Very late initiation of HAART impairs treatment response at 48 and 96 weeks: results from a meta-analysis of randomized clinical trials

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Received 2 August 2011; returned 8 September 2011; revised 16 October 2011; accepted 19 October 2011

Background: Initiation of highly active antiretroviral therapy (HAART) with low CD4 lymphocyte counts is associated with AIDS-related and non-AIDS-related events and increased mortality. However, no clear association has been found with an increased rate of treatment failure.

Methods: We conducted a meta-analysis including randomized clinical trials of currently recommended HAART in naive patients to evaluate treatment response in very late starters (VLSs). Studies with information on response in at least one of the two strata (≤50 versus >50 CD4 cells/mm³ and/or ≤200 versus >200 CD4 cells/mm³) and follow-up of at least 48 weeks were analysed. A pooled odds ratio of the effect of starting HAART with ≤50 versus >50 or ≤200 versus >200 CD4 cells/mm³ for each arm by fitting a random-effect logistic regression model was computed. Sources of heterogeneity [sex, age, year of study initiation, nucleos(t)ide pair and third drug] were investigated.

Results: We included 25 treatment arms from 13 randomized clinical trials. Being a VLS consistently impairs treatment outcomes at 48 and 96 weeks. Only hepatitis C virus (HCV)/hepatitis B virus (HBV) coinfection was associated with a reduced impact of late initiation of HAART; at 48 weeks for 50 and 200 cells/mm³ thresholds (P=0.013 and P=0.032, respectively). None of the remaining sources of heterogeneity explored was significantly associated with the impact of being a VLS.

Conclusions: We found that initiation of antiretroviral therapy with very low CD4 lymphocyte counts is consistently associated with poorer outcomes of HAART. This effect could be modulated by HBV/HCV coinfection, but not by the individual components of the HAART regimen.

Keywords: antiretrovirals, antiretroviral therapy, meta-analysis, naive

Introduction

The primary goal of antiretroviral therapy is to reduce HIV-associated morbidity and mortality. Since the introduction of highly active antiretroviral therapy (HAART), both have fallen dramatically. HAART has also made it possible to reduce the frequency of HIV-associated inflammation, related complications and HIV transmission, and has led to an improvement in HIV-associated nephropathy and attenuation of the progression of liver disease in persons coinfected with hepatitis B virus (HBV), hepatitis C virus (HCV) or both. HAART has the potential to reduce the incidence of non-AIDS-associated malignancy and neurocognitive impairment. Currently recommended HAART regimens have enabled a substantial proportion of HIV-infected patients to achieve HIV RNA levels of <50 copies/mL for up to 7 years of follow-up. Nevertheless, a significant part of these beneficial effects is lost when patients start therapy late (with <200–250 CD4 cells/mm³). For example, mortality and the frequency of AIDS-related and non-AIDS-related events are higher, immune recovery is slower and often suboptimal, and antiretroviral toxicity is greater. In the long term, these poorer response rates could have a negative effect on virological control or...
recovery of CD4 lymphocyte counts, which would reach their highest point much later.

The relationship between late initiation of HAART and an increased rate of treatment failure has not been clearly established. In clinical trials, the number of patients with very low CD4 lymphocyte counts (<50 cells/mm³) at the beginning of treatment is usually not high. Therefore, it is often difficult to make comparisons with sufficient power to show differences in treatment efficacy between patients with more or less than 50 cells/mm³ at the start of therapy and to determine how particular treatment combinations are affected by a low CD4 lymphocyte count. In fact, most information comes from cohort studies, where individual treatment regimens are generally not taken into consideration and treatment response rates are not specifically analysed.16,19,20,23,26,27 Consequently, it is difficult to know the impact of poorer treatment efficacy (evaluated at 48–96 weeks) on long-term outcome or even whether the short-term response rate is relevant.

We analysed a number of randomized controlled trials to assess whether the efficacy of HAART in treatment-naive HIV-1-infected patients is poorer in those who start therapy with CD4 lymphocyte counts of <50 cells/mm³ or <200 cells/mm³ [very late starters (VLSs)] than in those who start treatment with counts above these levels (non-VLSs). If this were the case, we hypothesized that the negative effects of very late initiation observed in cohort studies could be related in part to an increased rate of treatment failure. We also determined whether this effect was associated with specific antiretroviral combinations.

