Once-a-Day Highly Active Antiretroviral Therapy: A Systematic Review

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We analyzed the available evidence about the efficacy and tolerability of once-a-day highly active antiretroviral therapy (HAART), searching databases, conference proceedings, and journals. Two reviewers independently selected 6 uncontrolled and 2 randomized clinical trials of at least 24 weeks duration and with 80% participant follow-up. Regimens included didanosine (ddI), emtricitabine (FTC), and efavirenz (EFV) (2 studies, 326 patients); ddI, lamivudine (3TC), and EFV (3 studies, 147 patients); ddI, 3TC, EFV, and adefovir dipivoxil (1 study, 11 patients); ddI, nevirapine, and EFV (1 study, 15 patients); and ddI, 3TC, indinavir, and ritonavir (1 study, 10 patients). Virological efficacy ranged between 70% and 91%. Preliminary randomized clinical trials showed that once-a-day regimens (ddI, 3TC, and EFV or ddI, FTC, and EFV) had a virological efficacy at least similar to that of conventional HAART. The overall CD4 cell increase was at least 114 lymphocytes/μL. Tolerability was good, with a low discontinuation rate.

Adherence to HAART is a determinant factor in obtaining the greatest therapeutic efficacy [1, 2]. The major limitations for adherence to HAART are the burden of pills and dosing of the drugs [3]. Patients with hectic lifestyles and those requiring directly observed therapy (DOT) would benefit most from once-daily administration of antiretroviral drugs. No systematic review to date has evaluated the information available about the efficacy of once-daily administration of antiretroviral drugs. Our study is a comprehensive review of the literature, to determine the proportion of patients with an undetectable HIV RNA load, the increase in CD4 lymphocyte cell counts, and the tolerability of HAART administered once daily.

MATERIALS AND METHODS

Eligibility criteria. Studies of HIV-infected patients with detectable virus loads were chosen, and intervention was defined as once-a-day administration of at least 3 antiretroviral drugs. A low dose of ritonavir to boost other protease inhibitors was not considered to be an additional drug to the regimen. A favorable outcome was defined as an undetectable virus load at 24 and 48 weeks of follow-up. The study design included published and unpublished clinical trials in any language with at least 80% participant follow up.

Search strategy. We searched the MEDLINE (1996–January 2002), AIDSLINE (1980–December 2000), and EMBASE databases, using the terms “antiretroviral therapy, highly active” and “anti-HIV agents/therapeutic use.” We restricted the search to articles that included the term “one” in their titles or abstracts and only those clinical trials in which all antiretroviral drugs were administered once daily. We also hand-searched abstracts presented at major infectious diseases meetings between 1998 and 2002.

Selection. Each of us independently reviewed each title or abstract, to identify relevant articles. We further independently assessed relevant citations for inclusion, using the full publication, or abstracts, if they were never published in full. We contacted 14 authors of articles with ambiguity in their study data, asking them to clarify issues before we included their data, of whom 5 replied. For the other studies, we based our decision on the available information. We measured our agree-
ment on selecting articles for further evaluation and for finally including studies. Disagreement was resolved by consensus. Duplicate or updated publications were identified. We included only the most complete data set in our review.

Data extracted. Each of us independently collected the following data: patient characteristics, HAART regimen, number of patients with an undetectable virus load at the end of follow-up, CD4 lymphocyte increase, and adverse events reported. Adverse events classified as “severe” were those associated with death or requiring drug withdrawal. In addition, we collected data on adherence rates and whether treatment administration was directly observed.

Statistical analysis. We used weighted $\kappa$ statistics to measure the chance-corrected agreement between independent reviewers in the selection and inclusion of studies [4]. We estimated the proportions and 95% confidence limits of patients with an undetectable HIV RNA load at the end of follow-up. We used the total number of patients entering the study as the denominator, and we imputed virological failure to all patients lost to follow-up (analysis by the intention-to-treat principle).

RESULTS

The search screened for retrieval a total of 226 published studies, but 219 were excluded because they were neither clinical trials nor studies in which all antiretroviral drugs were administered once a day. Among published studies of HAART administered once daily, 1 study was excluded because the outcome was assessed at only 12 weeks of follow-up [5], and 2 studies (done by the same group of investigators) were excluded because of a high dropout rate, with ≥20% participants lost to follow-up [6, 7]. That left 4 published studies for detailed evaluation. We found 25 potentially valid studies from conference meetings. After detailed evaluation, 21 unpublished studies were excluded because of duplicated or updated data ($n = 13$), having insufficient data on outcome variable or showing <80% participant follow-up ($n = 5$), or having been carried out retrospectively ($n = 3$). Of the 14 authors contacted, 5 (36%) responded to our request for additional information on their studies. Therefore, after exhaustive scrutiny, 8 studies were left for the present work: 4 published [8–11] and 4 unpublished [12–15]. The agreement of the 2 reviewers was 0.91 for the selection and 0.84 for the inclusion of the studies.

