ABSTRACT

The clinical success of highly active antiretroviral therapy (HAART) in the treatment of human immunodeficiency virus disease is one of the great medical accomplishments of the past 50 years, but several unanswered questions concerning multiple decision points remain. The Department of Health and Human Services (DHHS) has issued guidelines for the use of HAART. Because these guidelines are often followed too rigidly, rather than used as information to guide treatment, many patients may be started on therapy before they are ready. The result is a high probability of failure. This article briefly reviews the DHHS guidelines and discusses their application based on experience in the Moore Clinic of the Johns Hopkins Hospital, which largely serves a disenfranchised population from inner-city Baltimore, Maryland. Regimens are also discussed, with emphasis on special-needs patients: those for whom complicated regimens are not an option, those with very high viral loads, and those receiving treatment at a methadone clinic.

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DESpite the wealth of efficacy data from human immunodeficiency virus (HIV) antiretroviral drug therapy trials, none offer critical information on the optimal time to start therapy. Clinicians feel a need to have a threshold for the CD4 value; a specific number has been proven by researchers to be the appropriate point to initiate antiretroviral therapy. Several years ago, guidelines recommended that threshold to be a CD4 value of less than 500 cells/mL. The medical community has accepted this number rigidly, as a strict cut-off point, rather than as the brushstroke that guidelines are meant to be.

To date, clinical trials have not determined the perfect time to initiate therapy. The best data are from cohort studies, which show no clear benefit when highly active antiretroviral therapy (HAART) is started when the CD4 count is 200 cells/mm³ or higher. Nevertheless, some data suggest that earlier treatment may have some advantages, and the medical community is reluctant to put the bar at its lowest point of the clearly demonstrable benefit. In response, the most recent guidelines from the Department of Health and Human Services (DHHS) have used 350 cells/mm³ as the new CD4 threshold. Table 1 outlines the most recently recommended parameters, which include viral load as a confounding variable based on the Multicenter AIDS Cohort Study (MACS) data. Thus, patients with CD4 counts between 200 and 350 cells/mm³ and with viral loads greater than 20 000 copies/mL should be offered treatment. Patients with CD4 counts above 350 cells/mm³ and viral load less than 55 000 copies/mL should defer treatment. For those with a viral load of greater than 55 000 copies/mL should defer treatment.
copies/mL and CD4 count greater than 350 cells/mm³, the recommendation is to treat or to follow the CD4 count more closely.

These recommendations are based to a large extent on data from the MACS. According to a communication with Muñoz, patients with a CD4 count of 200 to 350 cells/mm³ and a viral load less than 20 000 have a very low probability of progressing to acquired immune deficiency syndrome (AIDS) in 3 years (Table 2). A consistency in the guidelines is that HAART is recommended for patients with a 15% probability of developing an AIDS-defining complication within the next 3 years. The value of 15% is arbitrary, but it is an attempt to obtain a standard based on prognosis. Therefore, if a patient has a CD4 count between 200 and 350 cells/mm³, the clinician could further refine the decision based on viral load.

GOALS OF HIV THERAPY

Defining the goals of HIV therapy can be difficult. The 1998 DHHS panel identified a single goal: to drive the viral load as low as possible for as long as possible. "As low as possible" may be translated into "no detectable virus," but what does that mean? Is it 500 copies/mL or 20 to 50 copies/mL? The next generation of viral load tests will be able to detect as few as 5 copies/mL, resulting in the possibility of defining a new, even more difficult goal to achieve.

A major reason for the low threshold is to prevent drug resistance. Drug-resistant strains appear infrequently until the viral load falls below 500 copies/mL, although continuing viral evolution is seen when the viral load is in the range of 5 to 500 copies/mL. Opportunistic infections rarely occur when viral load is less than 5000 copies/mL. As these figures indicate, the threshold for an acceptable viral load is somewhat difficult to define. Is the goal to prevent the complications of opportunistic infection, prevent all resistance, or prevent most resistance? Although the goal of fewer than 20 to 50 copies/mL has become a consensus objective, this goal may be unrealistic for some patients and may result in poor quality of life, drug toxicities, and elimination of future drug options.