Methods

Efficacy was measured as the proportion of participants with an undetectable viral load at 48 weeks and 96 weeks by intent-to-treat analysis. Very late initiation of any HAART regimen was defined as starting treatment with a CD4 lymphocyte count of <50 cells/mm³ and/or <200 cells/mm³ (depending on the data available in each trial). Therefore, for each antiretroviral regimen, we defined two comparison groups (VLSs and non-VLSs) at two different thresholds (≤50 versus >50 CD4 cells/mm³ and ≤200 versus >200 CD4 cells/mm³). The interventions considered as HAART regimens were those mostly recommended for initial therapy (first-line or alternative therapy) in European and American guidelines in 2010,28–31 namely, two nucleos(t)ides plus a third drug [a protease inhibitor boosted with ritonavir (PI/R), a nonnucleoside reverse transcriptase inhibitor (NNRTI), an integrase inhibitor or a CCR5 receptor antagonist].

We included randomized, controlled, open-label, single-blind or double-blind clinical trials with no limit on CD4 lymphocyte count at inclusion. Follow-up had to be at least 48 weeks. The only studies included were those that provided information on response in at least one of the two groups in the primary comparison (≤50 versus >50 CD4 cells/mm³ and/or ≤200 versus >200 CD4 cells/mm³). The literature search was performed using the following databases (no language restrictions): last review of the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed (1998–2010), EMBASE (1998–2010) and ClinicalTrials.gov. We also consulted the abstract books and web pages of the main scientific meetings in the fields of HIV infection/AIDS for the period 2005–10 (Conference on Retrovirus and Opportunistic Infections, World AIDS Conference, International AIDS Society Conference, European AIDS Conference, Interscience Conference on Antimicrobial Agents and Chemotherapy, and International Congress on Drug Therapy in HIV Infection). The bibliographic references of potentially relevant articles and of previous reviews in this field were analysed. The search strategy was limited to adolescents and adults, and included the following free terms: antiretroviral therapy, highly active OR anti-retroviral agents AND HIV OR AIDS OR AIDS and clinical trial. The time limit was set to restrict the studies to those comparing first-line HAART regimens as recommended by most guidelines at the time of the search (last search 30 December 2010). The terms were adapted for searches in EMBASE.

Two of the authors (J. A. P.-M. and M. D.-M.) reviewed and selected all those studies identified using the title and abstract. In the case of studies considered to have the potential for inclusion in the review, the complete text was appraised. Disagreement between reviewers was resolved with the help of a third investigator. Data were retrieved in duplicate using a standardized form.

We conducted a meta-analysis of randomized clinical trials of currently recommended HAART regimens in naive patients to evaluate the virological response in VLSs (CD4 cell count ≤50 versus >50 cells/mm³ or ≤200 versus >200 cells/mm³). For each arm of each clinical trial we collected baseline demographics and the proportion of patients achieving plasma HIV-1 RNA levels of <50 copies/mL at 48 and 96 weeks. We computed a common odds ratio (OR) of the effect of starting HAART with ≤50 versus >50 or ≤200 versus >200 cells/mm³ by fitting a random-effect logistic regression model with virological response as the dependent variable. Trials could contribute two different estimations of the effect of starting HAART (≤50 and/or >200 cells/mm³), one for each trial arm. We accounted for the correlation between intra-study estimations by computing empirical standard errors using the robust sandwich estimator.

We explored different sources of heterogeneity by including in the above model an interaction term between the indicator variable (CD4 lymphocyte count level) and the corresponding covariates. We used a univariate model to explore the following patient characteristics: mean age, sex (measured as the percentage of women) and percentage of patients coinfected with HBV, HCV or both. We also explored the following characteristics that were typical of the type of study, namely, start date, third drug in the combination (PI or NNRTI) and nucleos(t)ide pair (didanosine or zidovudine or stavudine/lamivudine, abacavir/lamivudine or tenofovir/emtricitabine). Age was analysed as a centred continuous variable (by subtracting the mean), and the variable year of study start was fixed at the year 2000 (start date 2000). The effect of the nucleos(t)ide pair was analysed as the indicative variable, taking didanosine or zidovudine or stavudine/lamivudine, abacavir/lamivudine or tenofovir/emtricitabine. Treatment failure was defined as undetectable viral load at 48 and 96 weeks. We computed a common odds ratio (OR) of the effect of starting HAART with ≤50 versus >50 or ≤200 versus >200 cells/mm³ by fitting a random-effect logistic regression model with virological response as the dependent variable. Trials could contribute two different estimations of the effect of starting HAART (≤50 and/or >200 cells/mm³), one for each trial arm. We accounted for the correlation between intra-study estimations by computing empirical standard errors using the robust sandwich estimator.

