Minireview

Advance in Treatment Strategy and Immune Reconstruction against HIV-1 Infection

Shuzo Matsushita* and Tetsuya Kimura

Department of Clinical Retrovirology and Infectious Diseases, Center for AIDS Research, Kumamoto University, Kumamoto, Kumamoto 860-0811, Japan

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Abstract: HIV-1 can be considered an infection of the immune system, resulting in progressive and ultimately profound immune suppression. The availability of highly active antiretroviral therapy (HAART) has resulted in dramatic changes in the disease course in persons fortunate enough to have access to these medications, but long-term therapy is limited by the development of resistance as well as toxicities of the potent medication regimens. Emerging data indicate that individuals who have non-progressive clinical course control HIV-1 immunologically. This has bolstered hope that the immune response might be effectively augmented in persons with HIV infection. Recent data indicating that immediate treatment of acute infection leads to augmentation of antiviral immune responses have provided evidence that the immune system might be enhanced in certain situations. Therefore, investigation in the reconstitution of anti-HIV immune response in patients under HAART should provide encouragement for continuing to explore methods to obtain meaningful and durable immune enhancement as an adjunct to HAART in HIV-1 infection.

Key words: Human immunodeficiency virus type 1 (HIV-1), Highly active antiretroviral therapy (HAART), Antiviral drug resistance, Structured treatment interruption or supervised treatment interruption (STI)

Introduction

Over the past 6 years, advances in human immunodeficiency virus type 1 (HIV-1) clinical research and data on the effectiveness of potent combination therapy have substantially influenced the overall perspective of the long-term management of HIV-1 disease. It is now generally accepted that the benefits of mono- and bitherapy for HIV-1 infection are only transient due mainly to virus drug resistance. To obtain continued benefit from antiviral therapy, current guidelines recommend at least triple-drug combinations, or so-called highly active antiretroviral therapy (HAART).

Three classes of drugs have been approved by the US and the Japanese government and they target two events of the HIV replication cycle: reverse transcription of viral RNA and the processing of viral proteins by the viral protease. Reverse transcriptase (RT) and protease (PR) are the virus-specific enzymes that are essential for virus replication. They are, therefore, excellent targets for antiviral therapy. As listed in Table 1 seventeen antiretroviral agents are currently available for combination therapy in Japan. Many of them have been approved for clinical use in the past three years. There are two classes of RT inhibitors: nucleoside RT inhibitors (NRTIs) such as Zidovudine (AZT, ZDV), Didanosine (ddI), Zalcitabine (ddC), Stavudine (d4T), Lamivudine (3TC) and Abacavir (ABC), acting as competitive inhibitors or DNA chain terminators, and non-nucleoside RT inhibitors (NNRTIs) such as Nevirapine (NVP), Delavirdine (DLV) and Efavirenz (EFV), which bind allosterically to a hydrophobic pocket close to the active

Abbreviations: ABC, Abacavir; APV, Amprenavir; CTL, cytotoxic T cell; ddC, Zalcitabine; ddI, Didanosine; DHHS, Department of Health and Human Services; DLV, Delavirdine; d4T, Stavudine; EFV, Efavirenz; HAART, highly active antiretroviral therapy; HIV-1, human immunodeficiency virus type 1; IDV, Indinavir; MACS, Multicenter AIDS Cohort Study; NFV, Nelfinavir; NNRTI, non-nucleoside RT inhibitor; NRTI, nucleoside RT inhibitor; NVP, Nevirapine; PI, protease inhibitor; PR, protease; RT, reverse transcriptase; RTV, Ritonavir; SQV, Saquinavir; STI, supervised treatment interruption; 3TC, Lamivudine; ZDV, Zidovudine.
The currently used protease inhibitors (PIs) such as Indinavir (IDV), Ritonavir (RTV), Saquinavir (SQV), Nelfinavir (NFV), Amprenavir (APV) and Lopinavir/RTV (LPV/r) are targeted to the active site of the catalytic site. Following the introduction of HAART marked decreases in AIDS-related morbidity and mortality have been observed. However, in some patients, HAART can be problematic, either because it is difficult to remain compliant or because previous suboptimum therapies have limited the choice of drugs. For compliant drug-naive patients, HAART should offer long-term virus suppression, when changing from first- to second- to third-line HAART following drug failure. Long-term treatment might ultimately result in multi-drug resistance leaving few options for salvage therapy. HIV-1 drug resistance testing to enable salvage therapy, and the development of new drugs and immunotherapeutic agents to allow new options will therefore remain priorities in HIV-1 research.