The DHHS guidelines have suggested that after the decision for therapy has been made, an aggressive attack with 3 to 4 drugs should be initiated. The recommended regimens include 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus a protease inhibitor (PI), 2 PIs, or a nonnucleoside RTI (NNRTI). Examples of possible combinations are shown in Table 3. How do those recommendations apply to an HIV clinic? At the Moore Clinic, an HIV clinic, 4605 adults have been followed to date. Of

<table>
<thead>
<tr>
<th>CD4 (cells/mL)</th>
<th>VL x 1000 (copies/mL)</th>
<th>Probability of AIDS in 3 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>200-350</td>
<td>&lt; 20</td>
<td>4%</td>
</tr>
<tr>
<td>20-55</td>
<td>&gt; 55</td>
<td>36%</td>
</tr>
<tr>
<td>&gt; 55</td>
<td></td>
<td>64%</td>
</tr>
</tbody>
</table>

Table 1. DHHS Guidelines: When to Start HAART

<table>
<thead>
<tr>
<th>CD4 (cells/mL)</th>
<th>VL (copies/mL)</th>
<th>HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 350</td>
<td>&gt; 20K</td>
<td>Treat</td>
</tr>
<tr>
<td>&gt; 20K</td>
<td></td>
<td>Consider</td>
</tr>
<tr>
<td>&lt; 20K</td>
<td></td>
<td>Treat</td>
</tr>
</tbody>
</table>

Table 2. MACS Data

A. Muñoz, personal communication.
those, 47% have used intravenous drugs and 40% are active drug users. One fourth have an Axis I psychiatric disorder, 75% of all patients are black, and the median annual income is below $5000. The payer mix is 40% Medicaid, and 41% have no medical coverage. Clearly, this clinic caters to a disenfranchised population that has traditionally been excluded from the health care system. The ability of the Moore Clinic to care for these patients is entirely dependent on the Ryan White Care Act, which was created in 1990 to help states, communities, and families cope with the growing impact of the AIDS epidemic. The program is administered by the HHS Health Resources and Services Administration and supports systems of care for people with AIDS who do not have adequate health insurance or other resources. It emphasizes outpatient care and support services. Since the first grants were awarded in 1991, $6.4 billion in federal funds have been appropriated under the Act. The program serves approximately 500 000 individuals with HIV and AIDS per year. The benefit of this program is convincingly shown with the HIV Cost and Services Utilization Study study, which showed that approximately 70% of all low-income patients with HIV who merited HAART received this type of therapy.

With regard to mental illness, Dr T reisman describes the Moore Clinic population in his article in this issue "The Infectious Disease Specialist and The Psychiatrist: Understanding the Psychiatric Issues in the Treatment of HIV-Infected Patients". According to Dr T reisman, most of the patients are extroverts (ie, they are reward seeking, not risk avoiding) and have unstable temperaments (ie, their actions are unpredictable and inconsistent). As a result, patients are often of very different personality and temperament from the people who treat them, who tend to be introverted and stable. The intended messages for patients in terms of treatment regimens and their importance may make sense to the clinic staff but may not make sense to the patients.

The practical application of this observation is particularly important for adherence, which is a critical factor for treatment success. One study found that 95% adherence to the HAART dosing regimen was necessary to achieve an 80% probability of no detectable virus (ie, viral load less than 500 copies/mL after 24 weeks). Below 95% adherence, the probability of no detectable virus fell to 50%.

### Special-Needs Populations

Many patients presenting to HIV clinics are considered to have special needs or unique requirements and would be considered outside the general population. These include a need for once-daily dosing and separate recommendations when viral loads are greater than 100 000 copies/mL. Although several regimens may be equally effective with this baseline viral load, the 2 that have been reported to have excellent records are efavirenz- and lopinavir/ritonavir-based HAART.

