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Review

Goals and milestones during treatment of HIV-1 infection with antiretroviral therapy: a pathogenesis-based perspective

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Abstract

Highly active antiretroviral therapy (HAART) has reduced the morbidity and mortality related to infection with the human immunodeficiency virus-1 (HIV-1) through its ability to suppress viral replication and preserve and reconstitute specific immune responses in many infected individuals. However, the complete eradication of HIV-1 with current HAART regimens is not considered possible by most experts. Moreover, many current antivirals have metabolic complications and limiting side effects. Consequently, the treatment paradigm has shifted from 'hit hard and early' to delaying the initiation of therapy until later in the course of HIV-1-related disease, with corresponding modifications of consensus treatment guidelines. Factors that need to be considered in deciding when to initiate therapy and with what regimen include the patient's risk of disease progression, the possible adverse drug effects, the patient's ability to adhere to the prescribed therapy, and the need to preserve future therapeutic options. In this article, we discuss the issues surrounding the initiation of HAART, and describe the virologic and immunologic milestones that may be achieved with effective antiretroviral therapy.

Keywords: HIV/AIDS; Prognostic indicators; Treatment; Treatment guidelines

1. Introduction

The use of highly active antiretroviral therapy (HAART) has changed human immunodeficiency virus-1 (HIV-1) infection from an almost uniformly fatal disease to one that can be managed chronically in many cases. Following the introduction of HAART in the mid 1990s, the morbidity and mortality associated with HIV-1 infection began to decrease significantly (Palella et al., 1998; Mocroft et al., 1998). The development of protease inhibitors (PIs), the use of triple-drug combination therapies (Gulick et al., 1997; Hammer et al., 1997), and the employment of assays capable of accurately quantifying plasma HIV-1 RNA (Gibson et al., 1993; Urdea et al., 1993) were largely responsible for an improved ability to achieve and maintain suppression of HIV-1 replication in vivo. The results of early studies of HIV-1 steady state dynamics led to the hypothesis that eradication might be achieved after 2–3

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years of complete suppression of viral replication with antiviral therapy (Perelson et al., 1997). Consequently, the treatment paradigm directed clinicians to 'hit hard and early' with HIV medications; however, many groups have since demonstrated that current HAART regimens are unable to effect complete suppression and, therefore, are unlikely to eradicate HIV-1 infection within a meaningful period of time (Lewin et al., 1999; Zhang et al., 1999; Furtado et al., 1999; Gunthard et al., 1999; Dornadula et al., 1999; Sharkey et al., 2000). Nevertheless, it is clear that the proper and strategic use of HAART has had a large impact on the clinical outcomes of patients who have HIV/AIDS. As no clinical data have shown long-term benefits of initiating antiviral therapy early (rather than later) in asymptomatic chronically infected patients, the decision when to begin HAART in such patients must be based upon an individualized risk-to-benefit ratio analysis, taking into account the latest guidelines. The purpose of this article is to provide clinicians with current information regarding when to start antiretroviral therapy in individuals with HIV-1 infection, and in those individuals who initiate therapy, what virologic and immunologic responses might occur.

2. Initiation of therapy

As clinical experience with treatment regimens and knowledge of HIV-1 pathogenesis have accumulated, guidelines concerning the initiation of antiretroviral therapy have evolved. Most recently, guidelines were issued by the International AIDS Society–USA Panel (IAS–USA) in January 2000 (Carpenter et al., 2000) and by the Department of Health and Human Services (DHHS) in February 2002 (Panel on Clinical Practices for Treatment of HIV Infection, 2002). The objective of the guidelines is to provide basic recommendations to physicians treating patients with HIV-1 infection, based on the current understanding of HIV-1 pathogenesis and the most recent results of clinical trials. 'By their nature, consensus guidelines take moderate positions on complex issues that must be considered in each case by the HIV-infected individual and their physician' (Fischl, 1999).

