Early Initiation of Antiretroviral Therapy for Infection with Human Immunodeficiency Virus: Considerations in 1996

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In this AIDS Commentary, Dr. Nadler provides a rationale for early initiation of antiretroviral therapy in patients infected with human immunodeficiency virus (HIV). Although no definitive clinical trials have been published that are relevant to the question of whether early treatment will produce long-term benefit, many experienced investigators believe that early reduction in the level of viral replication will effectively prolong clinical latency of the infection and immunologic stability. A second question is that of the best combination of antiretroviral agents to be used for early treatment of HIV infection. A third issue is whether initial therapy should be continued until there is evidence of virological, immunologic, or clinical progression of disease, or alternatively, whether a course of induction therapy with the most potent combination of agents should be followed by a treatment-free period or by less-aggressive maintenance therapy. These issues will continue to be debated over the next several months. Dr. Nadler’s review is timely, and it is a useful statement of the questions to be answered regarding treatment of early HIV infection.

—John P. Phair

A series of events has occurred since the nihilism following the IX International Conference on AIDS in Berlin; these events once again compel us to consider early initiation of antiretroviral therapy for HIV infection as the preferred course of action. The data supporting early initiation of therapy are compelling and consistent, and the rationale has been validated clinically, immunologically, and virologically.

Seminal studies have led to a consensus that HIV-infected patients who are severely immunocompromised, as indicated by a severely depressed CD4 lymphocyte count and/or the occurrence of AIDS-defining clinical events, should be offered antiretroviral therapy to slow the rate of immunologic decline, reduce the number of secondary AIDS-associated illnesses, and delay death [1–4]. Several studies also strongly support the administration of antiretroviral therapy to patients who are less severely immunocompromised (i.e., those with CD4 lymphocyte counts of \( \leq 500/\mu L \)) but have symptoms consistent with immunologic abnormalities [5–7].

Further studies of immunologically comparable but asymptomatic patients were initially interpreted as supporting routine treatment of such patients (“early therapy”), but the Concorde study findings, combined with the lack of reduction in mortality in some studies and loss of clinical benefit with time in others, led investigators to question the validity of early therapy with the then-available agents [6, 8–10].

What these studies had in common was the use of clinical endpoints as the “gold standard,” which was based on the historical recognition of HIV disease as a clinical syndrome of infectious etiology. Second, it was noted that CD4 lymphocyte counts generally correlate with the stage of HIV disease and rise and fall in response to the effectiveness of antiretroviral therapy or to its failure [11]. CD4 lymphocyte counts were accepted as a surrogate marker, albeit limited, for the clinical effect of therapy and were used both in clinical management and for (tentative) regulatory approval of therapeutic agents [12, 13]. The imperfections of this marker and the temporal and quantitative limitations of nucleoside antiretroviral monotherapy had become obvious by the time of the conference in Berlin. A strong movement emerged to restrict the administration of therapy to those patients with the most obvious symptoms and advanced clinical disease who would clearly survive longer with therapy.

Many early-therapy advocates remained, basing their opinions on clinical and immunologic data. Observational data, such as those from the Multicenter AIDS Cohort Study, show that symptomatology becomes increasingly common as the CD4 lymphocyte count declines below 500/\( \mu L \). Antiretroviral therapy is better tolerated by patients with higher CD4 lymphocyte counts and/or fewer underlying symptoms (this observation is based on the adverse events described in published studies). Furthermore, immunologic and pathogenetic data have emerged that support earlier initiation of therapy: there is a
loss of CD8 lymphocyte-mediated suppression of HIV, which is associated with a decline in the number of CD4 lymphocytes below normal [14].

Decline of the CD4 lymphocyte count to <500/µL is associated with clonal expansion and emergence of syncytium-inducing virus and other more pathogenic viral variants [15–17]. A switch from the predominance of TH1-type cytokines to TH2-type cytokines, which is associated with B-type symptomatology and possibly up-regulation of HIV production, occurs as the CD4 lymphocyte count declines below 500/µL [18]. Recent research suggests that when CD4 lymphocyte counts decline below 500/µL, more rapid immunologic disease progression often occurs; changes include the emerging predominance of CD38+/CD8− cells and the expression of TAP2.1 over TAP2.3 class 3 HLA (human leukocyte antigen) proteins [19, 20].

Recent advances in knowledge of the pathophysiology of HIV infection, which have been made by studying the dynamics of viral and lymphocytic flux in response to therapeutic perturbation, play a critical role in treatment decisions [21, 22]. It has been well substantiated that there is a continuous high level of viral production, even in early asymptomatic disease [23]. PCR and the branched-chain (bDNA) test permit reliable quantification of the serum component of the viral load, which represents ~99% of actively replicating virus [21, 22]. The serum viral titer correlates with risk of disease progression following the acute retroviral syndrome, in mildly symptomatic HIV disease, and in an initially asymptomatic cohort of chronically infected patients who were observed prospectively [24–26].

