Strategies of Antiretroviral Therapy in Adults
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Strategies of Antiretroviral Therapy in Adults

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Key Words. HIV · Treatment strategies · AIDS · Antiretroviral treatment · HIV therapy

ABSTRACT
Recent progress in antiretroviral treatment has led to dramatic improvements in HIV-related morbidity and mortality. These improvements have been fostered by advances in our understanding of HIV-related pathogenesis, the use of plasma HIV RNA levels to monitor patients, and the availability of 11 licensed antiretroviral drugs, including the potent protease inhibitors. Numerous drug combinations, especially those containing three agents, can suppress plasma HIV RNA levels below the lower limit of detection in the majority of treated patients. However, the limitations of this therapeutic response—patient compliance, drug resistance, and a residual burden of chronically infected cells which are refractory to treatment—should be familiar to the oncologist. The Oncologist 1998;3:111-118

INTRODUCTION
Tremendous popular interest is focused on the development of new treatments for HIV-infected persons, and the pendulum of public understanding has swung from euphoria over the availability of antiretroviral combinations which provide complete suppression of plasma viremia to despair over treatment failure in patients who have exhausted all available options. An objective summary of progress in the last three years clearly identifies dramatic treatment successes, tempered by the realization that HIV disease is a chronic infection for which we have no immediately curative therapy. Many reports now describe marked decreases in AIDS-related complications, hospitalizations, and deaths [1, 2]. Within the Adult Infectious Diseases Clinic at Duke University Medical Center, the number of persons dying from AIDS has declined from 144 in 1995 to a projected total of 30 in 1997. Three major advances underlie these improvements in clinical outcomes: a better understanding of HIV-related pathogenesis, the ability to directly and sensitively measure HIV activity with plasma HIV RNA levels, and the availability of an increasing number of new therapeutic agents with potent antiretroviral activity, differing mechanisms of action, and nonoverlapping patterns of resistance. Given the marked expansion in the tools to monitor and treat HIV-infected persons, we must now develop the optimal strategies to guide clinical practice. In many respects, the evolution of HIV medicine is similar to oncology 20 years ago. The paradigms of oncologic medicine may offer important models for the development of new HIV treatment strategies.

RELEVANT PATHOPHYSIOLOGY

Acute HIV Infection
After the acquisition of HIV, most commonly through sexual contact, the initially infected cells appear to be macrophages within the genital tract. Macrophage-tropic HIV strains, also possessing the in vitro culture characteristic of not inducing syncytia, are most commonly transmitted [3]. Animal studies suggest that a regional lymphadenitis soon follows [4]. From this initial localized infection HIV disseminates hematogenously, and the virus may then localize on follicular dendritic cells throughout lymphoid tissue [5, 6]. From the surface of follicular dendritic cells, HIV can then infect CD4 lymphocytes trafficking through the germinal centers of lymphoid tissue. This process creates a large reservoir of chronically HIV-infected cells within lymph nodes, the entire reticuloendothelial system, lymphoid tissue in the gut, and microglial cells in the central nervous system [5, 6]. During acute HIV infection, high-grade viremia can be documented by high titers of culturable plasma virus or high levels of plasma HIV RNA [7, 8]. Resolution of this high-grade viremia may correspond to the development of an anti-HIV cytotoxic T-lymphocyte response [9].

Most diagnostic tests for HIV infection measure anti-HIV antibodies. The serologic response against HIV usually takes 4-12 weeks to develop, and therefore conventional diagnostic tests are not useful during acute HIV infection. More useful tests during this period, such as p24 antigen levels...
Established HIV Infection

“Established” HIV infection infers that the dissemination of HIV has occurred and the reservoir of chronically infected cells has been created. In patients with established infection, virus within plasma and peripheral blood mononuclear cells exists in a dynamic state of turnover [12, 13]. It has been observed that 10^{10} virions are produced every day within an HIV-infected person. Within this background of rapid virus turnover, it is easy to appreciate the potential for the rapid emergence of drug-resistant HIV strains. The mechanisms of CD4+ lymphocyte depletion are not yet fully elucidated, but it appears that chronic viral replication contributes both directly and indirectly to CD4+ lymphocyte decline.