The risk of progression of HIV-1 disease is a primary consideration in timing the initiation of therapy (Carpenter et al., 2000). The likelihood of disease progression can be estimated from measurements of plasma HIV-1 RNA and $CD4^+$ T cells (Kim et al., 2000; Mellors et al., 1996, 1997). The IAS–USA and DHHS guidelines both recommend that severely symptomatic HIV-1-infected patients and those with AIDS be treated regardless of $CD4^+$ cell count or plasma HIV RNA. The DHHS recommends that asymptomatic patients with a $CD4^+$ cell count < 200 cells/mm^3 should receive treatment regardless of plasma viral load. Individuals with $CD4^+$ cell counts of 201–249 cells/mm^3 should be offered treatment, although controversy exists. Among asymptomatic patients with $CD4^+$ cell counts > 350 cells/mm^3 and plasma HIV RNA levels $> 55\,000$ c/ml by bDNA or RT-PCR, the 3-year risk of developing AIDS is $>$ 30% if treatment is not initiated (Panel on Clinical Practices for Treatment of HIV Infection, 2002; Mellors et al., 1997). Treatment can be considered for these patients, although the optimal course of management has not been determined. Among asymptomatic patients with $CD4^+$ cell counts > 350 cells/mm^3 and plasma HIV RNA levels $< 55\,000$ c/ml by bDNA or RT-PCR, the 3-year risk of developing AIDS is $< 15\%$ if treatment is not initiated. Many experts would choose to delay therapy in these patients, instead, favoring observation (Panel on Clinical Practices for Treatment of HIV Infection, 2002). Notably, the DHHS plasma HIV RNA cutoff of 55 000 c/ml is the same whether the measurement is made by the bDNA or the RT-PCR method. Although there was a 2–2.5-fold difference between RT-PCR and the first bDNA assay (version 2.0), with the current bDNA assay (version 3.0), values obtained by bDNA and RT-PCR are similar except at the lower end of the linear range, i.e. < 1500 copies/ml (Panel on Clinical Practices for Treatment of HIV Infection, 2002).

3. Virologic milestones

3.1. The steady state

Shortly after primary infection with HIV-1, a rapid burst of unchecked viral replication occurs in most patients (Daar et al., 1991). Viremia declines as HIV-1-specific cellular immunity develops, and about 6–9 months after infection a viral 'set point' is reached. At this set point, the rate of virion production approximates the rate of virion clearance, and serial plasma viral load measurements appear to remain constant over a relatively short time. Patients are described as being in a 'steady state', and can remain clinically stable for many years. However, despite prolonged clinical latency, there is no virologic latency. Throughout its course, HIV-1 infection is characterized by repetitive, extremely high levels of replication in vivo, which drives the rapid turnover of $CD4^+$ T cells (Perelson et al., 1996). In the absence of effective HAART, the viral set point is the strongest independent predictor of disease progression (Mellors et al., 1996). Furthermore, during the 3 years after seroconversion, the rate of change of the plasma viral load over time (i.e. the slope) is inversely correlated with the length of AIDS-free time (Lyles et al., 2000).

3.2. Viral dynamics after the initiation of HAART

The primary aim of initiating antiretroviral therapy is to achieve durable and maximal suppression of plasma HIV RNA. Virologic failure is twice as likely to occur in patients with previous exposure to HAART, suggesting that the first regimen has the best chance of virologic success (Paredes et al., 2000). When effective HAART is initiated in a patient at steady state, the abrupt interruption of the rapid rounds of viral replication usually results in a precipitous decrease in HIV-1 viremia. This exponential decrease is referred to as the first phase of viral decay, and reflects two processes: the clearance of free plasma virions, and the decay of productively infected $CD4^+$ cells, which generate 99% of the plasma virions (Perelson et al., 1996). Quantitatively, the plasma viral load should drop by at least one order of magnitude during the initial 14 days of treatment. Failure to achieve such a decline may indicate poor adherence to the drug regimen, the presence of drug-resistant variants, or inadequate drug absorption.