**Advance and Controversy in the Current Guideline for the Treatment of HIV-1 Infection**

There is widespread agreement that symptomatic patients and patients with AIDS require antiretroviral therapy. There is also some support for the treatment of individuals with the acute retroviral syndrome or with very early HIV-1 infection, based on evidence that early antiretroviral therapy may preserve HIV-specific immune responses. The timing of antiretroviral therapy in the asymptomatic patient is less clear-cut. The US Department of Health and Human Services (DHHS) guidelines have recently been revised to reflect a more conservative trend among HIV experts and treaters, characterized by a preference for delayed therapy and also by the re-emergence of the CD4⁺ cell count as the most important criterion for initiation of treatment. The new guidelines suggest that treatment be considered for individuals with CD4⁺ cell counts less than 350 cells/mm³ or plasma HIV-1 RNA greater than 30,000 (by bDNA assay) or 55,000 (by RT-PCR assay) copies/ml. These criteria are based on data from the Multicenter AIDS Cohort Study (MACS) regarding risk of progression among untreated individuals although it should be noted that patients with CD4⁺ cell counts between 200 and 350 cells/mm³ who have very low viral loads have a relatively low risk of progression according to the MACS data. The rate of progression is a function of the CD4⁺ cell count and the viral load, which predicts the slope of the decline in CD4⁺ cell count.

The changes in current guideline about when to initiate therapy have come about for the following five reasons: 1) Current hypotheses regarding viral reservoirs have diminished the enthusiasm and rationale for early therapy. Although there are two competing models, both have negative implications for early therapy. One model holds that eradication is impossible with any regimen, although effective HAART may prevent resistance and permit long-term control. The other model holds that eradication is potentially achievable with more potent regimens than those used today, but that current regimens are insufficiently potent and will inevitably result in eventual resistance and treatment failure. 2)
increasing recognition of long-term antiretroviral toxicity has led us to question whether patients will be able to tolerate therapy for decades. 3) The degree of adherence required to avoid antiretroviral resistance is unrealistic for many patients. 4) Evidence from multiple cohorts demonstrates that the CD4+ cell count is a more important predictor of clinical progression, mortality, and benefit from antiretroviral therapy than is viral load, and that patients who defer therapy do as well as those who start therapy at an earlier stage. 5) There is considerable concern over the high rates of virologic failure in the clinical setting and the poorer response to therapy observed in patients on second- or third-line regimens.

Although there is theoretical benefit to antiretroviral therapy for patients with CD4+ T cell counts greater than 200 cells/mm³, no studies have been conducted comparing immediate versus delayed potent combination antiretroviral therapy in these patients. A major dilemma confronting patients and practitioners is that the antiretroviral regimens currently available that have the greatest potency in terms of viral suppression and CD4+ T cell preservation are medically complex, are associated with a number of specific side effects and drug interactions, and pose a substantial challenge for adherence. Furthermore, the development of mutations associated with drug resistance can render therapy less effective or ineffective. Thus, decisions regarding treatment of asymptomatic, chronically infected individuals with CD4+ T cell counts > 200 cells/mm³ must balance a number of competing factors that influence risk and benefit. Table 2 summarizes the potential benefits and risks of early and of delayed initiation of therapy in the asymptomatic patient that the clinician and the patient must consider in deciding when to initiate therapy.