Results

We found 2576 studies and 130 conference reports (Figure 1). After eliminating duplicates (420 studies) and reading the title and abstract, we ruled out 2171, as they were not original studies, were carried out on animals, were review articles, were not performed in naive or adult patients, were observational studies or used non-recommended combinations. After reading the 115 remaining studies, we ruled out 99, mainly because they did not perform CD4 cell subanalysis (Figure 1). We finally chose 13 studies (corresponding to 16 articles) that yielded 25 treatment arms for comparison. Table 1 shows details of the studies meeting the inclusion criteria.

The mean age ranged from 34 to 40 years. The proportion of women was less than one-third for most studies (12.8%–38.2%), and this was somewhat lower for those including efavirenz (with the exception of the study by van Leth et al.47). Coinfection with HBV, HCV or both was present in 6%–30% of subjects, although in five trials this information was not provided. Regarding immunovirological status, baseline median CD4
lymphocyte count ranged from 52 to 259 cells/mm$^3$, the percentage of patients with more than $10^5$ HIV RNA copies/mL ranged from 29.0% to 87.4% and the percentage of patients with diseases classified as C category ranged from 4.0% to 45.7%.

At 48 weeks, the nucleos(t)ide combinations forming part of the HAART regimens compared were tenofovir/emtricitabine (8 arms), abacavir/lamivudine (5), stavudine/lamivudine (4), zidovudine/lamivudine (3), and didanosine/lamivudine (1); at 96 weeks there were only two nucleos(t)ide combinations being compared: tenofovir/emtricitabine (8 arms) and abacavir/lamivudine (2). As for the third drug, at 48 weeks, 12 arms included a boosted PI, 7 an NNRTI, 1 unboosted atazanavir and 1 raltegravir. All 10 arms compared at 96 weeks included a boosted PI.

Pooled analysis of the trials showed that starting antiretroviral therapy with low CD4 lymphocyte counts gave rise to a poorer virological response than starting earlier (Table 2). This effect was consistently observed inter-analysis (no heterogeneity between studies) and intra-analysis (through CD4 lymphocyte strata and follow-up time thresholds). Forest plots for this pooled analysis are shown in Figures 2–5. A lower proportion of response was observed at both 48 weeks and 96 weeks of follow-up, although the differences reached statistical significance only at 96 weeks for the 50 CD4 cells/mm$^3$ threshold and at 48 weeks for the 200 CD4 cells/mm$^3$ threshold. Of note, all antiretroviral regimens analysed at 96 weeks included a boosted PI. Inter-study variability was small, as quantified by the $I^2$ statistic, and was not statistically significant in any case (Table 2).

After univariate analysis to determine sources of heterogeneity, we found that only HCV/HBV coinfection was associated with a reduced impact of late initiation of HAART for the threshold of 50 and 200 CD4 cells/mm$^3$ at 48 weeks ($P=0.013$ and $P=0.032$, respectively; Table 3). Consequently, the association between CD4 cell count and treatment outcome is significantly less marked as the proportion of HCV-coinfected patients increases. None of the remaining sources of heterogeneity explored [sex, age, year of study initiation, third drug and nucleos(t)ide pair] was significantly associated with the impact of starting HAART with low CD4 lymphocyte counts. Publication bias was only detected for the results provided for 96 weeks of follow-up and for the 200 CD4 cells/mm$^3$ threshold ($P=0.001$).