### Once-Daily Dosing Requirements

Obviously, simplifying the HAART regimen and still retaining potency is a desirable goal. Once-daily therapy is in this category. NRTIs that can be given once daily are ddI and thymidine kinase; NRTIs that can probably be given once daily are stavudine (d4T) and abacavir. For NNRTIs, efavirenz is given once daily and nevirapine should be given once daily as well. No PIs can be given once daily, but ritonavir-boosted regimens with indinavir, fludarabine, lopinavir, or saquinavir will probably work with once-daily administration, although tolerance may be an issue.

### Table 3. DHHS Guidelines for Initial Therapy: 2 NRTIs + a Protease Inhibitor

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>Protease Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>d4T/3TC</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>AZT/ddI</td>
<td>Indinavir</td>
</tr>
<tr>
<td>ddI/3TC</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>AZT/3TC</td>
<td>Saquinavir/ritonavir</td>
</tr>
<tr>
<td>d4T/ddI</td>
<td>Lopinavir/ritonavir</td>
</tr>
<tr>
<td></td>
<td>Indinavir/ritonavir</td>
</tr>
</tbody>
</table>

Are less frequent dosings clinically effective? Table 4 summarizes the evidence available for once-daily dosing.\textsuperscript{11-15}

\textbf{Very High Viral Loads}

Only 2 regimens have shown efficacy in patients with viral loads of greater than 100 000 copies/mL: 2 NRTIs plus efavirenz or 2 NRTIs plus lopinavir/ritonavir. Regimens that will probably be effective, although the evidence is weaker, are: abacavir plus a protease inhibitor or NRTI; 2 NRTIs plus 2 protease inhibitors (ie, ritonavir plus indinavir, amprenavir, or saquinavir); or 2 NRTIs plus a protease inhibitor plus a nonnucleoside NRTI.\textsuperscript{16-17}

\textbf{Methadone Interactions}

Drug-drug interactions that reduce methadone levels have been noted with abacavir, efavirenz, nevirapine, amprenavir, lopinavir, saquinavir, and ritonavir. By contrast, didanosine (ddl), d4T, zalcitabine (ddC), and zidovudine (AZT) have no effect on methadone. With ddl, the problem is a decrease in serum ddl levels. The interactions that are most problematic for methadone withdrawal occur with efavirenz and nevirapine.

One of the advantages of treating HIV-infected patients in a methadone clinic is the established connection with directly observed therapy (DOT), so once-daily dosing is particularly attractive in this setting. In fact, the concept of DOT is receiving a lot of attention recently as data accumulate regarding its effect on virologic outcomes. Much of the enthusiasm for DOT emerges from results of treating tuberculosis (TB). One researcher compared the differences in DOT between TB and HIV and showed that HIV treatment has several significant differences compared to DOT in TB treatment. The treatment goals for both are to reduce transmission and resistance, but TB treatment offers a cure; HIV treatment can only suppress active infection. TB therapy is administered twice weekly for 6 to 9 months; HIV therapy is administered at least 1 to 2 times per day for the rest of the patient’s life. Finally, the consequences for nonadherence to TB treatment is jail, but HIV-infected patients who do not adhere to their treatment regimen do not face legal consequences. The data indicate that the regimens and the cost associated with DOT are very different between the 2 diseases.

Several DOT programs have been established. One group of researchers achieved reduction to their definition of “no detectable virus” (ie, viral load less than 400 copies/mL) in 100% of the patients in their study with DOT in a correctional facility in Florida.\textsuperscript{19} This is the ideal system to assure compliance. Flanagan et al at Brown University offer a community-based DOT program in which the daily treatment is administered in home visits.\textsuperscript{20} Whol et al use a modified DOT program in Los Angeles that is also community-based in which 1 dose is observed and the other is self-administered.\textsuperscript{18} Jones et al in Detroit use a modified DOT program in which the patients are given a financial reward of $5 for every day they receive their therapy by DOT plus $15 if they adhere to the regimen for an entire week. They report adherence at 90%.\textsuperscript{18} And finally, McCance-Katz et al in New York City administer their HIV therapy DOT through the methadone clinic.\textsuperscript{18} The results of these researchers at the methadone clinic have shown that treatment with efavirenz, stavudine, or didanosine can alter methadone levels or that methadone can alter the HIV drug levels. In fact, many patients taking methadone entered methadone withdrawal once HAART was initiated; however, those patients chose to continue with HIV therapy.\textsuperscript{18}

