**Perspectives**

**Evolving Approaches to Initial Antiretroviral Therapy: When to Start and With What**

Factors to be considered in the decision of when to initiate antiretroviral therapy, current recommendations regarding initial regimen options, and recent data from clinical trials assessing regimen options were discussed by Roy M. Gulick, MD, MPH, at the International AIDS Society–USA course in Washington, DC, in May.

**When to Begin**

Although there is no longer an emphasis on starting antiretroviral treatment as early in HIV infection as possible, there remains considerable debate regarding when therapy is optimally begun. Factors motivating earlier treatment include the recognition that HIV disease is progressive, the ability of effective therapy to suppress HIV RNA levels, thereby suppressing emergence of resistance, and to increase CD4+ cell counts, thereby improving immune function; and the accumulating data showing that viral suppression can be maintained for a prolonged period (the potential for 5 or more years of suppression has been demonstrated). Arguments for delaying therapy can be based on the low risk of clinical progression in early disease, such practical factors as difficulty in adherence to regimens and the potential for toxicity to outweigh benefits in early disease, and the fact that long-term effects of treatment remain unknown.

Five studies assessing the question of when to begin therapy were reported at the 8th Conference on Retroviruses and Opportunistic Infections this year. In general, the findings of these case-control, observational, or population-based studies support the notion that delaying treatment somewhat is not associated with a remarkable loss of effect in preventing clinical disease progression.

One exception to this trend in findings is the Swiss HIV Cohort case-control study reported by Opravil and colleagues (8th CROI, 2001). In this study, rates of disease progression in 358 patients beginning antiretroviral therapy between January 1996 and December 1999, with CD4+ cell counts above 350/µL, were compared with rates in 358 patients aged 485/µL and 487/µL, respectively).

**Starting antiretroviral treatment as early as possible is no longer emphasized, but there remains considerable debate regarding when therapy is optimally begun**

HIV-infected patients not receiving therapy who were matched for CD4+ cell count (485/µL and 487/µL, respectively), age, HIV RNA level (4.26 log₂ and 4.10 log₁₀ copies/mL, respectively), and date of enrollment in the cohort. Median durations of follow-up were 2.3 years in the antiretroviral treatment group and 1.3 years in the matched controls, with 14% of the former and 28% of the latter group being lost to follow-up. Instituting therapy at this relatively high CD4+ cell count was associated with highly significant reductions in clinical progression, including reductions in symptomatic disease (Centers for Disease Control and Prevention [CDC] category B/C) from 17% to 4% (P < .0001) and AIDS (CDC category C) from 5% to 1% (P = .0001), and a reduction in all-cause mortality from 5% to 1% (P = .0006).

Two studies providing evidence of absence of harm in delaying treatment are a CDC observational study reported by Kaplan and colleagues (8th CROI, 2001) and a University of British Columbia population-based study reported by Hogg and colleagues (8th CROI, 2001). In the CDC study, risk of HIV-related death was assessed as a function of CD4+ cell count at the time of starting antiretroviral therapy in 5110 patients observed in the Adult and Adolescent Spectrum of Disease project (a review of medical records in various US cities), who started 2- or 3-drug regimens in 1994 or thereafter. Median follow-up was 1.4 years. Table 1 shows Kaplan-Meier estimates of 2-year survival by CD4+ cell count stratum and the hazard ratio for death in each stratum compared with the ≥500/µL stratum. The hazard ratio for each stratum below 200/µL was significantly increased compared with the stratum ≥500/µL. However, no significant increase in hazard ratio was seen for strata within the 200/µL to 499/µL interval, indicating no significant increase in risk for death among patients beginning therapy at these cell counts compared with counts of 500/µL or more for this limited period of time. Limitations of the study include its observational design, short follow-up, absence of evaluation of resistance, and lack of confirmation that patients followed up were antiretroviral-naïve at the start of the study treatment periods.

In the University of British Columbia study, survival was analyzed in patients receiving antiretroviral therapy in the province between January 1996 and September 1999 (n=1219) according to CD4+ cell count at initiation of therapy. Median follow-up was 3 years. Survival in those beginning treatment with a
CD4+ cell count below 350/µL was significantly lower than that in patients starting at counts of 350/µL to 499/µL and in those with counts of 500/µL or more, with no significant difference in rates between the latter groups. It is of interest that stratification by initial HIV RNA level suggested no substantive differences in survival according to pretreatment viral load.