Methodological Quality

Only 2 of 9 studies were randomized controlled clinical trials [14–15], whereas the other 7 were noncomparative clinical trials [8–13]. Follow-up was ≥95% in all studies. Studies were carried out in countries from the European Union ($n = 4$) and in the United States ($n = 4$) between 2000 and 2002 (table 1).

Patients

Patients entering the studies were mostly men who were antiretroviral-therapy naive, with CD4 lymphocyte cell counts of 164–471 cells/µL and an HIV-1 load of 4.47–5.78 log_{10} copies/mL. Only 2 studies reported the patients’ HIV transmission category to be “intravenous drug user” (table 1).

Intervention

Once-a-day HAART regimens included the combinations didanosine (ddI), emtricitabine (FTC), and efavirenz (EFV) (2 studies; 326 patients); ddI, lamivudine (3TC), and EFV (3 studies; 147 patients); and ddI, 3TC, EFV, and adefovir dipivoxil (1 study; 11 patients). Other combinations used were ddI, nevirapine (NVP), and EFV (1 study; 15/26 patients being treatment naive); ddI, 3TC, indinavir (IDV), and ritonavir (RTV) (1 study; 10 patients); and ddI, 3TC, saquinavir (SQV), and RTV (1 study; 17 patients). DOT was used in 1 study. Only 1 study reported the rate of adherence measured by pill count, and, in 4 other studies, adherence was self-reported by the patients (table 1).

Outcomes

Undetectable virus load. HIV-1 load was measured at 24 weeks in 2 studies, at 32 weeks in 1 study, and at ≥48 weeks in the remaining 5 studies. The lower limit of detection was set at 400 copies/mL in 1 study and at 50 copies/mL in 7 studies.

Intention-to-treat analysis showed that once-a-day regimens had a virological efficacy of 70%–91% (table 2). One randomized controlled trial showed that a once-a-day combination of ddI, 3TC, and EFV (34 patients) had a greater virological efficacy (HIV-1 RNA load, <50 copies/mL at 32 weeks of follow-up) than twice-a-day zidovudine (ZDV), 3TC, and nelfinavir (34 patients) (79% vs. 50%; $P = .02$) but similar to that of twice-a-day ZDV, 3TC, and EFV (34 patients) (81% vs. 79%; $P$ not significant). Another randomized, double-blind controlled trial showed that once-a-day ddI, FTC, and EFV (286 patients) had greater efficacy (HIV-1 RNA load, <50 copies/mL at 24 weeks of follow-up) than the reference group, who received ddI and stavudine immediate release twice daily plus EFV (285 patients) (81% vs. 65%; $P < .001$).

CD4 lymphocyte recovery. A successful immunologic recovery was observed in every once-a-day combination, with a median increase of at least 114 CD4 lymphocytes/µL at the end of follow up.