Prognostic Markers

Within the past several years, the prognostic value of plasma HIV RNA measurements has become more clearly appreciated [14-16]. Interestingly, plasma HIV RNA levels may reach a temporary steady state following the resolution of acute HIV infection [14]. This level has been described as the viral “set point” and clearly portends the risk of clinical progression to AIDS or death over the next 10 years. Measurement of plasma HIV RNA levels throughout the course of HIV disease, not just at the set point, also offers important prognostic information concerning the risk of clinical progression to AIDS and death [15, 16] and the risk of vertical transmission [17]. Therapeutic interventions which decrease plasma HIV RNA levels are associated with an improved clinical prognosis [18-22]. Recognition of the prognostic value of plasma HIV RNA levels has led to the incorporation of their measurement in routine clinical practice, usually on a quarterly schedule [23]. Plasma HIV RNA levels may display considerable variability, and changes up to twofold may not be considered biologically important [24]. Immunizations and intercurrent illnesses have been demonstrated to transiently increase plasma HIV RNA levels [25], and measurement following these events may be misleading. The methods for measuring plasma HIV RNA include RT-PCR, bDNA, and NASBA. All offer relatively consistent measurements, although they differ in their lower limit of detection. Clinical trial results now suggest that the nadir of plasma HIV RNA levels on treatment may be very important in determining the durability of an antiretroviral regimen [26]. This observation carries a profound implication for clinical practice, and strongly suggests that the goal of treatment for all patients should be the complete suppression plasma HIV RNA below the lower limit of detection. In addition, great efforts are under way to improve the sensitivity of plasma HIV RNA measurements to even lower levels, (i.e., “ultra-sensitive” assays which measure down to 20 copies/ml).

Absolute CD4+ cell counts also offer important prognostic information for HIV-infected persons and complement the measurement of plasma HIV RNA levels. Absolute CD4+ cell counts remain important predictors of complicating opportunistic infections. Many clinicians now measure absolute CD4+ cell counts every six months unless a patient is near a decision point for the initiation of prophylaxis for an opportunistic infection.

Available Agents

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

General Observations

The NRTIs are the most extensively evaluated class of antiretroviral drugs. NRTIs require intracellular triphosphorylation to become activated. When used alone, NRTIs typically offer 0.5-1.0 log_{10} decreases in plasma HIV RNA levels, and when two NRTIs are combined, the decreases are usually 1.0-1.5 log_{10} copies/ml. They may be combined with non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the protease inhibitors (PIs). Specific NRTIs are shown in Table 1.

Combinations

NRTIs may be combined with one definite exception: zidovudine and stavudine. These two drugs have exhibited both in vitro and in vivo antagonism [27]. Zalcitabine should probably not be combined with stavudine or didanosine due to overlapping toxicities. Stavudine may be combined with didanosine cautiously, but patients should be followed closely for peripheral neuropathy and pancreatitis [28].

NNRTIs

General Observations

NNRTIs are potent inhibitors of HIV in vitro and in vivo, but their use can be complicated by the rapid development of resistance through a single mutation. As a
result, they must be combined with other antiretroviral drugs. A new NNRTI, DMP-266, may require the acquisition of at least two mutations for resistance, perhaps enhancing its usefulness. NNRTIs require no intracellular phosphorylation and distribute well throughout the body, including the CNS and across the placenta. NNRTIs are commonly metabolized through the cytochrome p450 system and therefore may interact with PIs. NNRTIs may share a common toxicity—a macular erythematous rash which is usually self-limited. Specific NNRTIs are shown in Table 2.

**Combinations**

NNRTI combinations cannot be recommended because of potential cross-resistance. NNRTIs should always be combined with other antiretroviral agents, either NRTIs or PIs. When combined with PIs, pharmacokinetic interactions may occur which require PI dosage adjustment.

**Protease Inhibitors**

**General Observations**

PIs represent the most potent class of antiretroviral agents. They require no intracellular activation and enter the CNS in relatively low concentrations due to plasma protein binding. Careful attention to dosing schedule is crucial because low trough levels of the drug are clearly associated with the appearance of resistance mutations. In the future, therapeutic drug monitoring may become important for use with PIs. PIs should not be used as monotherapy because of potential resistance. PIs may interact with many other drugs, including NNRTIs, because of their extensive cytochrome p450 metabolism. Specific PIs are shown in Table 3.