**Discussion**

The results of this meta-analysis showed that initiating antiretroviral therapy with very low CD4 lymphocyte counts is associated with poorer outcomes and that this effect is not related to the individual antiretrovirals comprising the therapeutic regimen. A large body of evidence highlights the dangers associated with late initiation of HAART. Most studies are observational,
# Table 1. Summary of principal characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year started/ follow-up (weeks)</th>
<th>Design</th>
<th>Primary analysis</th>
<th>Antiretroviral treatment</th>
<th>Mean age (years); women (%)</th>
<th>Baseline median CD4 cell count/mm³; % VL ≤ 100000 copies/mL; % category</th>
<th>Plasma HIV RNA &lt;50 copies/mL (%) by CD4 lymphocyte stratum (cells/mm³) at 48 (96) weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gathe et al.</td>
<td>2000/48</td>
<td>open RCT</td>
<td>VL &lt;400 copies/mL, M=F</td>
<td>FMP/RT + ABC + 3TC (322)</td>
<td>36; 30.0; 26.0</td>
<td>166; 42.0; 21.0</td>
<td>45/62 (72.6) 177/260 (68.1) NR</td>
</tr>
<tr>
<td>van Leeh LL et al.</td>
<td>2000/48</td>
<td>open RCT, centralized randomized</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>d4T + 3TC + NVP (607)</td>
<td>34; 38.2; 14.6</td>
<td>181; 31.4; 21.4</td>
<td>41/73 (56.2) 34/75/34 (65.0) 184/312 (59.0) 204/295 (69.3)</td>
</tr>
<tr>
<td>Molina et al.</td>
<td>2002/96</td>
<td>open RCT</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>LPVr + QD + TRV (115)</td>
<td>39; 19.0; NR</td>
<td>214; 44.0; NR</td>
<td>30/50 (60.0) 36/65 (55.4)</td>
</tr>
<tr>
<td>Berenguer et al.</td>
<td>2004/48</td>
<td>open RCT</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>LPVr + BID + RTV (75)</td>
<td>37; 25.0; NR</td>
<td>232; 29.0; NR</td>
<td>20/36 (55.5) 20/39 (51.3)</td>
</tr>
<tr>
<td>Malan et al.</td>
<td>2004/48</td>
<td>open RCT</td>
<td>VL &lt;400 copies/mL, M=F</td>
<td>ATV + 3TC + d4T + Ter (105)</td>
<td>40; 24.0; 25.0</td>
<td>216; 54.0; 24</td>
<td>9/14 (64.3) 71/115 (61.7) 43/70 (61.4)</td>
</tr>
<tr>
<td>Echeverría et al.</td>
<td>2005/48</td>
<td>open RCT</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>KXV + EFV (63)</td>
<td>39; 14.0; NR</td>
<td>193; 38.1; 7.3</td>
<td>59/77 (55.4) 42/50 (84.0)</td>
</tr>
<tr>
<td>Hicks et al.</td>
<td>2005/96</td>
<td>open RCT</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>FMP/QR + KXV (58)</td>
<td>39; 19.0; NR</td>
<td>259; 34.0; 7.0</td>
<td>6/4 (66.7) 34/52 (65.4) 16/23 (69.6) 22/35 (62.9)</td>
</tr>
<tr>
<td>Molina et al.</td>
<td>2005/48</td>
<td>open RCT</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>ATV + QD + TRV (440)</td>
<td>34; 31.0; 14.0</td>
<td>205; 51.0; 4.0</td>
<td>45/58 (77.6) 291/373 (78.0) 158/209 (75.6) 178/222 (80.2)</td>
</tr>
<tr>
<td>Molina et al.</td>
<td>96</td>
<td>open RCT</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>LPVr + TRV (443)</td>
<td>36; 12.0; 12.0</td>
<td>204; 47.0; 5.0</td>
<td>30/48 (62.5) 307/391 (78.5) 155/211 (73.5) 182/228 (79.8)</td>
</tr>
<tr>
<td>Ortiz et al.</td>
<td>2005/48</td>
<td>open RCT</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>ATV + QD + TRV (343)</td>
<td>35; 30.0; 13.0</td>
<td>228; 34.0; 8.0</td>
<td>25/30 (66.7) 250/316 (79.1) 104/148 (70.3) 166/198 (83.8)</td>
</tr>
<tr>
<td>Mills et al.</td>
<td>96</td>
<td>open RCT</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>LPVr + TRV (346)</td>
<td>35; 30.0; 14.0</td>
<td>218; 34.0; 10.0</td>
<td>111/141 (78.7) 160/202 (79.2)</td>
</tr>
<tr>
<td>Sierra-Madero et al.</td>
<td>2005/48</td>
<td>open RCT</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>LPVr + TRV (346)</td>
<td>35; 30.0; 14.0</td>
<td>218; 34.0; 10.0</td>
<td>111/141 (78.7) 160/202 (79.2)</td>
</tr>
<tr>
<td>Gathe et al.</td>
<td>2006/48</td>
<td>open RCT</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>ZDV + 3TC + EFV (95)</td>
<td>36; 16.8; NR</td>
<td>64; 87.4; 37.8</td>
<td>33/42 (78.6) 34/53 (64.1) 22/45 (48.9) 28/49 (57.1) 22/45 (48.9) 28/49 (57.1)</td>
</tr>
<tr>
<td>Gonzalez-García et al.</td>
<td>96</td>
<td>open RCT</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>LPVr + BID + TRV (331)</td>
<td>38; 23.3; NR</td>
<td>214; 58.3; NR</td>
<td>42/53 (79.2) 212/278 (76.2) 115/153 (75.2) 139/178 (78.1)</td>
</tr>
<tr>
<td>Lennox et al.</td>
<td>2006/48</td>
<td>double-blind, RCT, centralized randomized</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>PLL + TRV (282)</td>
<td>37; 19.0; 6.0</td>
<td>218; 55.0; 14.0</td>
<td>13/18 (72.2) 198/298 (66.4) 97/150 (64.7) 119/182 (65.4)</td>
</tr>
<tr>
<td>Carosi et al.</td>
<td>2007/48</td>
<td>open RCT</td>
<td>VL &lt;50 copies/mL, M=F</td>
<td>FMP + (1400 mg)/r QR + KXV (106)</td>
<td>37; 25.0; 12.0</td>
<td>251; 47.0; 8.0</td>
<td>18/24 (75.0) 68/82 (82.9)</td>
</tr>
</tbody>
</table>