The first phase is followed by a slower second phase of viral decay that represents the gradual elimination of at least three secondary sources of viral particles: tissue macrophages and dendritic cells, which are long-lived and can be productively infected; virions trapped on the surface of follicular dendritic cells (Smith et al., 2001); and latently infected resting $CD4^+$ memory T cells, which maintain the long-term potential to produce infectious virus upon activation and are referred to as the latent reservoir (Siliciano, 1999; Pierson et al., 2000). Of these secondary sources, the latent reservoir, which is established very soon after infection, is the most important barrier to eradication (Chun et al., 1998). The size of the latent reservoir is surprisingly small, between 10^4 and 10^7 cells (Chun et al., 1997). Estimates of its half-life have ranged from as short as 6 months to as long as 44 months (Ramratnam et al., 2000; Finzi et al., 1999). This variability may be related to the observation that the rate of decay of the latent reservoir is intimately related to the level of ongoing replication during HAART (Ramratnam et al., 2000). The greater the number of isolated measurable episodes of viremia, known clinically as 'blips', the slower the rate of decay of the latent reservoir (Ramratnam et al., 2000). Interestingly, these blips do not appear to be associated with treatment failure or the emergence of drug resistance (Havlir et al., 2000). Second phase viral decay characteristics can vary significantly from patient to patient. However, the HIV RNA level should fall to < 400 c/ml after 24 weeks of therapy (Powderly et al., 1999). Failure to maintain a negative viral decay slope during the first 24 weeks of therapy may be an early sign of virologic failure.

4. Immunologic milestones

4.1. Immunopathogenesis of HIV

Infection with HIV-1 exerts multiple deleterious effects on the immune system, including a depletion of $CD4^+$ T cells, an imbalance in the ratio of naive to memory $CD4^+$ and $CD8^+$ T cells, chronic immune cell activation, and T-cell maturation abnormalities (McCune, 2001; Pantaleo et al., 1993; Nokta et al., 2001). Ho et al. (1995) proposed the 'tap and drain' hypothesis to explain $CD4^+$ T-cell depletion during HIV-1 infection. Stated simply, the hypothesis asserts that the source of $CD4^+$ T cells (the 'tap') is eventually unable to keep up with the massive elimination of $CD4^+$ T cells (the 'drain') caused by the direct cytopathic effects of HIV-1. However, studies of telomere length and K_i67 staining in vivo demonstrated that other compartments were equally proliferative (Autran et al., 1997; Wolthers et al., 1996). Therefore, it was concluded that the effects of HIV-1 infection on the turnover of $CD4^+$ T cells could not be solely the result of direct virus-mediated cell death.

Recent studies of lymphocyte dynamics using markers of cell cycling have provided further insights into the immunopathogenesis of HIV. Bromodeoxyuridine (BrdU)-labeling of actively replicating cells in macaques demonstrated accelerated proliferation and death of naive and memory $CD4^+$ and $CD8^+$ T cells after infection with simian immunodeficiency virus (SIV) (Mohri et al., 1998). Plasma levels of SIV RNA were found to correlate directly with the rates of cell proliferation and death. A state of generalized immune activation induced by SIV was suggested to account for these findings. Subsequent studies using deuterated-glucose and BrdU as markers for cell turnover replicated these findings in humans (Mohri et al., 2001) Significantly higher rates of $CD4^+$ and $CD8^+$ T-cell proliferation and death were found in HIV-1-infected individuals compared with uninfected controls. Furthermore, treatment with HAART significantly reduced T-cell turnover, which nearly normalized after 1 year of antiviral therapy. The results of these studies suggest that progressive $CD4^+$ cell depletion is a consequence of multiple events, including immune activation, increased cell proliferation, and increased cell death.

Other processes may also affect T-cell depletion. Some studies suggest that T-cell production is compromised during untreated HIV-1 infection. T-cell-receptor excision circles (TRECs) are products of T-cell receptor recombination events, the majority of which are believed to occur in the thymus. The concentration of TRECs present in the peripheral blood may indicate levels of recent emigration of T cells from the thymus, and perhaps is a measure of thymic function (Douek et al., 1998). Douek et al. (2001) measured peripheral blood TREC levels in patients in different stages of HIV-1 infection. These researchers demonstrated an inverse association between T-cell proliferation and TREC levels. They found no increase in the proliferation rate of naive $CD4^+$ T cells during early HIV-1 infection, despite a loss of TRECs within these cells. Their results suggested that $CD4^+$ cell depletion during HIV-1 infection results not only from increased proliferation, but from decreased thymic output. Currently the effect of HIV-1 infection on the production of T cells remains unclear and controversial.

