ABSTRACT

Although many highly active antiretroviral therapy (HAART) regimens using 3 drugs have demonstrated potent and durable antiretroviral effects, cohort studies have shown that treatment failure occurs in about 30% to 50% of patients. This failure rate prompts a closer look into the causes of treatment failure and how to modify or overcome these causes with new and more effective therapeutic regimens.

Adherence to therapy may be the single most important factor affecting treatment outcomes with HAART. Factors affecting adherence include side effects of therapy, regimen complexity, total number of pills per day, pill size, food restrictions, water requirements, and dosing frequency. To improve adherence to HAART, dosing regimens must be simplified by reducing tablet load, removing food restrictions, and reducing dosing frequency. However, increased regimen convenience to achieve maximal adherence must be balanced with antiretroviral potency to achieve the lowest possible nadir.

With a larger proportion of patients now beginning therapy with high viral loads and low CD4 cell counts, it is likely that many may not reach nadir on standard HAART regimens with 3 drugs. Therefore, maximized HAART regimens and 4-drug (quadruple) regimens have been suggested and are being investigated. When given as initial HAART, quadruple regimens have shown promising preliminary results in recently completed studies and in ongoing comparative studies.

Many highly active antiretroviral therapy (HAART) regimens using 3 drugs have shown potent and durable antiretroviral effects in reducing plasma human immunodeficiency virus-1 (HIV-1) ribonucleic acid (RNA) in HIV-infected individuals. Despite initial declines in plasma HIV-1 RNA with triple HAART regimens, however, cohort studies have shown that treatment failure occurs in about 30% to 50% of patients. Causes of treatment failure include nonadherence to therapy because of side effects, complex regimens, and lifestyle conflicts, treatment-limiting toxicity, pharmacologic variations in potency and durability, and the emergence of drug-resistant HIV-1.

Whatever the reasons, the high failure rate of initial triple therapy has prompted investigators to consider therapy with 4 agents—quadruple therapy—with enhanced potency, good adherence to therapy, and no increase in adverse side effects or toxicity to ensure...
maximal viral suppression in today's HIV treatment population, which is characterized by higher viral loads and lower CD4 levels.

**Adherence to Therapy**

Adherence to therapy may be the single most important factor affecting treatment outcomes with HAART. In the absence of active drug concentrations, viral replication continues and inevitably leads to increased genetic diversity and viral load, thereby increasing the risk of drug-resistant mutations.

In addition to adverse side effects, many other factors contribute to nonadherence to therapy. These include patient characteristics, clinical-care settings, patient-provider relationships, and drug-regimen characteristics.

In a randomized study (CNA3014) comparing abacavir plus a single tablet of lamivudine + zidovudine with indinavir plus the combination tablet as initial therapy in a real-life setting in antiretroviral-naïve adults, the investigators found that HIV-1 RNA efficacy declined as adherence to therapy declined and that adherence levels above 95% were associated with the best treatment effect. In a survey evaluating regimen convenience and adherence at week 48 of therapy in this study, 72% of patients receiving abacavir with lamivudine + zidovudine achieved greater than 95% adherence vs 45% of patients receiving indinavir plus the combination (P < .001); 91% of patients vs 62% of patients, respectively, reported that none of their drugs were difficult to take (P < .001).

A study evaluating the impact of different regimen characteristics on patient adherence (RESA41071) found that the total number of pills per day, dosing frequency, and food restrictions or water requirements had the largest impact on adherence. Specifically, regimens with 2 to 5 pills per day, small- or medium-sized pills, single-drug therapy or 2-drug combinations, no food or water restrictions, and once- or twice-daily dosing frequency helped adherence. Regimens with 10 to 16 pills per day, large pills, 3 doses per day, and food restrictions, such as having to take the pills on an empty stomach or avoiding high-fat foods, hurt adherence.