ABC, abacavir; ATV, atazanavir; BID, twice daily; ddi, didanosine; DRV, darunavir; d4T, stavudine; d4T or stavudine extended release; EFV, efavirenz; FMP, fosamprenavir; KXV, abacavir/ lamivudine in combination; LPV, lopinavir; M=F, missing equals failure; M+F, missing not considered as failure; NR, not reported; NVP, nevirapine; QD, once daily; r, low-dose ritonavir (100 mg); RAL, raltegravir; RCT, randomized clinical trial; TRV, tenofovir/emtricitabine in combination; VL, HIV-1 RNA viral load; ZDV, zidovudine; 3TC, lamivudine.

aFor purposes of the lymphocyte subanalysis, the published results of the nevirapine once-daily and twice-daily arms were combined. Primary efficacy analysis was performed with a threshold of <400 copies/mL, but <50 copies/mL was selected for homogeneity. The lower CD4 lymphocyte stratum in this study was ≤25 cells/mm³ instead of ≤50 cells/mm³.

bPrimary efficacy analysis was performed with a threshold of ≤400 copies/mL, but <50 copies/mL was selected for homogeneity.

cIn the study of Sierra-Madero et al., higher viral load is defined as >75000 copies/mL.

dIn the study of Carosi et al., lower CD4 count was defined as <150 cells/mm³ instead of <200 cells/mm³.
and only two are clinical trials. However, these studies focus almost exclusively on clinical events (death and/or AIDS-defining illnesses) and do not describe how the efficacy of HAART is affected by CD4 lymphocyte count at baseline. Although control of plasma viraemia is not a good marker of virus inactivity and late initiation of HAART is associated with non-modifiable end organ damage by antiretroviral treatment, it is important to know which part of the deleterious effect of late initiation of HAART leads to a subsequent loss of efficacy. It must be remembered that late diagnosis of HIV infection still affects 30%–60% of patients.

There is evidence of a link between late initiation of antiretroviral therapy and treatment failure, although this comes only from non-interventional studies in which lower CD4 lymphocyte counts at the initiation of HAART were associated with a higher probability of drug failure. It is noteworthy that this effect was not observed in all cases. In our meta-analysis, we compared the rate of response to HAART according to baseline CD4 lymphocyte count (<50 versus ≥50 or ≤200 versus >200 cells/mm³). We found that initiating HAART with ≤50 or ≤200 CD4 cells/mm³ was associated with poorer outcomes in comparison with initiating HAART above these levels. In addition, we found that this effect was consistent throughout follow-up periods and for the different CD4 lymphocyte thresholds (consistency intra-analysis). No heterogeneity was observed across studies (consistency inter-analysis), as we did not detect any interaction between virological response and a specific antiretroviral combination, probably reflecting the high efficacy of current HAART, even in patients with low CD4 lymphocyte counts. Nevertheless, these findings cannot be extended to novel antiretrovirals, given that only one clinical trial (raltegravir compared with efavirenz) could be included.