Recommendations for when to start treatment include those offered by the US Department of Health and Human Services (DHHS; available at http://www.hivatis.org) and by the guidelines panel convened by the International AIDS Society–USA (IAS–USA, Carpenter et al, JAMA, 2000). The DHHS recommendations, updated as of April 23, 2001, recommend treatment in patients with CD4+ cell counts below 200/µL, offering of treatment to those with counts of 200/µL to 350/µL, deferral of treatment in those with counts above 350/µL if viral load is less than 50,000 HIV RNA copies/mL, and treatment or deferral in those with counts above 350/µL if viral load is more than 50,000 copies/mL. The IAS–USA guidelines, published in 2000, recommended treatment in patients with CD4+ cell counts below 200/µL and 200/µL to 350/µL.

Recommendations for treatment in those with cell counts above 350/µL were based on viral load as well as clinical and individual patient factors. The IAS–USA panel is currently drafting updated recommendations. A guiding clinical principle, as stated by the May 5, 1999 version of the DHHS guidelines, is that “…[T]he patient should make the final decision regarding acceptance of therapy following discussion with the health care provider of specific issues relevant to his/her own clinical situation.”

What to Start With

As of this writing, there are 16 antiretroviral drugs available for use, including 6 nucleoside reverse transcriptase inhibitors (nRTIs), 6 protease inhibitors, 3 nonnucleoside reverse transcriptase inhibitors (NNRTIs), and an investigational nucleotide reverse transcriptase inhibitor available through an expanded access program. Currently the IAS–USA recommends beginning treatment with a regimen consisting of 1 protease inhibitor plus 2 nRTIs, 2 protease inhibitors plus 2 nRTIs, or 1 NNRTI plus 2 nRTIs, with the published guidelines providing discussion of relative benefits or drawbacks of individual drugs and combinations in these classes. The DHHS recommends combining 1 drug from among efavirenz, indinavir, nelfinavir, saquinavir/ritonavir, indinavir/ritonavir, or lopinavir/ritonavir with one from among the dual nRTI options of stavudine/didanosine, stavudine/lamivudine, zidovudine/didanosine, and zidovudine/lamivudine.

Selection of the initial regimen should be based on a number of factors, including:

- Antiretroviral activity—ie, effects on viral load and CD4+ cell count and clinical response
- Demonstrated durability of response
- Tolerability, including acute adverse effects and risk of chronic adverse effects
- Convenience, including number of pills, dosing interval, and food/fast-ing requirements
- Potential for preserving future treatment options
- Stage of HIV disease, including consideration of concomitant illnesses and medications and potential drug interactions
- Access and cost

Table 1. Survival and Hazard Ratio for Death According to CD4+ Cell Count at Initiation of Antiretroviral Therapy in Centers for Disease Control and Prevention Observational Study

<table>
<thead>
<tr>
<th>CD4+ Cell Count Stratum (cells/µL)</th>
<th>Person-Years</th>
<th>Deaths</th>
<th>2-Year Survival</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>8428</td>
<td>902</td>
<td>81%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>0-49</td>
<td>2918</td>
<td>603</td>
<td>65%</td>
<td>5.5</td>
<td>3.0-10.1</td>
</tr>
<tr>
<td>50-99</td>
<td>873</td>
<td>114</td>
<td>78%</td>
<td>3.6</td>
<td>1.9-6.8</td>
</tr>
<tr>
<td>100-149</td>
<td>734</td>
<td>57</td>
<td>86%</td>
<td>2.7</td>
<td>1.4-5.2</td>
</tr>
<tr>
<td>150-199</td>
<td>504</td>
<td>24</td>
<td>90%</td>
<td>2.3</td>
<td>1.1-4.7</td>
</tr>
<tr>
<td>200-249</td>
<td>636</td>
<td>27</td>
<td>96%</td>
<td>1.9</td>
<td>0.9-3.8</td>
</tr>
<tr>
<td>250-299</td>
<td>541</td>
<td>21</td>
<td>94%</td>
<td>1.9</td>
<td>0.9-3.9</td>
</tr>
<tr>
<td>300-349</td>
<td>538</td>
<td>21</td>
<td>93%</td>
<td>1.8</td>
<td>0.9-3.7</td>
</tr>
<tr>
<td>350-399</td>
<td>489</td>
<td>11</td>
<td>96%</td>
<td>1.1</td>
<td>0.5-2.4</td>
</tr>
<tr>
<td>400-449</td>
<td>372</td>
<td>11</td>
<td>Not estimable</td>
<td>1.5</td>
<td>0.7-3.5</td>
</tr>
<tr>
<td>450-499</td>
<td>259</td>
<td>2</td>
<td>98%</td>
<td>0.4</td>
<td>0.1-1.8</td>
</tr>
<tr>
<td>≥500</td>
<td>564</td>
<td>11</td>
<td>97%</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Adapted with permission from Kaplan et al, 8th CROI, 2001.
Three recent studies have examined the effects of preferred nRTI pairs in combination with indinavir in treatment-naive patients and have found no substantive difference among the combinations. In the START I study (Squires et al, AIDS, 2000), viral load of less than 50 HIV RNA copies/mL was achieved in 47% to 49% of patients receiving stavudine/lamivudine/indinavir or zidovudine/lamivudine/indinavir at 48 weeks. In START II (Eron et al, AIDS, 2000), viral load of less than 50 copies/mL was achieved at 48 weeks in 35% to 41% of patients receiving stavudine/didanosine/indinavir or zidovudine/lamivudine/indinavir. In Oz-Combo-1 (Carr et al, AIDS, 2000), viral load of less than 50 copies/mL was achieved with stavudine/lamivudine/indinavir, zidovudine/lamivudine/indinavir, and stavudine/didanosine/indinavir in 58% of patients at 12 months. Larger studies may be better equipped to evaluate smaller differences among the dual nRTI combinations.