Potential benefits of early therapy include earlier suppression of viral replication; preservation of immune function; prolongation of disease-free survival; and decrease in the risk of viral transmission. Risks include the adverse effects of the drugs on quality of life; the inconvenience of most of the suppressive regimens currently available leading to reduced adherence; development of drug resistance over time because of early initiation of therapy; limitation of future treatment options due to premature cycling of the patient through the available drugs; the risk of transmission of virus resistant to antiretroviral drugs; serious and unknown toxicities associated with some antiretroviral drugs (e.g., elevations in serum levels of cholesterol and triglycerides, alterations in the distribution of body fat, insulin resistance and even frank diabetes mellitus); and the unknown durability of effect of the currently available therapies. The benefits of delayed therapy include minimization of treatment-related negative effects on quality of life and drug-related toxicities; limitation of future treatment options; and delay in the development of drug resistance. Risks of delayed therapy include the theoretical possibility that some damage to the immune system that might otherwise be salvaged by earlier therapy is irreversible; the possibility that suppression of viral replication may be more difficult at a later stage of disease; and the increased risk of HIV-1 transmission to others during a longer untreated period. The strength of the recom-
Fig. 1. Representative clinical course of patients under highly active antiretroviral therapy (HAART). Solid lines: CD4 positive cell counts/mm$^3$, solid bars: HIV-RNA copies/ml (measured by Amplicor/Roche). The emergence of amino acid substitution that confers drug resistance is indicated for RT (reverse transcriptase) or PR (protease) sequences. Amino acid abbreviations are as follows: A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine. Other abbreviations: GCV, ganciclovir; FOS, foscarnet; CMV, cytomegalovirus; RTV, Ritonavir; 3TC, Lamivudine; AZT, Zidovudine; NFV, Nelﬁnavir; d4T, Stavudine; SQV, Saquinavir; APV, Amprenavir; EFV, Efavirenz; ABC, Abacavir; LPV/r, Lopinavir/RTV.
medication for therapy must balance the readiness of
the patient for treatment; consideration of the prognosis
for disease-free survival in the absence of treatment as
determined by baseline CD4+ T cell count, viral load,
and the slope of the CD4+ T cell count decline; and
assessment of the risks and potential benefits associated
with initiating antiretroviral therapy.

In the majority of treatment-naïve patients starting
with HAART, viral load remained undetectable for a
considerable period and in some patients, clearance of
the virus from lymph nodes and partial immune restoration
was evident (3, 9). Figure 1 demonstrates the response
to two representative patients to HAART. The first patient
who received 600 mg bid of RTV together with 150
mg bid of 3TC and 100 mg qid of AZT succeeded in
suppressing viral replication at the lowest level for more
than 5 years and did not develop resistance mutations.
Very recently, RTV was replaced by LPV/r because
RTV was no longer recommended as a first line drug in
the latest guideline (23). On the other hand, responders
with very low but still detectable viral load and thus
ongoing low-level HIV-1 replication may be the subject
of potential treatment failure. The second patient in
Fig. 1 is one such case in that the viral replication was not
fully suppressed. In the course of triple therapy using
AZT, 3TC and RTV, mutation in RT which conferred
AZT resistance (T215Y) and 4 secondary mutations in
protease was observed. Because of the treatment failure
AZT and RTV were replaced with three new antivirals
(NFV, SQV, d4T). The emergence of primary resistance
mutation to RTV (V82A) was observed after transient
response to the new regimen. Finally 200 mg bid of
RTV was added to enhance the plasma concentration of
SQV and NFV. Although the resistance mutation to
RTI or PI was accumulating the surrogate makers includ-
ing plasma viral load and CD4+ T cell counts remained
stable for about a year. Very recently we started the
salvage combination therapy consisting of LPV/r, ABC,
d4T and EFV. As shown in the last part of the Fig. 1 this
regimen were able to decrease the amount of circulating
virus below detectable level (< 50 copies/ml). It is
therefore important to measure the efficacy of HAART
with viral load assays that are as sensitive as possible, so
that decisions on changing a drug when viral load does
not quite reach undetectable levels can be made in time,
before resistance starts to develop.