Side effects. Few studies provided data on the safety of once-a-day HAART regimens. Overall tolerance was fair, and the number of severe adverse effects requiring drug withdrawal was low. No death was observed to be directly associated with once-a-day HAART. The number of patients (7/10) who developed nephrotoxicity on the adefovir dipivoxil, ddI, 3TC, and EFV regimen was noteworthy. It was also remarkable that pa-
<table>
<thead>
<tr>
<th>Clinical trial type, author [reference]</th>
<th>Country</th>
<th>Year</th>
<th>No. of patients</th>
<th>Mean patient age, years</th>
<th>No. (%) of patients male</th>
<th>No. (%) of patients IVDUs</th>
<th>Mean or median baseline HIV-RNA load, log₁₀ copies/mL</th>
<th>Mean or median baseline CD4 cell count, cells/µL</th>
<th>No. (%) of patients antiretroviral therapy naive</th>
<th>HAART regimen (dose per day)</th>
<th>No. (%) of patients receiving DOT</th>
<th>No. (%) of patients adherent</th>
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<tbody>
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<td>Noncontrolled</td>
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<tr>
<td>Maggioio [8]</td>
<td>Italy</td>
<td>2001</td>
<td>75</td>
<td>37.5</td>
<td>59 (79)</td>
<td>37 (49)</td>
<td>5.09</td>
<td>251</td>
<td>75 (100)</td>
<td>ddI (300 mg), 3TC (300 mg), EFV (600 mg)</td>
<td>13 (17)</td>
<td>73 (98)*</td>
</tr>
<tr>
<td>Moie [9]</td>
<td>US</td>
<td>2001</td>
<td>10</td>
<td>43</td>
<td>10 (100)</td>
<td>NR</td>
<td>4.47</td>
<td>254</td>
<td>10 (100)</td>
<td>ddI (initially 4 × 100 mg then 2 × 200 mg with empty stomach, 30-60 min before meals), 3TC (2 × 150 mg), IDV (3 × 400 mg), RTV (4 × 100 mg)</td>
<td>NR</td>
<td>— (&gt;90)*</td>
</tr>
<tr>
<td>Molina [10]</td>
<td>France</td>
<td>2000</td>
<td>40</td>
<td>33</td>
<td>35 (88)</td>
<td>1 (3)</td>
<td>4.77</td>
<td>373</td>
<td>40 (100)</td>
<td>ddI (60 kg 400 mg, &lt;60 kg 250 mg), FTC (200 mg), EFV (3 × 200 mg)</td>
<td>NR</td>
<td>39 (97)*</td>
</tr>
<tr>
<td>Skowron [11]</td>
<td>US</td>
<td>2000</td>
<td>11</td>
<td>&gt;18</td>
<td>10 (91)</td>
<td>NR</td>
<td>4.99</td>
<td>471</td>
<td>11 (100)</td>
<td>ddI (400 mg), 3TC (300 mg), EFV (600 mg), adefovir dipivoxil (60 mg)</td>
<td>NR</td>
<td>10 (89)*</td>
</tr>
<tr>
<td>Jordan [12]</td>
<td>US</td>
<td>2000</td>
<td>15</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>4.59</td>
<td>351</td>
<td>15 (100)</td>
<td>ddI (400 mg), EFV (600 mg), NVP (400 mg)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Landman [13]</td>
<td>France</td>
<td>2001</td>
<td>40</td>
<td>37</td>
<td>20 (50)</td>
<td>0 (0)</td>
<td>5.56</td>
<td>164</td>
<td>40 (100)</td>
<td>ddI (400 mg for weight ≥60 kg and 200 mg if weight &lt;80 kg), 3TC (300 mg), EFV (600 mg)</td>
<td>0 (0)</td>
<td>36 (90)*</td>
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<td>Randomized controlled</td>
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<tr>
<td>Maggioio [14]</td>
<td>Italy</td>
<td>2002</td>
<td>102</td>
<td>38.5</td>
<td>86 (84)</td>
<td>26 (26)</td>
<td>5.19</td>
<td>176</td>
<td>102 (100)</td>
<td>ddI, 3TC, EFV (n = 34) vs. ZDV, 3TC, EFV (n = 34) vs. ZDV, 3TC, NFV (n = 34) (doses NR)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Saag [15]</td>
<td>US</td>
<td>2002</td>
<td>571</td>
<td>NR</td>
<td>485 (85)</td>
<td>NR</td>
<td>4.90</td>
<td>288</td>
<td>571 (100)</td>
<td>ddI, FTC, EFV (n = 286) vs ddI, d4T immediate release, EFV (n = 285), double blind study</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**NOTE.** 3TC, lamivudine; d4T, nelfinavir; ddI, didanosine; DOT, directly observed therapy; EFV, efavirenz; FTC, emtricitabine; IDV, indinavir; IVDU, intravenous drug user; NR, not reported; NVP, nevirapine; RTV, ritonavir; d4T, stavudine; US, United States.

* Self-reported.
* Pill count.
* Updated data.
Table 2. Efficacy of once-a-day HAART.

