationale for target viral load <50 copies per mL

While the exact level of viral suppression associated with optimal clinical benefit is not known, evidence supports using a target viral load as low as possible (or, more accurately, lower than detectable) to improve the patient's chances of a sustained response to therapy. For example, Raboud and colleagues looked at the relationship between the viral load nadir and the risk for future virologic failure (defined as VL>5000) [33]. They found that those who achieved a nadir of <20 copies per mL were significantly more likely to achieve sustained virologic suppression than those with a higher nadir (Figure 1). Since the current standard for “undetectable” is <50 copies per mL, this is the threshold used in clinical practice, for treatment guidelines, and in many clinical studies.

Transient changes (“blips”) and persistent low-level viremia

Once a patient is suppressed on antiretroviral therapy, a challenge in patient care (and clinical trials) can be deciding what to do when low-level viremia is subsequently detected. These increases, commonly referred to as “blips”, can occur in up to 40% of patients suppressed on HAART [44]. Blips are best described as *low-level* and *transient* occurrences that resolve spontaneously. To understand this phenomenon, it is useful to recall that, even when “suppressed” on antiretrovirals, patients may continue to have low-level viremia (3–20 copies/mL) below the 50 copies/mL limit of detection [24,45,46]. Thus, the etiology of transiently detectable viremia can be postulated to be due to a) variation in assay (due to statistical or technical factors) [24,30], b) statistical or biological fluctuation around the patients' steady state viremia [24,46], or c) a perturbation within a patient due to external factors such as illness, vaccination, non-adherence, or drug-interactions [4,47].

A number of studies have found that blips do not result in increased risk of virologic or clinical failure, even in highly treatment-experienced patients [24,42,44,48]. In a rigorous study of low-detectable viremia, Nettles and colleagues [24] performed intensive sampling (every 2–3 days) on ten patients who were virally suppressed on HAART. They found that 9 of 10 patients had transient episodes of detectable low-level viremia during the 3–4 month study period. The

authors' analysis suggested that the episodes of detectable viremia were directly related to the frequency of sampling and represented statistical and assay variation around a steady state below the limit of detection.

A study by Moore and colleagues [5] also attempted to address the question of significance of transient viremia. They studied 553 patients who achieved viral load of <50 copies/mL over a median follow up of 56 weeks. They found that 35% of patients experienced some value >50 copies/mL, but only 8% experienced virologic failure (defined as two consecutive values >400 copies/mL). The authors also noted that 28% of patients with transient increases started a new agent (and 5% started three new agents), suggesting that misinterpretation of blips as virologic failure may lead to unnecessary changes in treatment.

However, these results are tempered by studies finding that even very low detectable viremia is associated with increased risk of future virologic failure, development of resistance, and lower CD4 increases on antiretroviral therapy [4,49,50]. Furthermore, unlike transient "blips", there is good evidence that *persistent* low level viremia and consecutive rebounds are associated with progression to failure [51,52] and the development of resistance [2,50]. These patients may have worse clinical outcomes and should be changed to a fully active regimen if possible.

In summary, "blips" that are truly low (around the limit of detection) and occur only once, may not be predictors of future failure. HIV RNA should be re-evaluated in 2–4 weeks to determine if low-level detectable viremia persists. As long as the patient returns to their previous level of viral suppression, it is reasonable to follow these transient detections of virus without modifying ARV therapy. In contrast, patients with persistent low-level viremia, should be considered treatment failures. Finally, *any* change in the level of viral suppression (transient or not) should trigger prompt re-evaluation of the patient with attention paid to regimen tolerability, adherence and other risk factors for failure.

When to switch?

Studies have shown that patients who switch therapy at lower rather than higher viral loads have a greater chance of subsequent successful suppression [53], and a recent study found that delay in modification of failing regimens was associated with increased mortality, especially with non-PI based regimens [1]. Furthermore, time on a failing regimen allows for the development of resistance. The guidelines discussed above all recommend changing "early" when possible, particularly for patients failing on an NNRTI-based regimen (for whom resistance may develop more quickly and multiple mutations could risk efficacy of newer available NNRTIs) [15,16]. Thus, when failure is detected, a resistance test should be done (if possible) and therapy modified with the goal of complete viral suppression.