**Combinations**

PIs may be combined based upon drug interactions and resistance patterns. Attractive combinations may include

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**Table 1. Specific NRTIs**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Toxocities</th>
<th>Unique characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>200 mg tid or 300 mg bid</td>
<td>MACROCYTIC ANEMIA, NEUTROPHENIA, MYOPATHY, NAUSEA, FATIGUE,</td>
</tr>
<tr>
<td>(ZDV, AZT, Retrovir)</td>
<td></td>
<td>HEADACHES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>200 mg bid</td>
<td>PERIPHERAL NEUROPATHY, PANCREATITIS, NAUSEA, BLOATING, DIARRHEA</td>
</tr>
<tr>
<td>(DDI, Videx)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>0.75 mg tid</td>
<td>PERIPHERAL NEUROPATHY, APHTHEOUS ULCERS, RASH</td>
</tr>
<tr>
<td>(DDC, HIVID)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td>40 mg bid or 30 mg bid &lt; 60 kg</td>
<td>PERIPHERAL NEUROPATHY, PANCREATITIS, TRANSMIINITIS, AGITATION</td>
</tr>
<tr>
<td>(D4T, Zerit)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>150 mg bid</td>
<td>PANCREATITIS, PERIPHERAL NEUROPATHY, NAUSEA</td>
</tr>
<tr>
<td>(3TC, Epivir)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unapproved:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>300 mg bid</td>
<td>NAUSEA, HEADACHES</td>
</tr>
<tr>
<td>(GW 1592, Ziagen)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Specific NNRTIs**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Toxocities</th>
<th>Unique characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>200 mg qd × 2 weeks, then 200 mg bid</td>
<td>RASH, NAUSEA, TRANSAMINITIS</td>
</tr>
<tr>
<td>(Viramune)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delaviridine</td>
<td>400 mg tid</td>
<td>RASH</td>
</tr>
<tr>
<td>(Rescriptor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unapproved:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etavirenz</td>
<td>600 mg qd</td>
<td>NAUSEA, DIZZINESS</td>
</tr>
<tr>
<td>(DMP-266, Sustiva)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ritonavir and saquinavir (20-30 × increase in saquinavir levels) \[29\], nelfinavir and saquinavir (2-3 × increase in saquinavir levels) \[30\], ritonavir and indinavir (under evaluation), and ritonavir and nelfinavir (under evaluation). The combination of indinavir and saquinavir has demonstrated in vitro antagonism. PIs may be combined with NRTIs, but may require dosage adjustments when combined with NNRTIs.

**TREATMENT STRATEGIES**

**General Principles**

Acknowledging the current availability of 11 antiretroviral agents and anticipating the FDA approval of several new agents within the next year, it is critical to identify the guiding principles for antiretroviral therapy. These principles should include the following considerations:

**The Perceived Benefit Must be Greater Than the Toxicities, Imposition, and Cost**

Clear decreases in the risk of clinical progression to AIDS or death have been demonstrated for patients with late-stage HIV disease (absolute CD4+ cells < 200/mm³), receiving triple combination therapy including a protease inhibitor \[31, 32\]. For patients with an intermediate stage of HIV disease, (absolute CD4+ cells < 500/mm³), combination therapy with two NRTIs offers improved clinical outcomes over ZDV monotherapy \[33, 34\]. For patients with early HIV disease (absolute CD4+ cells > 500/mm³), there is no clinical trial yet completed which has evaluated clinical outcomes in the recipients of combination therapy. Therefore, it may be reasonable to delay therapy in patients at low risk of clinical progression (low plasma HIV RNA, high absolute CD4+ cells), with close monitoring \[35\].

**Compliance is Crucial!**

Antiretroviral drug resistance is most likely to occur in regimens which incompletely suppress virus replication. Lower trough plasma levels of protease inhibitors are associated with the appearance of mutations conferring protease inhibitor resistance \[36\]. Taken together, these observations underscore the need for patient adherence to antiretroviral regimens. Patients who develop resistant virus may also transmit these mutant strains to their sexual partners \[37\]. Careful patient selection and education before initiating treatment are crucial strategies for therapeutic success.

**All Regimens Should Include at Least Two Drugs**

Most currently prescribed antiretroviral regimens include two NRTIs, to which a third drug such as a protease inhibitor or NNRTI is added. Two NRTIs commonly suppress plasma HIV RNA levels by 1.0-1.5 log₁₀ copies/ml in previously untreated patients \[38\]. Therefore, unless pretreatment plasma HIV RNA levels are less than 5,000-10,000 copies/ml, it is unlikely that a two-NRTI combination can suppress levels below the lower limit of detection. In most patients, a three-drug combination will be required to achieve full suppression, and it is possible that in patients with very high baseline plasma HIV RNA levels, four drugs may be required to reach full suppression.