\textbf{Coinfection with Hepatitis C Virus}

Coinfection with hepatitis C virus (HCV) is very common among intravenous drug users infected with \textbf{Table 4. Evidence to Support Once-Daily Dosing}

<table>
<thead>
<tr>
<th>Class</th>
<th>Established (mg)</th>
<th>Probable (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>ddl (400)\textsuperscript{11}</td>
<td>3TC (300), ABC (600), Tenofovir (300)\textsuperscript{12}</td>
</tr>
<tr>
<td>N NRTIs</td>
<td>EFV (600)\textsuperscript{13}</td>
<td>NVP (400)</td>
</tr>
<tr>
<td>Pls</td>
<td>APV (1200)/RTV (100) FTV (1600)/RTV (100-200)\textsuperscript{14}</td>
<td>LPV/RTV (800/200) IDV (1200)/RTV (400)\textsuperscript{15} SQV (1800)/RTV (200)\textsuperscript{14}</td>
</tr>
</tbody>
</table>

\textsuperscript{NRTIs = nucleoside reverse transcriptase inhibitors; N NRTIs = non-nucleoside reverse transcriptase inhibitors; Pls = protease inhibitors; ddl = didanosine; 3TC = lamivudine; ABC = abacavir; EFV = efavirenz; NVP = nevirapine; APV = amprenavir; RTV = ritonavir; LPV = lopinavir; IDV = indinavir; SQ V = saquinavir.}
HIV. Seroprevalence is 95% among those who have injected drugs for more than 5 years. As a result of increased longevity with HAART, liver disease is increasingly becoming a cause of hospital admission for those coinfected with HIV and HCV. Having poor results on examination of a liver biopsy specimen is equivalent to the CD4 count in determining candidacy for HCV treatment. The criteria are bridging fibrosis and inflammation plus necrosis, no contraindications, and stable HIV. The recommended treatment is pegylated interferon plus ribavirin, and the cure rate is approximately 50%. These recommendations may be considered arbitrary and are constantly being reevaluated. Confounding treatment for coinfection is that all 13 antiretroviral drugs are hepatotoxic, although none of these drugs appear to be more hepatotoxic in patients with HCV than in unaffected patients.20

Recommendations for HCV-HIV coinfected patients will be issued in June 2002. In the meantime, the general policy used by the Moore Clinic is as follows:

- With CD4 counts above 350/mm³, HCV treatment should be given for 24 to 48 weeks.
- With CD4 counts less than 200/mm³, both diseases should be treated separately, but drug-drug interactions should be avoided by separating the start date of each therapy by 1 to 2 months.
- For those with ongoing HIV treatment, add HCV treatment.
- If the HIV is unstable, stabilize it first.
- If hepatotoxicity is encountered with cotherapy, interrupt the HIV therapy.

**Prevention**

HIV prevention has received inadequate attention until recently. Originally, the goal of the Centers for Disease Control and Prevention (CDC) was to educate the general public on HIV prevention. A major change in philosophy at the CDC in the last 6 months has shifted the focus of that message to those who are infected. Their recently updated guidelines are now out for public comment and will be published in the latter half of 2002.21

One of the greatest benefits of prevention is to reduce the probability of transmission. According to one study of discordant couples, for every 10-fold decrease in viral load, a 2.5-fold decrease in transmission is seen.22

**Conclusion**

Despite the clinical successes observed with HAART, several controversies remain, including the appropriate time to start therapy, realistic and defined goals of therapy, the role of DOT in increasing adherence, and the need to address the special needs of disenfranchised populations.

**References**