Thus, to improve adherence to HAART, dosing regimens must be simplified by reducing tablet load, removing food restrictions, and reducing dose frequency. Tablet load and dosing frequency can be reduced by using fixed-dose combinations and consistent dosing (ie, all drugs are taken twice a day) so that all drugs can be taken at the same time.

**Once-Daily Dosing**

A once-daily dosing regimen would appear to fulfill most of the criteria for improving adherence to HAART. However, there are advantages, disadvantages, and dietary, timing, and other restrictions associated with once-daily dosing.

**Table 1. Once-Daily Dosing Considerations and Restrictions**

<table>
<thead>
<tr>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
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<tbody>
<tr>
<td>• Convenience to patient</td>
<td>• No demonstrated benefit in adherence in once-daily vs twice-daily dosing</td>
</tr>
<tr>
<td>• Benefits in certain settings (eg, prison, methadone clinic)</td>
<td>• Impact of missed dose(s) linked to differential pharmacokinetics</td>
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<tr>
<td>• Potential to improve adherence</td>
<td>• Resistance rates may increase</td>
</tr>
<tr>
<td>• Consistent timing of morning meals</td>
<td>• Trade-off between pharmacokinetics and convenience</td>
</tr>
<tr>
<td>- Even easier if no dietary restrictions</td>
<td>- Higher C&lt;sub&gt;max&lt;/sub&gt; may increase toxicity</td>
</tr>
<tr>
<td>- No issues for people who work late or go out for an evening</td>
<td>- Lower C&lt;sub&gt;trough&lt;/sub&gt; may blunt efficacy, durability, resistance selection</td>
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</table>

**RESTRICTIONS**

- Dietary/timing restrictions
  - Some drugs must be taken with food (eg, tenofovir)
  - Some drugs must be taken on an empty stomach (eg, didanosine)
  - Some drugs must be taken at bedtime (eg, efavirenz)
- Once-daily regimens may have to be split ("false" once-daily regimens)
- Once-daily regimens are associated with different drug-combination products and at least 3 pills per day
- Some once-daily regimens are associated with unpleasant adverse effects
- Once-daily regimens are less forgiving

\[ C_{\text{max}} = \text{maximum drug level; } C_{\text{trough}} = \text{minimum drug level.} \]
ciated with once-daily dosing (Table 1). Thus, the net benefit of any once-daily regimen depends on total daily pill burden and on whether all the drugs in the regimen can be taken at the same time and without any dietary or timing restrictions.

Increased regimen convenience, however, must be balanced with antiretroviral potency, with the aim being to achieve the lowest possible nadir for maximum potency and durability. With current treatment guidelines calling for the delay of therapy until the CD4 cell count is below 350 cells/mm³, a larger proportion of patients are beginning therapy with high viral loads and low CD4 cell counts. As a result, many patients receiving standard HAART (triple) regimens may not reach nadir (or may reach it at a slower rate because of the high baseline viral load) but will continue to replicate at low, undetectable levels. Other possible consequences are that therapy has no effect on sanctuaries and cellular reservoirs, full immunologic recovery is impaired, there is a greater risk of selection of resistance mutations, and response is less durable.

**Maximized HAART and Quadruple Regimens**

To ensure maximal viral suppression in today’s HIV treatment population, maximized antiretroviral therapy (ART) and HAART regimens as well as quadruple regimens have been suggested and are being investigated. The objective of any ART regimen should be maximal suppression of HIV replication, and the first ART regimen chosen should be a potent one with long-lasting efficacy, because subsequent regimens are always less effective. HAART potency should be tailored to the patient’s baseline disease stage, CD4 count, and plasma viral load. Moreover, the regimen chosen should fit the needs and expectations of the patient regarding convenience and tolerability.

Maximized regimens diverge from the “hit hard and early” ART paradigm of 1996 to 1998, and reflect the new ART paradigm: that is, when you hit, hit harder. With more drugs, more options, and more compact and convenient regimens available, hitting harder is possible with simple regimens.