**Relative Potency is Greatest for the Protease Inhibitors**

PIs can suppress plasma HIV RNA levels by 1.5-2.0 log₁₀ copies/ml \[39, 40\], greater than the decrease observed with currently available NRTIs or NNRTIs. Therefore, PIs should be considered the backbone of the most active antiretroviral combinations. In the future, NRTIs such as abacavir and NNRTIs such as efavirenz may offer similar suppression.

### Table 3. Specific PIs

<table>
<thead>
<tr>
<th>Approved:</th>
<th>Dose</th>
<th>Toxicities</th>
<th>Unique characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir (Fortovase)</td>
<td>1200 mg tid</td>
<td>Nausea</td>
<td>New formulation has improved bioavailability</td>
</tr>
<tr>
<td>Ritonavir (Norvir)</td>
<td>Initial 300 mg bid</td>
<td>Nausea, diarrhea, perioral paresthesias, triglyceride elevations, transaminits</td>
<td>Increase to full dose over first one to two weeks; potential drug interactions; must be refrigerated; may be taken with food</td>
</tr>
<tr>
<td></td>
<td>Full 600 mg bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir (Crixivan)</td>
<td>800 mg q8h</td>
<td>Nausea, bloating, hyperbilirubinemia, nephrolithiasis</td>
<td>Cannot be taken with food; must drink at least 1.5 l/day to prevent stones</td>
</tr>
<tr>
<td>Nelfinavir (Viracept)</td>
<td>750 mg tid</td>
<td>Diarrhea, nausea</td>
<td>Should be taken with food</td>
</tr>
<tr>
<td>Unapproved:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amprenavir (GW 141; VX-478)</td>
<td></td>
<td>Nausea</td>
<td></td>
</tr>
</tbody>
</table>

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All Regimens are Likely to have a Finite Period of Effectiveness

Current evidence suggests that the potent suppression of plasma HIV RNA levels is accompanied by suppression of HIV RNA within lymphoid tissue, although HIV DNA in chronically infected cells does not appear to be decreasing [41, 42]. These observations suggest that antiretroviral therapy achieves suppression only, without any reduction in the chronic viral reservoir. Antiretroviral combinations can suppress plasma HIV RNA levels below the lower limit of detection in up to 90% of subjects for 48 weeks [43], but the longer-term durability of this response remains uncertain. It seems unlikely that this level of suppression can persist indefinitely.

Old Drugs May Not be Recyclable

The available evidence suggests that resistant strains appear in the plasma and lymphoid tissue almost simultaneously [44]. When a given antiretroviral drug is discontinued, the predominant plasma isolates no longer display drug resistance. However, soon after the reintroduction of the same antiretroviral drug, these resistant strains rapidly reappear within the plasma. Taken together, these observations suggest that lymphoid tissue may serve as an important reservoir for drug-resistant strains and that drugs from a previously failed regimen are unlikely to be effective when reintroduced.

Drug Interactions are Important

The PIs and NNRTIs are extensively metabolized through the cytochrome p450 system. As a result, the clinician must be aware of potential drug interactions involving these agents.

Monitor the Success of Treatment

Plasma HIV RNA levels decline rapidly following the initiation of antiretroviral therapy with a t1/2 <12 hours. If patients require early positive reinforcement for their commitment to antiretroviral adherence, measuring plasma HIV RNA levels at two to three weeks may be helpful. Preliminary evidence suggests that a plasma HIV RNA level <1,000 copies/ml at week 12 correlates with a level below the lower limit of detection at week 24 [26]. If patients have not achieved this landmark by week 12, questions should be raised about compliance and should lead to the consideration of treatment intensification with the addition of one to two new antiretroviral drugs. Once on a stable regimen, most clinicians follow plasma HIV RNA levels every three months.

Immune Reconstitution?

When plasma HIV RNA levels fall below the lower limit of detection, absolute CD4+ cells usually increase by 100-150/mm³ [43]. However, the functional status of these cells remains uncertain [45, 46]. Treated patients have a lower risk of opportunistic infections and death [31, 32] and refractory complications of progressive HIV disease such as molluscum contagiosum may resolve [47], suggesting that some degree of meaningful immunologic reconstitution is achieved. However, most clinicians are reluctant to discontinue opportunistic infection prophylaxis, especially for Pneumocystis carinii pneumonia, until clinical trials results clarify these issues.