In some cases, early switching may be complicated by the inability to obtain reliable resistance testing (i.e., if the patients has HIV RNA < 1000 copies/ mL). If reliable historical data is available, and if clear options exist, a switch can be considered without a resistance test. However, in highly experienced patients, for whom the selection of a salvage regimen may be complex, it is reasonable to wait until the viral load is sufficient for resistance testing [17]. If switching to a fully suppressive regimen is not an option, there is a clinical benefit in continuing the failing regimen [54,55], particularly if the viral load remains low (e.g. <10,000) [56–58]. However, this should rarely be necessary in resource-rich settings with the availability of newer agents targeted at treatment experience patients.

DEFINING TREATMENT FAILURE IN RESEARCH SETTINGS

Early in the AIDS epidemic, the clinical endpoints of progression to AIDS or death were commonly used to define treatment failure for ARV studies. However, the acceptance of viral load and CD4 count as surrogate endpoints for clinical disease progression prompted a shift to the use of those endpoints in clinical research (and clinical practice). The relevance of these endpoints was again validated in a recent large observational cohort study. Olsen and colleagues evaluated the relationship between HIV RNA, CD4 count and clinical disease progression in the modern HAART era with a focus on differences by antiretroviral regimen. They found that viral load and CD4 continue to be surrogates for AIDS and death, regardless of regimen [59]. Currently, virtually all studies of antiretrovirals include a virologic endpoint, though virologic and clinical endpoints may be combined or evaluated separately, depending on the study question.

The endpoint selected in clinical research may affect the study outcomes. To better understand the effects of different treatment failure endpoints on results in clinical trials, Ribaud and colleagues applied different virologic thresholds to the data from two large AIDS Clinical Trials Group studies (ACTG 5095 and ACTG 5142) [6*]. They evaluated the FDA Time to Loss of Virologic Response (TLOVR) composite endpoint (which combines HIV RNA above threshold, death and discontinuation) and purely virologic endpoints using <50 copies/ml or <200 copies/ml as virologic failure thresholds. The TLOVR composite endpoint resulted in 50% of the designated failures being due to medication discontinuation. When comparing the virologic endpoints, they found that 50 copies/ml resulted in high rates of false positives (i.e. defining “failure” in a subject who went on to suppression of <50 copies/ml without change in antiretroviral regimen). Based on these data, the authors concluded that a virologic endpoint of >200 copies/ml at 24 weeks would avoid unacceptably high numbers of false positive “failures”.

Furthermore, different endpoints may give different information about potency, tolerability, and overall efficacy of therapy. When assessing how a patient might be expected respond in the clinical setting, it is reasonable to include discontinuations in the “failure” group, if they are due to higher toxicity of the study drug. When assessing potency of one drug to another, use of very sensitive VL assays and stricter thresholds may be helpful. But if goal is to see clinical benefit, then drugs might be considered equivalent if both achieve some clinically significant endpoint, such as <200 copies per ml. In that case, it would be useful to also assess a composite endpoint taking into account other causes of failure such as tolerability [60,61]. Often, more than one type of viral load endpoint is reported in clinical trials and results are most robust when there is concordance between endpoint measures.

CONCLUSIONS

Much has changed in the 10 years since the acceptance of HIV RNA as a surrogate for HIV disease progression. More is known about the deleterious effects of uncontrolled viremia and about the benefits of viral suppression. The development of newer antiretrovirals, including new classes of agents, has allowed a goal of full virologic control for all patients on therapy, even those with extensive treatment experience. The current guidelines recommending full virologic suppression below the assay limits of detection are based on considerable evidence of the benefits of viremia control. However, it is possible that overly strict adherence to “undetectable” criteria may lead to unnecessary regimen changes or may complicate the evaluation of endpoints in clinical studies, and a virologic failure threshold of 200 copies/mL may be appropriate in clinical trials. There is limited data which confirms the specific threshold to use (i.e., <50 copies/mL) to define treatment failure, but the benefits of viremic control are

clear. Thus, the viral load has become the mainstay in evaluating the success of antiretroviral therapy in both the clinical and research settings.

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FIGURE 1.
Probability of maintaining plasma viral load (pVL) below 5000 copies/ml according to pVL nadir. Raboud et al. AIDS 1998 [36]

TABLE 1

summary of current guidelines for defining treatment failure in resource-rich settings

DHHS, "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents", US Department of Health and Human Services. November 3, 2008. [15]

IAS-USA, "Antiviral Treatment of Adult HIV Infection: 2008 Recommendations of the International AIDS Society-USA Panel" JAMA, 2008. [16]

EACS, "European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of HIV-infected adults." HIV Medicine, 2008. [17]