HAART and Reconstitution of Anti-HIV Immunity

The availability of HAART has resulted in dramatic
changes in the disease course, but long-term therapy is
limited by the development of resistance as well as tox-
icities of the potent medication regimens. Life-long
therapy will almost certainly be required to treat this
disease, since viral eradication is not likely to occur (4,
8). The failure of viral eradication with currently avail-
able therapeutic interventions has spawned new
approaches to limiting drug exposure. A novel area of
investigation has been sparked by the observation that
some persons remain healthy 20 or more years after
infection, with normal plasma HIV-1 RNA levels in the
absence of antiviral therapy (10, 11). Emerging data indi-
cate that these persons control HIV immunologically.
This has bolstered hope that the immune response might
be effectively augmented in persons with HIV infec-
tion. Recent data indicating that immediate treatment of
acute infection leads to augmentation of antiviral immune
responses have provided evidence that the immune sys-

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can be compared by intracytoplasmic staining of cytokine producing cells following antigenic stimulation. As shown in Fig. 3, HIV-specific γ-interferon (γ-IFN) producing Th cells were detected at high level in a patient with long-term nonprogressive clinical course. In contrast, the frequency of such Th cells was found to be low even in a patient who successfully suppressed the viremia and recovered the high number of CD4+ cells under HAART. The loss of HIV-specific Th cells occurred early in infection and recovery of such Th cells has not been demonstrated even for the patient with good clinical outcome.

Effects of HAART in chronically infected patients, with regard to neutralizing antibody responses against autologous isolates are poorly understood. Recently, we investigated the longitudinal change of neutralizing antibody response against an autologous HIV-1 in 19 chronically infected patients who were on HAART (12). Reconstitution of neutralization activities was observed in 3 of 6 patients with no significant activities at the
initiation of HAART. The reconstituted antibody which was detected more than 1 year after starting HAART and which represented limited cross-reactivity showed some similarity to antibodies which developed in primary infection. Thirteen out of 19 patients initially showed significant activities, but these were relatively weak in many subjects and most sustained the activities during HAART. Figure 4 demonstrated the four cases who developed the significant neutralization activity under HAART. These patients had relatively low CD4$^+$ T cell counts (<200/mm$^3$) at the start of HAART with a prolonged viral suppression during HAART developed or increased neutralizing antibodies against autologous isolate. The development of these neutralization activities was detected at over 12 months after starting HAART. This period corresponds to the period of recovery of the CD4$^+$ naive subset (16) and HIV-specific CD4$^+$ T cells (2) which have an important role in the development of antigen-specific humoral immunity.

**Perspectives for Goals of Therapy**

Eradication of HIV infection cannot be achieved with currently available antiretroviral regimens; in large measure, this is due to the establishment of a pool of latently infected CD4$^+$ T cells during the very earliest stages of acute HIV infection (5) that persists with an extremely long half-life, even with prolonged suppression of plasma viremia to <50 copies/ml. The primary goals of antiretroviral therapy are maximal and durable suppression of viral load, restoration and/or preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality. Partial reconstitution of immune function induced by HAART may allow for elimination of unnecessary therapies, such as some of those used for prevention and maintenance therapy against opportunistic infections. The appearance of naive T cells, partial normalization of perturbed T cell receptor V repertoires, and evidence of residual thymic function in patients receiving HAART suggest that partial immune reconstitution occurs in these patients.

Although as many as 70–90% of antiretroviral drug-naive patients achieve maximal viral load suppression 6–12 months after initiation of therapy, only about 50% of patients in a city clinic setting achieve similar results. Predictors of virologic success include low baseline viremia and high baseline CD4$^+$ T cell count, rapid decline of viremia, decline of viremia to <50 HIV RNA copies/ml, adequate serum levels of antiretroviral drugs, and adherence to the drug regimen. While optimal strategies for achieving the goals of antiretroviral therapy have not yet been fully delineated, efforts to improve patient adherence to therapy are likely important. Another tool to maximize the benefits of antiretroviral therapy is the rational sequencing of drugs and the preservation of future treatment options for as long as possible.

As Dr. D. Richman described in his recent review article (19), current accomplishment of HAART against HIV-1 infection defines following 4 challenges: 1) the discovery of drugs with increased potency, decreased toxicity and activity against drug-resistant viruses; 2) the elimination of viruses in poorly accessible tissue compartments and latent cellular reservoirs; 3) the induction of virus-specific immunity to supplement the benefits of chemotherapy; and 4) the identification of regimens that can benefit developing countries where the epidemic is most severe. Certainly, none of these issues are easy to solve but they have to be addressed as urgently as possible.

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