Early in the course of HIV-1 infection, a decrease in the number of circulating $CD4^+$ T cells and an increase in the number of circulating $CD8^+$ T cells are observed (Cooper, 1998; Fauci et al., 1996). As HIV-1 infection progresses, a preferential depletion of naive T cells occurs (Autran et al., 1997). Immune activation associated with unchecked viral replication drives the expansion of the memory cell compartment. Ongoing depletion of the $CD4^+$ T cells results in the partial or total loss of various clones, and 'holes' are created in the $CD4^+$ T-cell repertoire. This is demonstrated by decreased lymphocyte proliferation to neoantigens and recall antigens, absent proliferation to HIV-1-specific antigens, decreased plasma levels of $CD4^+$ T cell-derived cytokines, and a diminished ability to mount delayed-type hypersensitivity skin reactions (Empson et al., 1999; Maas et al., 1998). Similarly, $CD8^+$ T cells become activated and proliferate in a nonspecific manner with HIV-1 disease progression (Orendi et al., 1998). Certain $CD8^+$ T-cell clones may be lost

after activation, further contributing to holes in the immune repertoire. Activation of monocytes and macrophages also appears to occur during HIV-1 infection, as evinced by increases in monocyte-derived cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) (Alonso et al., 1997; Ullum et al., 1996). These cytokines increase the rate of viral replication, and their levels are correlated with plasma viral load (Lederman et al., 2000; Biswas et al., 2001).

4.2. HAART and reduced T-cell activation

Effective HAART may result in clinically significant quantitative and qualitative changes in T-cell subsets. In many patients, these changes are associated with laboratory and clinical responses that appear consistent with immune reconstitution. As the plasma viral load falls during therapy, nonspecific activation of $CD4^+$ and $CD8^+$ T cells decreases (Evans et al., 1998), resulting in a reduced proliferation and subsequent death of these cells (Angel et al., 2001). The numbers of circulating naive $CD4^+$ and $CD8^+$ T cells increase with ongoing therapy, whereas the number of memory $CD8^+$ T cells decreases (Kaufman et al., 2000; Seth et al., 2001). After HAART is instituted, TNF-α production by monocytes decreases, as does expression of the activation markers CD38 and HLA-DR on $CD4^+$ and $CD8^+$ T cells (Seth et al., 2001; Franco et al., 1999). Studies of the T-cell repertoire in chronically HIV-1-infected subjects before and during HAART suggest that in many patients the skewed pretreatment cell population returns to a more normal pattern, likely due to the repopulation of $CD4^+$ T cells, particularly those in the naive subset (Evans et al., 1998; Bisset et al., 1998).

4.3. Restoration of antigen-specific immune response

Specific immunity to non-HIV-1 recall antigens usually returns soon after HAART is initiated. Li et al. have demonstrated that such recovery is directly correlated with several factors: the amplitude and duration of the reduction in viral load following the initiation of HAART, the absolute increase in the $CD4^+$ T-cell count, and the absolute increase in memory $CD4^+$ T cells (Li et al., 1998). Responses to commonly encountered antigens are the ones that are most likely to be restored, as evinced by a return or increase in reactivity to skin testing (Empson et al., 1999; Weiss et al., 1999).

Prophylaxis against many opportunistic infections no longer appears to be required after $CD4^+$ cell counts increase to levels greater than the threshold for the institution of the specific prophylactic therapy. The ACTG Group 362 Study Team found that patients with a history of a $CD4^+$ cell count < 50 cells/mm^3 and a sustained increase to > 100 cells/mm^3 on HAART can discontinue primary prophylaxis for *Mycobacterium avian intracellulare* (Currier et al., 2000). Whitcup et al. have shown that patients with stable cytomegalovirus (CMV) infection and $CD4^+$ cell counts > 150 cells/mm^3 can safely discontinue secondary CMV prophylaxis while remaining on HAART (Whitcup et al., 1999). Several studies have demonstrated that patients with a history of $CD4^+$ cell counts < 200 cells/mm^3 and a sustained increase to > 200 cells/mm^3 on HAART can safely discontinue both primary and secondary prophylaxis for *Pneumocystis carinii* pneumonia (Schneider et al., 1999; Furrer et al., 1999).