Other recently reported data provide some indication of the duration of effect achieved with preferred regimens. It is important to note that the virologic results described here generally cannot be compared among studies, since the studies were performed in patient populations with different characteristics and did not always employ the same viral load assay or method of analysis. When used in combination with dual nRTIs, viral load levels of less than 50 HIV RNA copies/mL were achieved in:

- 56% of patients receiving efavirenz at 2 years (intent-to-treat [ITT] population; Levy et al, 8th CROI, 2001)
- 65% of patients receiving indinavir at 3 years (ITT population, Gulick et al, Ann Intern Med, 2000)
- 60% of patients receiving nelfinavir at 2 years (on-treatment population; Petersen et al, 7th Eur Conf Clin Aspects Treatment HIV Infect, 1999)
- 66% of patients receiving ritonavir/indinavir at 48 weeks (method of analysis not specified; Boyd et al, 8th CROI, 2001)
- 78% of patients receiving lopinavir/ritonavir at 2 years (ITT population; Stryker et al, 2000)

In addition, viral load of less than 200 copies/mL was achieved in 55% of patients receiving ritonavir/saquinavir at 3 years (ITT population, Cameron et al, 7th CROI, 2000). It is encouraging that these regimens are capable of maintaining viral suppression in many patients for extended periods; nevertheless, our knowledge of duration of effect is very limited for what must be considered lifelong treatment.

A number of factors may be considered in deciding whether initial treatment should consist of a protease inhibitor or an NNRTI in combination with dual nRTIs. Protease inhibitor-based regimens have been assessed in trials in treatment-experienced patients and those with advanced HIV disease, including clinical end point trials, whereas NNRTI-based therapy has been assessed primarily in treatment-naive patients or those with earlier-stage disease. Follow-up terms now exceed 5 years with protease inhibitor-based regimens and 2 years with NNRTI-based regimens. The 2 drug classes and individual drugs therein are associated with different acute and chronic adverse effects. Protease inhibitors have a higher barrier to resistance, with accumulation of more resistance mutations generally being necessary for virologic breakthrough, compared with the high-level resistance that can be seen with single mutations in the case of NNRTIs. Initial use of protease inhibitor-based regimens spares NNRTI-based regimens for future use and vice versa. NNRTIs generally are easier to take than protease inhibitors in terms of numbers of pills, interval of dosing durations, and food restrictions.

A number of recent studies have compared the virologic effects of regimens recommended for initial therapy. In the Danish Protease Inhibitor Study (Katzenstein et al, J Infect Dis, 2000), 318 protease inhibitor-naive patients (46% antiretroviral-naive) with baseline viral load of 52,400 copies/mL and CD4+ cell count of 176/μL were randomized to treatment with 2 nRTIs (chosen individually) plus open-label indinavir, ritonavir, or ritonavir/saquinavir (400/400 mg bid). The initial report of 24-week findings in this study had indicated superiority in viral load suppression with the ritonavir/saquinavir-based combination. However, at 72 weeks, no significant differences between treatments were seen with regard to proportions of patients with viral load of 20 or fewer copies/mL (ITT analysis, Figure 1).

