LIMITS OF ANTI-HIV CHEMOTHERAPY

ABSTRACT
The human immunodeficiency virus (HIV) belongs to the lentivirus genus of retroviruses. HIV infection is typically characterized by a prolonged asymptomatic phase prior to the development of acquired immunodeficiency syndrome (AIDS)-related opportunistic infections and death. The hallmark of HIV infection is the progressive destruction of the CD4 T lymphocyte subset, cells that represent an essential component of the immune system. The appearance of antiretroviral therapy (HAART) has dramatically improved the clinical outcome for HIV-infected patients, that reduces viral load to undetectable levels and concomitantly increase CD4 T cell counts resulting with significant drop of morbidity and mortality associated with HIV. However, some patients with HIV who are experiencing antiretroviral treatment failure and the mechanisms responsible for discordant responses are not well understood. This review summarizes both improvement and failure of the virologic and immunologic responses in HIV-infected patients under HAART.

INTRODUCTION
Since HIV was first identified as responsible for AIDS (Barre-Sinoussi et al., 1983), the World Health Organization has estimated that 36 million people worldwide are currently living with HIV, three-quarters of them in sub-Saharan Africa, and some 20 million people have already died (UNAIDS, 2000). The use of biomedical intervention in the form of antiretroviral therapy (HAART) has transformed the face of AIDS in the developed world. Indeed, HAART (Highly Active
Antiretroviral Therapy) has substantially reduced the morbidity and mortality associated with HIV for those populations able to afford access (Palella et al., 1998), and has had a significant impact on preventing mother-to-child transmission (Marseille et al., 1999, De Cock, et al., 2000). However, when globally looked, the access to anti-retroviral therapy have been relevant to only a small proportion of the world’s population affected by HIV. Moreover, administering these antiretroviral regimens to long-term patients is difficult; expensive, and there are a growing number of potential adverse effects and complex drug interactions to consider (Flexner, 1998). Furthermore, AIDS constitutes one of the most serious crises currently facing human development, and threatens to reverse progress in the most severely affected countries by decades (reviewed by Piot et al., 2001).

ANTI-HIV THERAPY: HAART

Potent anti-retroviral therapies (HAART), including at least one protease inhibitor associated to one or more reverse-transcriptase inhibitors (Table 1) (Markowitz et al., 1995), have changed the course of HIV disease by dramatic decrease in plasma and tissue HIV RNA load, as well as, quantitative and functional recovery of peripheral CD4 T cells (Collier et al., 1996, Hammer et al., 1997, Cavert et al., 1997, Li et al., 1998). During HAART, the dramatic clearance in the levels of HIV RNA in plasma and infected cells in lymphoid tissue is attributable to, a first-phase, the death of infected activated CD4 lymphocytes and the prevention of new infection (Perelson et al., 1996). The second-phase, somewhat more variable among individuals, has been attributed to clearance of infected macrophages or to virions bound to dendritic cells in lymph nodes, but may also be due to chronically infected CD4 lymphocytes with a longer half-life and lower rates of virus replication (Perelson et al., 1997, Cavert et al., 1997, Zhang et al., 1999).

The immunological consequences of suppressing virus replication due to HAART are pronounced. The mechanisms that account for the rise in blood CD4 T cells following HAART are currently not completely understood. The initial rise of CD4 T cells would be due to the migration of memory T cells from the lymphoreticular tissues, where they are not trapped anymore by the virus, to the blood (Pakker et al., 1998). In a second phase after several weeks of HAART, the sustained rise in CD4 T cells would be the result of their peripheral proliferation, due to the removal of HIV-induced suppression (Hellerstein et al., 1999), increased thymic cell turnover and to the regulation of apoptosis levels. Indeed, rapidly after initiation of HAART, an important drop in spontaneous, activation-induced and CD95-triggered apoptosis is observed in both CD4 and CD8 T cells from all treated patients (Badley et al., 1999, Gougeon et al., 1999, Sloand et al., 1999, Grelli et al., 2000). In addition, immune enhancement and reconstitution has been observed by return of delayed-type hypersensitivity and lymphocyte proliferation responses (reviewed by Lederman, 2001).
Unfortunately, not all patients demonstrate a substantial increase in circulating CD4 T cells and/or HIV suppression. The limitations of HAART have been better realized during the past few years and we summarize this aspect in this review.

DISCREPANT VIROLOGIC AND IMMUNOLOGIC RESPONSES TO HAART

Failure to reduce HIV RNA under HAART to the limit of detection in currently available assay (below 50 copies per milliliter plasma), indicates inadequate suppression and risk of outgrowth of resistant virus (Carpenter et al., 2000). Unfortunately, a series of studies have clearly demonstrated persistent viruses and ongoing viral replication, even among patients who have sustaining HIV RNA levels below 50-copy for extended periods (Natarajan et al., 1999, Wong et al., 1997, Finzi et al., 1997). Based on this data, it was demonstrated that HIV might reside in a latent state in persistently infected, non-activated CD4 T lymphocytes in HIV-infected individuals (Wong et al., 1997, Finzi et al., 1997, Chun et al., 1997). Of importance, these cells represent a small fraction of infected cells during active infection and have long half-lives, with estimates ranging from 6 to 44 months (Finzi et al., 1999, Ramratnam et al., 2000). It would require up to 60 years of continuous effective HAART therapy to eradicate all the latent HIV (Lisziewicz et al., 1999, Lori et al., 2000). Consequently, cellular reservoir archives virus that can re-emerge and propagate after the withdrawal of chemotherapy. The existence of these cells has frustrated hopes of eradication of infection with current chemotherapy. In addition, the increase in CD4 T cells is not observed in all the patients, and the functional alterations in addition to the skewed TCR repertoire of the CD4 T helper subset are only partially corrected under HAART (Connors et al., 1997).