Quadruple regimens that are under investigation exhibit balanced potency and good adherence to therapy without compromising safety and future treatment options. The attributes of an ideal quadruple regimen are listed in Table 2.

Two small pilot studies, COL30336 with 38 patients and CNAF3008 with 31 patients, showed that the compact quadruple regimen of abacavir, lamivudine + zidovudine, and efavirenz had potent and durable antiviral activity over 48 weeks in therapy-naïve patients who presented with high plasma viral load. These findings are consistent with the results of the CNAF3008 study (Figure). Quadruple Induction Therapy with Abacavir, Lamivudine + Zidovudine, and Efavirenz (CNAF3008) and Maintenance with Abacavir + Lamivudine + Zidovudine Alone (AZLF3002).

**Table 2. Attributes of an Ideal Quadruple Regimen**

- Increased potency compared with 3-drug regimens
- Increased durability compared with 3-drug regimens
- Low pill burden
- Convenient dosing schedule
- No food or fluid restrictions
- Low potential for drug interactions
- Well tolerated, both short term and long term
loads and low CD4 cell counts. In study COL30336, patients were given abacavir, lamivudine + zidovudine, and efavirenz for 48 weeks. In study CNAF3008, all 31 patients were given abacavir, lamivudine + zidovudine, and efavirenz for 48 weeks, and 20 patients with plasma viral loads below 50 copies/mL were switched to therapy with a single tablet containing abacavir + lamivudine + zidovudine for an additional 48 weeks (study AZLF3002). After the switch to the single-tablet triple therapy, viral suppression seen after the first 48 weeks of quadruple therapy was successfully maintained, and the median CD4 level continued to rise significantly (Figure).

Quadruple regimens raise issues as well as opportunities regarding sequencing of therapy. For example, 2-class quadruple regimens may be better at preserving future treatment options compared with 3-class regimens. Also, the induction/maintenance strategy could limit exposure to the second class while sparing the third class.

The safety and tolerability profile of quadruple therapy in the pilot studies was similar to that of triple therapy regimens. In the COL30336 study, the most frequently cited adverse events related to treatment were bad dreams (13%), nausea (13%), dizziness (8%), sleep disorders (8%), decreased white blood cells (8%), malaise and fatigue (8%), and suspected hypersensitivity to abacavir (8%).

When compared with triple therapy as initial HAART, quadruple therapy including the single tablet of abacavir + lamivudine + zidovudine is associated with increased potency and durability, equal or increased salvageability, decreased short-term tolerability related to potential risk of abacavir hypersensitivity (incidence, 5%), and equal or increased long-term tolerability. Adherence to therapy is the same with both regimens because the pill burden, dosing frequency, and dietary constraints are the same. In terms of maximizing HAART effectiveness, however, initial quadruple therapy appears to have the edge; it has increased potency and a greater likelihood of improving adherence because of its lack of long-term toxicity and adverse events. It is also a convenient, compact, and patient-friendly regimen, particularly if 3 of the 4 drugs are taken as a single tablet.

Conclusions

With regard to maximizing HAART effectiveness, currently used triple therapy regimens are probably suboptimal in many patients, and probably suboptimal in most patients with advanced disease. Both a pathophysiologic rationale and drug availability are needed to construct maximized HAART regimens.

Regimens that incorporate both increased potency to decrease viral load and increase CD4 cell counts and maximal adherence to therapy are likely to facilitate long-term management of HIV-infected patients. Just as HAART effectiveness should not be compromised in the quest for optimal therapy, neither should convenience, adherence, and tolerability.

As initial HAART, quadruple regimens based on a single tablet of abacavir + lamivudine + zidovudine have shown promising preliminary results in recently completed investigations and in ongoing comparative studies. Induction/maintenance strategies need to be refined, but quadruple regimens may represent a new standard in therapy, perhaps in patients with high plasma viral loads.

References