<table>
<thead>
<tr>
<th>Clinical trial type, once-a-day HAART regimen [reference]</th>
<th>No. of patients entered</th>
<th>No. (%) of patients with complete follow-up</th>
<th>Follow-up, weeks</th>
<th>Lower limit of detection of HIV-1 RNA load, copies/mL</th>
<th>No. of patients with undetectable HIV-1 RNA</th>
<th>No. of patients with undetectable HIV-1 RNA/no. of patients entered in the study (%) [95% CI]</th>
<th>Mean or median CD4 cell count increase, cells/µL</th>
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<td>Noncontrolled</td>
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<td></td>
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<tr>
<td>ddI, 3TC, EFV [8]</td>
<td>75</td>
<td>72 (96)</td>
<td>48</td>
<td>50</td>
<td>59/75 [78 [69–87] 208</td>
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<td></td>
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<tr>
<td>ddI, 3TC, IDV, RTV [9]</td>
<td>10</td>
<td>9 (100)</td>
<td>24</td>
<td>50</td>
<td>7/10 [70 [42–98] 193</td>
<td></td>
<td></td>
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<tr>
<td>ddI, FTC, EFV [10]</td>
<td>40</td>
<td>39 (97)</td>
<td>64</td>
<td>50</td>
<td>35/40 [87 [77–97] 159</td>
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<td></td>
</tr>
<tr>
<td>ddI, 3TC, EFV [13]</td>
<td>40</td>
<td>40 (100)</td>
<td>48</td>
<td>50</td>
<td>31/40 [77 [64–90] 153</td>
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<td>Randomized controlled</td>
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<tr>
<td>ddI, 3TC, EFV [14]</td>
<td>34</td>
<td>34 (100)</td>
<td>32</td>
<td>50</td>
<td>27/34 [79 [65–94] 114</td>
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</tbody>
</table>

NOTE. 3TC, lamivudine; EFV, efavirenz; FTC, emtricitabine; IDV, indinavir; NVP, nevirapine; RTV, ritonavir.

tients who received once-a-day HAART with EFV or NVP showed a high proportion of methadone withdrawal symptoms. Patients who received regimens that contained EFV had a high proportion of CNS adverse effects (sleep disturbances, dizziness, depression, and mood changes) during the first days of therapy.

DISCUSSION

Our study shows that once-a-day regimens using ddI, FTC, and EFV or ddI, 3TC, and EFV had an efficacy at least similar to that of conventional HAART [14, 15]. Nevertheless, the remaining once-a-day HAART studies were clinical trials, with no reference group to assess their relative efficacy, compared with standard therapy. We did not try to make comparisons among different regimens, because there was a lot of variability among populations, follow-up periods, and lower limits of HIV-1 RNA detection. Few studies accurately evaluated once-a-day HAART adherence or its potential use as DOT. CD4 lymphocyte recovery was satisfactory in every once-a-day regimen.

The safety of once-a-day regimens was not consistently reported. Methadone withdrawal was the most common side effect for combinations that included NVP or EFV. This side effect is significant, because methadone maintenance programs are settings in which directly observed once-a-day HAART might be potentially implemented. One study showed that the addition of adefovir dipivoxil to a regimen containing ddI, 3TC, and EFV did not add efficacy but was associated with an excess of nephrotoxicity that required adefovir discontinuation. Overall, the proportion of patients requiring the discontinuation of once-a-day HAART regimens was low.

Our review included as important features a comprehensive literature review and, in some cases, additional information obtained from the authors of unpublished studies. Nevertheless, many once-a-day regimens have inconclusive data because of the lack of a reference group for comparison.

Currently, only 4 drugs have been approved in Europe and the United States for once-a-day dosing: ddI, 3TC, tenofovir, and EFV. Recently, the US Food and Drug Administration approved stavudine extended release as an additional once-a-day antiretroviral drug. Emtricitabine is a nucleoside reverse-transcriptase inhibitor similar to 3TC that is awaiting commercialization. NVP, although it is used in some once-a-day regimens, is still under study for once-a-day administration. Regarding once-a-day combinations with available protease inhibitors, all of them have as a major drawback the elevated burden of pills (between 7 and 10, in addition to reverse-transcriptase inhibitor drugs) and the possible interpatient pharmacokinetic variability when administered once a day [16]. Combinations that have been tested are IDV and RTV (1200 and 100 mg/day), SQV soft-gel capsules and RTV (1600 and 100 mg/day), amprenavir and RTV (1200 and 200 mg/day), and lopinavir and RTV (800 and 200 mg/day).

In summary, simpler treatment regimens have shown to improve adherence and treatment outcomes in other acute and chronic diseases. Preliminary data showed that some once-a-day HAART regimens had an efficacy at least similar to that of conventional HAART. Once-a-day HAART has potential advantages to be used as DOT or as first-line therapy in patients with hectic lifestyles.
Acknowledgments

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References