In the Abbott 863 study, 653 antiretroviral-naive patients with viral load of more than 400 copies/mL and any CD4+ cell count were randomized to double-blind treatment with stavudine/lamivudine plus either lopinavir/ritonavir or nelfinavir (Johnson et al, 5th Int Cong Drug Ther HIV Infect, 2000). At 48 weeks, viral load of less than 400 copies/mL was achieved in a significant-

![Diagram](chart.png)

**Figure 1.** Danish protease inhibitor study: Proportion of patients receiving dual nRTIs plus indinavir, ritonavir, or ritonavir/saquinavir with viral load ≤20 HIV RNA copies/mL over 72 weeks. Adapted with permission from Katzenstein et al, J Infect Dis, 2000.
ly greater proportion of patients receiving lopinavir/ritonavir on ITT analysis.

In the DuPont 006 study, 1266 patients naive to protease inhibitor, lamivudine, and NNRTI treatment with viral load of 10,000 or more copies/mL and CD4+ count of 50 cells/µL or more were randomized to open-label treatment with efavirenz/zidovudine/lambda-

vudine, indinavir/zidovudine/lamivudine, or efavirenz/indinavir (Leyvi et al., 8th CROI, 2001). A greater proportion of patients in the efavirenz/zidovudine/lamivudine group initially responded with viral load reduction to less than 50 copies/mL and a greater proportion remain at this level of response over 96 weeks of treatment. One criticism of this study is that there was a disproportionately dropout rate in the indinavir/zidovu-

dine/lamivudine group early in the study.

Finally, in a pilot study (Boyd et al., 8th CROI, 2001), 104 zidovudine-experi-

cenced patients with baseline viral load of approximately 10,000 copies/mL and CD4+ cell count of 168/µL received open-label zidovudine/lamivudine plus either indinavir (800 mg tid) or indi-
navir/ritonavir (800/100 mg bid). At 48 weeks, 66% to 70% of patients receiving these regimens had viral load of less than 50 copies/mL.

In addition to the suggested or preferred initial regimens, a number are considered to be under evaluation, including triple nRTI regimens and regi-

mens consisting of 1 protease inhibitor, 1 NNRTI, and 1 nRTI. Triple nRTI regi-

mens may be the easiest to take (eg, the coformulated lamivudine/zidovudine/ abacavir can be taken as 1 pill twice daily) and may be associated with fewer drug interactions than other regimens, in addition to sparing protease inhibitor- and NNRTI-based regimens for later use. There are no clinical end point data for such regimens; long-term virologic effects have yet to be defined (there is some concern regarding magnitude of response at higher initial viral loads), and there is some concern that possible nRTI-associated mitochondrial toxicity could be exacerbated with triple combinations. In addition, there are theoretical drawbacks to targeting a single step in the viral replication cycle.

A number of recent trials examining triple nRTI regimens have been report-
ed. In the CNA 3005 study (Staszewski et al., JAMA, 2001), 562 treatment-naive patients with a baseline viral load of approximately 65,000 HIV RNA copies/mL and CD4+ cell count of 360/µL were randomized to double-blind treatment with zidovudine/lamivudine and either abacavir or indinavir. On ITT analysis, there was no difference between groups with regard to proportion of patients with viral load of 50 copies/mL or less at week 48 (40% in abacavir group and 46% in indinavir group). However, among patients with baseline viral load of more than 100,000 copies/mL, a significantly greater proportion of indinavir patients had viral load of 50 copies/mL or less (45% vs 31%).

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Initial regimens under evaluation include 3 nRTI regimens and 1 nRTI / 1 NNRTI / 1 protease inhibitor regimens

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In the CNA 3014 study (Cahn, XIII Int AIDS Conf, 2000), 342 antiretroviral patients were randomized to treatment with the same triple regimens as in CNA 3005; however, treatment was open-label, permitting the abacavir regimen to be given in 2 daily doses and without the fasting and fluid restrictions required for indinavir administration. At baseline, median HIV RNA was 62,000 copies/mL in the abacavir group and 73,000 copies/mL in the indinavir group; median CD4+ cell count was 312/µL and 298/µL, respectively. At 24 weeks, viral load of less than 400 copies/mL was achieved in 87% of the abacavir group and 83% of the indinavir group on as-
treated analysis and in 68% of the abacavir group and 57% of the indinavir group on ITT analysis. Updated results presented at the First International AIDS Society Conference on HIV Pathogenesis and Treatment in July showed HIV-1 RNA of less than 400 copies/mL in 66% of the abacavir group versus 50% of the indinavir group at week 48 (ITT analysis, missing data equals failure, Vibhagool et al., 2001).