4.4. Restoration of an HIV-1-specific immune response

The degree to which HIV-1-specific immune responses return after the initiation of HAART is variable and may be related to the stage of disease at which therapy is begun. Several investigators have demonstrated that HIV-1-specific T-helper (T_h)-cell responses can be maintained in patients who achieve durable virologic suppression with HAART during acute infection (Rosenberg et al., 1997; Oxenius et al., 2000; Malhotra et al., 2000; Rosenberg et al., 2000). When HAART is begun in chronically infected patients, HIV-1-specific immune responses typically decline. Durable suppression of HIV-1 replication with HAART has been shown to result in the decay of HIV-1–specific cytotoxic T lymphocytes (CTLs) (Autran et

al., 1997; Rosenberg et al., 1997; Kalams et al., 1999; Ogg et al., 1999; Pontesilli et al., 1999). Less is known about the effects of HAART on HIV-1-specific $CD4^+$ T_h-cell responses in patients who initiate treatment during chronic infection, in part because the baseline levels of these responses typically are low or undetectable, reflecting the extremely early deletion of these clones. One study has shown that these responses declined with therapy in chronically infected patients (Pitcher et al., 1999). Decreases in HIV-1-specific $CD4^+$ and $CD8^+$ T-cell responses occur despite immune reconstitution to other antigens as outlined above, and despite increases in naive cells and cells of thymic origin (Douek et al., 1998).

Occasionally, subjects achieve adequate suppression of viral replication but fail to significantly repopulate the $CD4^+$ T-cell population. These individuals may have a production defect that could require additional immune-based therapies. Treatment with IL-2 may offer immunologic benefit to these individuals (David et al., 2001). Clinical trials of HAART with IL-2 are in progress, and the results are anxiously awaited.

Short-term data appear to indicate that the early initiation of HAART in asymptomatic patients, when $CD4^+$ cell counts are higher, significantly delays clinical and immunological deterioration related to HIV infection (Grabar et al., 2000). Conversely, mortality rises when HAART is initiated later in the course of the disease (e.g., $CD4^+$ cell count < 200, viral load $> 50\,000$, history of opportunistic infection) (Chen et al., 2001; Hogg et al., 2001). Pretreatment $CD4^+$ cell counts can be more predictive of response to HAART than plasma viral load measurements, particularly among individuals with advanced disease (Grabar et al., 2000; MacArthur et al., 2001). Long-term data favoring the early initiation of therapy in asymptomatic individuals are not available, and the decision to begin treatment should be based on careful consideration of possible risks and benefits by the patient and the physician, taking into account the recommendations of the DHHS (Panel on Clinical Practices for Treatment of HIV Infection, 2002).

4.5. Limitations of current HAART

It was once believed that HAART could result in the complete eradication of HIV-1 infection from the host. However, low levels of viral replication persist even when viral loads are undetectable by current commercial assays (Ramratnam et al., 2000). Another barrier to eradication is the fact that resting memory T cells that harbor proviral DNA may survive far longer than originally believed (Ramratnam et al., 2000). Therefore, current HAART must be considered lifelong. Close adherence to HAART regimens is usually required to achieve lasting viral suppression (Paterson et al., 2000; Bangsberg et al., 2000). However, adherence can be compromised by complex dosing regimens, high pill burdens, and long-term toxicities such as lipodystrophy, dyslipidemia, glucose intolerance, hepatitis, lactic acidosis, peripheral neuropathy, nephrolithiasis, and multi-organ-system failure (Carpenter et al., 2000; Carr et al., 1998; Henry et al., 1999; Carr and Cooper, 2000). Moreover, there is an increasing belief that the dyslipidemia associated with the use of HAART should be treated, particularly in patients at increased risk for cardiovascular disease (Schmitz et al., 2001). This would add a new level of complexity to already complicated HAART regimens.