Initiating Treatment

Timing

The decision to initiate therapy should be guided by three factors:

▲ Plasma HIV RNA levels
▲ Absolute CD4+ cell counts
▲ Patient acceptance

Currently, there are no clinical trial results to guide consideration of the proper plasma HIV RNA level at which to begin treatment. Therefore, recommendations must be made by extrapolating from cohort studies following plasma HIV RNA levels. Most clinicians would strongly encourage treatment at a plasma HIV RNA level >20,000 copies/ml, would encourage treatment with plasma HIV RNA levels = 10,000-20,000 copies/ml, and would carefully consider treatment with plasma HIV RNA levels <10,000 copies/ml. The International AIDS Society–USA Panel recently recommended therapy for all patients with plasma HIV RNA levels >5,000-10,000 copies/ml. Similarly, many clinicians would strongly encourage treatment with absolute CD4+ cells <200/mm³, would encourage treatment with cells 200-500/mm³, and would carefully consider treatment with cells >500/mm³. All recommendations to initiate treatment must involve an informed, committed patient. Poor compliance will inevitably lead to a shortened duration of activity and viral resistance.

Initial Combinations

The goal of all antiretroviral therapy should be suppression of plasma HIV RNA levels below the limit of detection. The optimal timing to achieve this goal remains to be determined, but should be reached by 24 weeks. The optimal initial regimen also remains to be determined. Here are some options:

▲ Two NRTIs: Extensive experience, well tolerated but offer only 1 log₁₀ suppression of plasma HIV RNA levels at one year.
▲ Two NRTIs + NNRTI: Limited experience, well tolerated, with suppression of plasma HIV RNA levels below detectable in 50%-60% at one year; spares the PIs for later.
Two NRTIs + PI: Moderate experience, well tolerated, extremely potent, with suppression of plasma HIV RNA levels below detectable in 80%-90% at one year.

Two PIs: Limited experience, appears to be well tolerated and extremely potent, with suppression of plasma HIV RNA levels below detectable in 80%-90% at six months; uncertain role as initial therapy.

Salvage Regimens
Given the apparent inability of antiretroviral treatment to significantly diminish the reservoir of chronically infected cells and the likelihood of the eventual emergence of resistant strains, all regimens of suppressive antiretroviral treatment will ultimately fail. Therefore, it is critically important to recognize failing regimens quickly and reinitiate effective treatment with a salvage intervention.

Timing
Most clinicians follow plasma HIV RNA levels every three months in treated patients. Currently, there is no absolute consensus on the proper plasma HIV RNA threshold at which to change treatment. It is likely that the kinetics of the increase in plasma HIV RNA levels may vary in individual patients depending upon the degree of antiretroviral resistance, viral fitness, and other presently unknown factors. However, many clinicians will agree on changing therapy when plasma HIV RNA levels are >5,000-10,000 copies/ml. In the future, it is very likely that decisions to change treatment may be guided by resistance assays.

New Combinations
The goal of salvage regimens is also to suppress plasma HIV RNA levels to below the limit of detection. This goal appears to be best achieved by including at least two new drugs without cross-resistance to previously used drugs. Some examples include:

NRTI₁ + NRTI₂ + NRTI₃ + PI
NRTI₁ + NRTI₂ + NNRTI → NRTI₃ + PI
NRTI₁ + NRTI₂ + PI₁ → NRTI₃ + PI₆
NRTI₁ + PI₆ + PI₅ + PI₄ + NNRTI

Critical Issues for the Future
Despite the tremendous treatment advances in the past three years, numerous clinical problems need solutions. A partial listing of these problems includes:

The need to optimize the performance of available regimens with considerations for the sequencing of combinations, enhancing compliance, and development of clinically useful resistance assays.

The continuous need for new salvage regimens through new drug development.

The need to diminish the reservoir of chronically infected cells by understanding their natural turnover and identifying methods to accelerate the turnover rate.

The need to assess immunologic reconstitution through the use of antiretroviral drugs alone and to consider methods for enhancing this reconstitution.

The need to define the potential benefits and optimal treatment strategies for important clinical circumstances such as acute HIV infection and HIV-infected pregnant women.

Summary
In 1997, HIV-treating clinicians and their patients enjoy far more treatment opportunities than in years past. However, the limitations of these treatments—patient compliance, drug resistance, and a residual population of chronically infected cells—should be familiar to the oncologist. Perhaps the therapeutic paradigms of clinical oncology will provide a fast track to further improvements in antiretroviral strategies.

References


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