

Hecht FM. Wang L. Collier A. Little S. Markowitz M. Margolick J. Kilby JM. Daar E. Conway B. Holte S. AIEDRP Network. **A multicenter observational study of the potential benefits of initiating combination antiretroviral therapy during acute HIV infection.** Journal of Infectious Diseases. 194(6):725-33, 2006 Sep 15.

Clinical Question:

Does HAART treatment during acute or early HIV infection improve long-term outcomes?

Study Population:

Registrants with the Acute Infection and Early Disease Research Program (AIEDRP) – a cohort of individuals enrolled within 1 year of HIV seroconversion and self-selecting for HAART treatment.

Inclusion Criteria:

Treated Subjects –

- Initiation HAART (≥3 antiretroviral agents) within 6 months of negative or indeterminate HIV Ab test result OR concurrent with an Optical Density EIA test of <0.75 (implying <6 months since seroconversion)
- Continue HAART for ≥12 weeks, and then stop treatment for at least 4 weeks

Untreated Subjects –

- at least 6 months of follow-up following AIEDRP enrollment

Exclusion Criteria: none cited

Intervention: Patients received HAART as dictated by site-specific study protocol or as chosen by the treating physician.

Group Assignment: Subjects self-selected whether to receive HAART, usually with knowledge of their CD4 count and viral load.

- Non-treatment group n = 337
- Treatment group was subdivided
 - Acute Treatment Group – receiving HAART within 2 weeks of seroconversion, n = 13
 - Early Treatment Group – receiving HAART 2 weeks to 6 months following seroconversion, n = 45

Endpoints: HIV RNA levels and CD4 T-cell counts at 24, 48 and 72 weeks

Analysis

- Statistical regression was used to model viral load and CD4 as non-linear variables – this was needed to adjust for differing frequency of measurement between groups and to allow for the calculation of values at 24, 48 and 72 weeks when these data points were unavailable.
- Of note, patients receiving >72 weeks of follow up were 3 (Acute), 13 (Early), and 50 (Untreated). Later data, therefore, increasingly relies upon statistical modeling
- The Acute group tended to have an HIV RNA higher than the Untreated Group (P = 0.07, and tended to have a lower CD4 count than either comparison group (P > 0.1)

Results:

Table 2. Differences in mean HIV-1 RNA levels (expressed as log₁₀ copies/milliliter) between treated and untreated subjects at follow-up time points.

Follow-up time point	Acute treatment ^a group minus untreated group		Early treatment ^b group minus untreated group	
	Unadjusted	Adjusted	Unadjusted	Adjusted
24 weeks	-0.48 ^c (-0.82 to -0.13)	-0.69 ^c (-1.01 to -0.38)	-0.49 ^c (-0.66 to -0.32)	-0.51 ^c (-0.68 to -0.35)
48 weeks	-0.29 (-0.17 to 0.13)	-0.59 ^c (-1.02 to -0.16)	-0.05 (-0.29 to 0.19)	-0.10 (-0.35 to 0.15)
72 weeks	-0.35 (-0.91 to 0.21)	-0.68 ^c (-1.30 to -0.07)	0.13 (-0.21 to 0.48)	0.10 (-0.27 to 0.47)

NOTE. Data in parentheses are 95% confidence intervals.

^a Subjects who started receiving HAART within 2 weeks of antibody seroconversion.

^b Subjects who started receiving HAART between 2 weeks and 6 months after antibody seroconversion.

^c P < .05.

Table 3. Differences in mean CD4⁺ T cell counts (expressed as cells/microliter) between treated and untreated participants at follow-up time points.

Follow-up time point	Acute treatment ^a group minus untreated group		Early treatment ^b group minus untreated group	
	Unadjusted	Adjusted	Unadjusted	Adjusted
24 weeks	112 ^c (20–205)	132 ^c (51–213)	116 ^c (75–157)	126 ^c (88–163)
48 weeks	103 (–2 to 207)	120 ^c (24–217)	110 ^c (57–162)	119 ^c (68–169)
72 weeks	112 (–15 to 213)	125 ^c (3–247)	70 ^c (2–138)	79 ^c (11–146)

NOTE. Data in parentheses are 95% confidence intervals.

^a Subjects who started receiving HAART within 2 weeks of antibody seroconversion.

^b Subjects who started receiving HAART between 2 weeks and 6 months after antibody seroconversion.

^c $P < .05$.

Discussion:

- Study Characteristics
 - The study design was retrospective
 - Assignment of patients was NOT random
 - Many patients were lost to follow up
 - There was no patient or personnel blinding
 - Treatment regimens varied significantly in nature and duration
 - Treatments other than HAART, as described above, were not analyzed, and therefore may have varied between groups
 - No data was provided regarding the group characteristics of those completing 72 week follow-up or possible significant inter-group variability
- Self-selection may enrich the control group for those with lower viral loads and higher CD4 counts, though this should be corrected by statistical adjustment. Self selection into treatment may also indicate increased health-seeking behavior, which would be enriched in the treatment groups, and can not be corrected statistically.
- Given trend toward higher baseline viral load and lower CD4 in the Acute group—which are known to be transient during acute infection—their statistical adjustment may overcorrect and increase the apparent treatment effects in this group
- HIV RNA results indicate an initially significant, though decreasing treatment effect over the time course of the study, with unclear implications for ultimate rate of progression.
- CD4 counts seem to indicate some arrest in disease progression as a result of HAART use, though it is unclear whether treatment alters the usefulness of CD4 count as a marker of progression or indicates a change in the natural course of untreated disease.
- Importantly, other important clinical outcomes, such as the development of resistant HIV strains, or adverse drug effects were not considered in this study, though they play key roles in motivating current practice, which limits the use of HAART in non-AIDS HIV patients

Search Strategy:

Database: Ovid MEDLINE(R) <1950 to August Week 1 2008>

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- 1 exp HIV/ or exp HIV Infections/ (200435)
 - 2 exp Acute Disease/ (160610)
 - 3 1 and 2 (1233)
 - 4 Antiviral Agents/ or Antiretroviral Therapy, Highly Active/ or Anti-HIV Agents/ or Zidovudine/ (69306)
 - 5 exp HIV Fusion Inhibitors/ or exp HIV Integrase Inhibitors/ or exp HIV Protease Inhibitors/ (9158)
 - 6 4 or 5 (74273)
 - 7 exp CD4-Positive T-Lymphocytes/ or exp CD4 Lymphocyte Count/ (69405)
 - 8 exp Disease Progression/ (56755)
 - 9 exp Viremia/ or exp RNA, Viral/ or exp Viral Load/ (61798)
 - 10 8 or 7 or 9 (179262)
 - 11 6 and 3 and 10 (97)
 - 12 limit 11 to (english language and humans and ("adolescent (13 to 18 years)" or "adult (19 to 44 years)" or "middle aged (45 plus years)")) (47)
 - 13 limit 12 to (clinical trial, all or clinical trial or controlled clinical trial or randomized controlled trial) (15)