Therefore, a percentage of HIV-infected patients receiving HAART exhibit a sustained CD4 T cell response, despite the therapy’s failure to kill the virus, or have persistently low CD4 cell counts, despite a significant decrease in plasma virus load (Kaufmann et al., 1998, Piketty et al., 1998, Renaud et al., 1999, Deeks et al., 2000). In this context, two prospective follow-up studies of a cohort of antiretroviral-experienced patients with advanced HIV disease demonstrated that the incidence of AIDS-defining events and deaths in the group of patients without an immunologic or virologic response (I-V-) was much higher than other groups; yet, the incidence follows in patients with no immunologic response, despite a virologic response (I-V+), then patients with immunologic response in the absence of a virologic response (I+V-) and finally, in full responder patients (I+V+) (Piketty et al., 1998 and 2001). The authors support the relevance of the CD4 cell marker over plasma HIV load for predicting clinical outcome in patients who do not achieve full immunologic and virologic responses.

Several mechanisms have been proposed to account for such paradoxical responses, including an alteration in T cell turnover kinetics, changes in viral fitness associated with acquired resistance mutations to protease inhibitors (Belec et al., 2000)
and the prevention of T cell apoptosis by protease inhibitors (Sloand et al., 1999, Weichold et al., 1999). Indeed, in spite of an important drop in T lymphocytes’ apoptosis from HAART treated-patients related by several studies (Badley et al., 1999, Gougeon et al., 1999, Sloand et al., 1999, Grelle et al., 2000), we recently reported that HAART is not systematically associated with suppression of T cell apoptosis in a cohort of patients experiencing in majority an increase of CD4 T cells (Pinto, et al., 2002). Interestingly, the levels of T cell apoptosis were significantly negatively correlated with the CD4/CD8 ratio under HAART, suggesting that T cell apoptosis plays a significant role in homeostasis of CD4 and CD8 T cells after initiation of potent therapy. In addition, CD4 T cell increase from baseline under HAART was negatively correlated with spontaneous apoptosis in CD4 T cells, suggesting that quantitative immunological recovery may depend on the control of T cell survival. We hypothesized that a higher susceptibility to T lymphocytes’ apoptosis in HIV-infected treated patients could account for the phenomenon of discrepant immunologic responses; it would be predictive to inefficacious response to anti-retroviral therapy (Pinto, et al., unpublished data).

### Table 1: Anti-retroviral drugs.

<table>
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<tr>
<th>Group</th>
<th>Drugs</th>
<th>Mechanism of action</th>
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<tbody>
<tr>
<td>Nucleosidic Reverse-Transcriptase Inhibitors or NRTI</td>
<td>Abacavir (ABC)</td>
<td>They are similar in structure to the building blocks that make up DNA. By incorporating themselves into the DNA nucleoside chain being produced by reverse transcriptase, they stop attachment of further nucleosides and so prevent ongoing viral DNA synthesis.</td>
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<tr>
<td></td>
<td>Didanosine (ddl)</td>
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<td>Lamivudine (3TC)</td>
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<td>Stavudine (d4T)</td>
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<td></td>
<td>Zalcitabine (ddC)</td>
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<td></td>
<td>Zidovudine (AZT)</td>
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<tr>
<td>Non-nucleosidic Reverse-Transcriptase Inhibitors or NNRTI</td>
<td>Efavirenz</td>
<td>They attach to the reverse transcriptase and affect the activity of the enzyme by restricting its mobility and making it unable to function.</td>
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<td>Delavirdine</td>
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<td>Nevirapine</td>
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<tr>
<td>Protease Inhibitors or PI</td>
<td>Amprenavir (AMP)</td>
<td>They block cleavage of precursors proteins gag and pol, resulting in the release of particles viral defective and un-infectious.</td>
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<td>Indinavir (IDV)</td>
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<td>Lopinavir (LPV)</td>
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<td>Nelfinavir (NFR)</td>
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<td>Ritonavir (RTV)</td>
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<td></td>
<td>Saquinavir (SQV)</td>
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Maenza and Flexner, 1998.
REFERENCES


Ramratnam, B.; Mittler, J.E.; Zhang, L. et al. 2000 The decay of the latent reservoir of replication-competent HIV-1 is inversely correlated with the extent of residual viral replication during prolonged antiretroviral therapy. Nat Med 6, 82-5.


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