### Table 2. Pooled analysis for the effect of very late initiation at 50 and 200 cells/mm³ thresholds

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Studies (n)</th>
<th>Trial arms (n)</th>
<th>P heterogeneity</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gathe51 (fAMP/r+ABC+3TC), 2000</td>
<td>1.24 (0.67, 2.30)</td>
<td>45/62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Leth47 (EFV+d4T+3TC), 2000</td>
<td>1.03 (0.54, 1.98)</td>
<td>32/47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Leth47 (NVP+d4T+3TC), 2000</td>
<td>0.69 (0.42, 1.13)</td>
<td>41/73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berenguer52 (EFV+ZDV+3TC), 2004</td>
<td>1.12 (0.35, 3.54)</td>
<td>9/14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berenguer52 (EFV+d4T+3TC), 2004</td>
<td>1.70 (0.53, 5.46)</td>
<td>15/19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molina55 (ATV+r+TRV), 2005</td>
<td>0.98 (0.50, 1.89)</td>
<td>49/58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molina55 (LPV+r+TRV), 2005</td>
<td>0.46 (0.24, 0.86)</td>
<td>30/48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortiz46 (DRV/r+TRV), 2005</td>
<td>0.60 (0.24, 1.46)</td>
<td>23/30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortiz46 (LPV+r+TRV), 2005</td>
<td>0.53 (0.24, 1.18)</td>
<td>20/30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sierra-Madero45 (EFV+CBV), 2005</td>
<td>2.05 (0.81, 5.18)</td>
<td>33/42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sierra-Madero45 (LPV+r+CBV), 2005</td>
<td>0.72 (0.32, 1.62)</td>
<td>22/45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gathe50 (LPV/r OD+TRV), 2006</td>
<td>0.77 (0.34, 1.74)</td>
<td>25/34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gathe50 (LPV/r BID+TRV), 2006</td>
<td>1.19 (0.58, 2.44)</td>
<td>42/53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lennox41 (EFV+TRV), 2006</td>
<td>0.70 (0.22, 2.20)</td>
<td>24/28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lennox41 (RLV+TRV), 2006</td>
<td>0.43 (0.13, 1.39)</td>
<td>21/25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (I²=11.6%, P=0.324)</td>
<td>0.85 (0.70, 1.04)</td>
<td>427/608</td>
<td>2966/3928</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Pooled analysis at 48 weeks comparing those patients who initiated HAART with ≤50 CD4 cells/mm³ versus >50 CD4 cells/mm³ at the start of treatment. ABC, abacavir; ATV, atazanavir; BID, twice daily; CBV, zidovudine/lamivudine; ddI, didanosine; DRV, darunavir; d4T, stavudine; EFV, efavirenz; fAMP, fosamprenavir; LPV, lopinavir; NVP, nevirapine; OD, once daily; r, ritonavir; RLV, raltegravir; TRV, tenofovir/emtricitabine; ZDV, zidovudine; 3TC, lamivudine. Odds ratios <1.0 represent poorer response rates for patients starting with ≤50 CD4 cells/mm³ versus >50 CD4 cells/mm³. Year of the study corresponds to the year the study started.
Figure 3. Pooled analysis at 96 weeks comparing those patients who initiated HAART with $\leq 50$ CD4 cells/mm$^3$ versus $>50$ CD4 cells/mm$^3$ at the start of treatment. ATV, atazanavir; BID, twice daily; fAMP, fosamprenavir; KVX, abacavir/lamivudine; LPV, lopinavir; r, ritonavir; QD, once daily; TRV, tenofovir/emtricitabine. Odds ratios $<1.0$ represent poorer response rates for patients starting with $\leq 50$ CD4 cells/mm$^3$ versus $>50$ CD4 cells/mm$^3$. Year of the study corresponds to the year the study started.