Finally, the Atlantic study (Squires et al., XIII Int AIDS Conf, 2000) assessed effects of combining stavudine/didano-
sine with indinavir, nevirapine (once daily), or lamivudine in open-label treatment of 298 treatment-naive patients with baseline viral load of approximately 18,000 copies/mL and CD4+ cell count of 406/µL. At 48 weeks, viral load of less than 50 copies/mL was achieved in 49% of the indinavir group, 49% of the nevi-
rapine group, and 40% of the lamivudine group on ITT analysis.

Several large ongoing studies will provide additional data to help answer the question of what to start with, including two AIDS Clinical Trials Group (ACTG) studies from which data are expected to be available in the near future. In ACTG 384, nearly 1000 treatment-naive patients with HIV RNA levels above 500 copies/mL have been ran-
domized to lamivudine/zidovudine (fixed-dosage) or didanosine stavudine plus efavirenz or nelfinavir or both. Patients with virologic failure are crossed over to an alternative study regimen. Scheduled follow-up in the study, which is near completion, is 2 or more years. This study may indicate which of the double nRTI regimens is superior for starting and whether an NNRTI, protease inhibitor, or both should be added for initial and subse-
quent treatment. In ACTG 388, 517 patients with advanced HIV disease (baseline HIV RNA level >80,000 copies/mL and CD4+ cell count <200/µL), have been randomized to lamivudine/zidovudine plus indinavir, indinavir/efavirenz, or indinavir/nelfi-

navir, with planned follow up of 2 or more years. Recent preliminary results suggest that the 4-drug regimen of zidovudine/lamivudine plus indinavir/ efavirenz had a superior virologic response rate. The INITIO study (Europe, Canada, Australia) and the FIRST study (CPCR 058) are large studies currently in progress that are explor-
ing the optimal initial regimen.

Initial regimens may need to be altered for reasons other than virologic failure, including adherence problems.
and toxicity. Current and future options in changing drugs for adherence reasons include new coformulated combinations and improved drug forms that reduce pill number and that permit once-daily dosing. Available coformulated combinations consist of lamivudine/zidovudine, lamivudine/zidovudine/abacavir, and lopinavir/ritonavir. With regard to improved formulations that reduce the number of required pills, delavirdine is now available in a 200 mg form; a 600 mg form of efavirenz and a 625 mg form of nelfinavir currently are in development. With regard to number of doses, didanosine can now be given once-daily in the newly approved didanosine enteric-coated form. A zidovudine sustained-release form and a stavudine extended-release form, which would permit once-daily dosing, are in development. Efavirenz is dosed once daily, and nevirapine, lamivudine, lopinavir/ritonavir, indinavir/ritonavir, saquinavir/ritonavir, and amprenavir/ritonavir each has potential for once-daily dosing. Investigational agents that permit once-daily dosing include the amprenavir produg GW 908 with ritonavir, emtricitabine, tenofovir, and the protease inhibitor atazanavir (BMS-232632). Dosing interval or number of pills required can be reduced with use of ritonavir or delavirdine as a pharmacokinetic enhancer.

A number of options are available for altering regimens due to toxicity. In some cases, instituting dose reductions for the nRTIs zidovudine, didanosine, and stavudine, or for ritonavir, may be useful, though reduced antiretroviral activity may be an issue. In addition there is a greater degree of comfort with within-class substitutions, including substitutions among protease inhibitors, substitutions among NNRTIs, and substitutions between stavudine and zidovudine or between didanosine and abacavir among the nRTIs. Class switches can also be considered—eg, from a protease inhibitor to an NNRTI- or abacavir-based treatment (please see page 18 in the accompanying article on metabolic complications for more information on switching drugs).

**Summary**

The optimal time to begin antiretroviral therapy remains unclear, as does the optimal form of initial therapy. With regard to the latter, currently recommended choices include combining 1 protease inhibitor (or 2 protease inhibitors) or 1 NNRTI with 2 nRTIs. Individualization of therapy based on patient circumstances is the primary clinical principle of treatment. Changes in initial regimens may be required due to adherence and tolerability issues, as well as due to virologic failure. Further research will help define optimal approaches to initial treatment.

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**Suggested Reading**


Kaplan J, Hanson D, Karon J, et al. Late initiation of antiretroviral therapy at CD4+ lymphocyte count <200 cells/µL is associated with increased risk of death. [Abstract 520] 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001, Chicago, Ill.


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**Update on Drug Resistance Mutations**