Initially asymptomatic patients in whom active viral proliferation of only a few thousand HIV copies per microliter was detected developed clinical disease and progressive immunologic dysfunction [26]. Analysis of the viral load in stored samples from several studies in which clinical and immunologic endpoints were achieved show this measurement to correlate best with the established clinical results [25, 27]. This finding has been confirmed by prospective studies in which viral, immunologic, and clinical endpoints in early and advanced HIV disease were used [28–33].

Combined insights from pathophysiological studies, quantitative viral assessments, and immunologic observations define a new goal in therapy for HIV infection: maximal viral suppression and preservation of immune function. Achievement of this goal should lead to a significant decrease in the occurrence of clinical HIV disease or a delay in its development. Early therapy based on a significantly elevated viral load (>100,000 viral particles/µL or >1,000,000 viral particles/µL in association with a CD4 lymphocyte count of <500/µL), a rapidly declining CD4 lymphocyte count (<500/µL), or symptomatic disease is the most consistent with this goal. Since immunologic decline and chronic clinical illness result from the viral load, it may be reasonable to treat all patients in whom viral replication is detected, i.e., levels of 1,000–10,000 viral particles/µL or greater (these levels approximate Mellors quartile 3 and above) [26]. To test this hypothesis a trial that assesses the clinical course of untreated patients vs. that of aggressively treated patients with CD4 lymphocyte counts of >500/µL who evidence active viral replication is needed.

Increased specific activity and enhanced duration of antiretroviral effect is seen with combination therapy, especially regimens that incorporate newer agents such as the protease inhibitors [28–30, 32, 33]. Use of combination therapy regimens reduces the emergence of drug-resistant virus [30]. The Kaplan-Meier curves remain separated far longer with combination therapy than with monotherapy regimens. The limitations of ACTG (AIDS Clinical Trials Group) 019, the Concorde study, and other trials of monotherapy in patients with early-stage disease are due to the modest and relatively transient antiretroviral activity of the nucleosides.

Early combination therapy, which is more effective than monotherapy [30, 33], should consist of two or three agents (or more) that are intended to totally suppress viral replication, as measured by an ultrasensitive PCR or second-generation bDNA test, and should prevent emergence of resistant virus. Clinical trials suggest this approach is viable [28, 29, 31, 32]. Further studies with patients whose CD4 lymphocyte counts at entry are ≤500/µL and higher are needed; these studies should measure clinical and immunologic endpoints, stratified by the viral load at entry and by achievable suppression (in logs) of viral load.

Initial HIV infection presents another potential opportunity for treatment. Kinloch-de Loes [34] showed that monotherapy with zidovudine decreased the number of HIV-associated clinical events and resulted in less reduction in the CD4 lymphocyte count following the acute retroviral syndrome (ARS) [34]. Mellors et al. [24] showed that the viral load at the time of ARS is a predictor of subsequent disease progression.

Trials of combination therapy that is designed to improve viral suppression during the ARS are under way; these trials include assessment of viral load. There may be a “window” in which to diagnose HIV infection and initiate treatment. A recent study shows viral load does not reach a plateau until ~4–6 months after an episode of ARS [35]. Studies are needed to explore the approach of altering the viral load “set point” of the ARS or of intervening in the later clinically quiescent period of the infection. It will be necessary to educate primary care physicians, the emergency medicine community, and patients at risk for HIV infection in the recognition of new HIV infection, allowing exploitation of the “window.”

How long should intensive multidrug antiviral therapy continue? This will depend on the lifespan of the cells latently infected with HIV, whether resistant virus emerges before these cells are ablated, and the residual immunologic capacity of the HIV-infected patient. Preliminary data suggest that the lifespan of the susceptible circulating mononuclear cell pool may be ~80 days [36]. This may represent another therapeutic oppor-
tunity: perhaps 1–2 years (four-to-eight lifespans) of multidrug induction therapy to eliminate the HIV-infected mononuclear cell pool can be followed by a lifelong two-drug regimen to suppress emergence of the virus from the pool of latently infected cells, resulting in maintenance of remission of the infection. The use of combination therapy would be employed to enhance viral suppression (>2 logs), attack a broad range of viral reservoirs, and prevent emergence of resistant virus [37]. Characterization of the latently infected mononuclear cell pool and its kinetics, which is the next critical step in studies of HIV pathogenesis, will lead to better application of the available therapeutic agents.

References

18. Clerici M, Shearer GM. A Tm1→Tm2 switch is a critical step in the etiology of HIV infection. Immunol Today 1993;14:107–11.