In addition to poor adherence, poor pharmacokinetics of most of the current first-generation PIs may allow for viral replication in the presence of subtherapeutic drug levels, thereby selecting for resistant variants. Drug-resistant viral strains that result from treatment failure can be transmitted from one individual to another, leaving the recipient with limited therapeutic options (Boden et al., 1999; Little et al., 2001). Unfortunately, the transmission of drug-resistant strains appears to be increasing (Little et al., 2001). The described limitations of current HAART regimens have contributed to a significant shift in the treatment paradigm, away from 'hit hard and early' to 'hit hard and later', in an

attempt to reduce drug exposure and consequently toxicity, nonadherence, and drug resistance. The increased reluctance of clinicians to initiate therapy in asymptomatic chronically infected patients is reflected in the 2002 DHHS treatment guidelines, as discussed previously.

4.6. Patient selection and regimen design

Once the decision has been made to initiate therapy in an asymptomatic patient with established infection, the goals should be to achieve maximal and durable suppression of viral replication, decrease HIV-1-related morbidity and mortality, and preserve and possibly reconstitute immune responses. A secondary goal may be to decrease the risk of HIV-1 transmission (Taylor and Pereira, 2001).

While drug potency may guide many treatment decisions, other factors should be considered when designing a regimen. The ability of a particular patient to adhere to his or her prescribed therapy should be taken into account. Adherence is likely to improve when medications are easy to take and produce few side effects. Adverse effect profiles for each of the prescribed drugs should be reviewed; these are described in both sets of guidelines. Overlapping toxicities and drug-drug interactions, including those among the antiretroviral agents themselves and those between anti-HIV drugs and other concomitant medications, should be avoided wherever possible. The poor bioavailability of many PIs may be improved by the addition of low doses of the PI ritonavir, which inhibits the cytochrome P450 CYP3A4 enzyme. However, such augmentation can also increase the severity of side effects associated with other PIs and even introduce new side effects associated with ritonavir (Gatanaga et al., 1999).

Both the IAS–USA and the DHHS guidelines recommend initiating antiretroviral therapy with PI-based or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based combination regimens. Specific recommendations include two nucleoside reverse transcriptase inhibitors (NRTIs) plus one or two PIs, and two NRTIs plus one NNRTI. Regimens using three NRTIs have been introduced recently, but their efficacy equals those of the PI- and NNRTI-based regimens only in patients with plasma viral loads of $< 100\,000$ c/ml (Staszewski et al., 2001). The initial regimen may be configured to spare a class of antiretroviral drugs to avoid class-related toxicities and to preserve susceptibility to the class. Both sets of guidelines outline the advantages and disadvantages of PI-based regimens, NNRTI-based ('PI-sparing') regimens, and triple-NRTI ('PI- and NNRTI-sparing') regimens.

Resistance testing should be considered in recently infected patients, especially those who live or work in areas with an appreciable prevalence of primary drug resistance (Carpenter et al., 2000). The presence of primary drug resistance would likely affect the design of the initial regimen.

5. Conclusion

The HAART era has dramatically altered the natural history of HIV-1 infection. Despite the many shortcomings of current antiretroviral drugs, HIV-1-related morbidity and mortality have improved significantly since the introduction of HAART. The timing of the initiation of HAART in asymptomatic chronically infected patients remains unclear. Treatment paradigms have shifted, and many questions remain unanswered. The decision to start therapy should be based upon an individualized evaluation of the benefits and risks of treatment. Once the decision is made, the goal is to achieve maximal and durable suppression of viral replication. Adherence may be improved by choosing a regimen that has a simple dosing schedule and produces minimal side effects. Effective HAART may result in favorable virologic and immunologic outcomes, thereby slowing or stopping the clinical progression of HIV-1 disease. However, our inability to achieve eradication is a clear reason to continue efforts in the development of treatment regimens that are more potent and less toxic, with an increased ability to promote immune reconstitution and improve clinical outcomes. New antivirals are currently in development, which address many of these issues.

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