Figure 4. Pooled analysis at 48 weeks comparing those patients who started HAART with $\leq 200$ CD4 cells/mm$^3$ versus $>200$ CD4 cells/mm$^3$ at the start of therapy. ATV, atazanavir; BID, twice daily; ddI, didanosine; DRV, darunavir; d4T, stavudine; d4T/xr, stavudine extended release; EFV, efavirenz; fAMP, fosamprenavir; KVX, abacavir/lamivudine; LPV, lopinavir; NVP, nevirapine; QD, once daily; r, ritonavir; RLV, raltegravir; TRV, tenofovir/emtricitabine; ZDV, zidovudine; 3TC, lamivudine. Odds ratios $<1.0$ represent poorer response rates for patients starting with $\leq 200$ CD4 cells/mm$^3$ versus $>200$ CD4 cells/mm$^3$. Year of the study corresponds to the year the study started.
both, the effect of starting with low CD4 lymphocyte counts is reduced. This may be secondary to poorer HIV-related outcomes in this coinfected population and could thus dilute the negative effect of the low CD4 lymphocyte count at the start of therapy.

One of the limitations of the present study is that it examines data from subanalyses in which patients were not necessarily randomized according to their CD4 lymphocyte count; consequently, the groups may not be homogeneous with respect to other prognostic variables. Variables such as HCV coinfection or baseline viral load could be associated with a poorer response to HAART and, simultaneously, with a low CD4 cell count. Unfortunately, this potential confounding bias cannot be addressed in a meta-analysis of pooled data. The only way to resolve the issue satisfactorily would be to perform a meta-analysis of individual patient data. Randomization was stratified by CD4 lymphocyte count in only three of the studies. Similarly, the efficacy analysis performed according to the CD4 lymphocyte count was set out \textit{a priori} in the methods section in only six of the studies. This finding could be associated with a possible publication bias detected at 96 weeks for the 200 CD4 cells/mm\(^3\) level. The characteristics of this study mean that publication bias is understood as failing to report the results of the efficacy subanalyses according to the CD4 lymphocyte count and not as non-publication of the results of the clinical trial. Consequently, those subanalyses that did not favour the regimens studied would have fewer chances of being reported; therefore, the potentially deleterious effect of late initiation would be diluted.

Our method for estimating the pooled averaged effect of very late initiation of HAART is more conservative than merely pooling effect estimates from individual studies using standard meta-analytical methods. In fact, we computed robust standard errors to estimate confidence intervals (CIs) of the pooled effect in order to account for the correlation that likely existed between the estimations of the effect of very late initiation of HAART obtained in an individual randomized controlled trial (intra-study correlation). Meta-regression analyses were also performed using the same analytical model. We formally assessed the impact of covariates (see the Methods section for the
variable list) on the estimated effect for CD4 cell count by introducing interaction terms in the model. Additionally, the study population was very homogeneous across the studies; all patients (from 1648 to 4663 depending on the comparison) were from clinical trials based on very standardized procedures that were started over a very short period of time (2000–07) and studied therapeutic regimens with similar efficacy.

The findings of this meta-analysis show that the effect of starting antiretroviral therapy with very low CD4 lymphocyte counts is associated with poorer outcomes. This effect could be modulated by HBV/HCV coinfection, but not by the individual components of the HAART regimen. Given that 30%–60% of naive patients start combination antiretroviral therapy late, the protocols of future studies should consider including CD4 lymphocyte stratification or, at least, an a priori efficacy subanalysis based on CD4 lymphocyte strata. Such an approach would add very valuable information on treatment efficacy, mainly for new drugs, where much less information is available. Another less costly approach to studying this subgroup of patients would be to design trials specifically focused on such a very immunosuppressed population. Finally, while data from our meta-analysis will not influence decisions on optimal timing for initiation of HAART, as cohort studies have provided extensive information on the deleterious effect of treatment initiation with low CD4 lymphocyte counts, they stress the negative consequences of late initiation of antiretroviral therapy, even at very low CD4 lymphocyte counts.

**Funding**

This work was supported by Bristol-Myers Squibb, who funded the literature search, bibliographic management and translation services. Bristol-Myers Squibb did not participate in the design of the protocol, retrieval and analysis of data, or drafting of the manuscript.

**Transparency declarations**

None to declare.

**References**


Systematic review


