

The effect of antiretroviral treatment of different durations in primary HIV infection

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Abstract

Background: The relative immunological, virological and clinical outcome of initiating HAART of different durations within 6 months of HIV seroconversion (SC) is not known. We compare such outcomes within an "early treatment" group and with those who deferred ART.

Method: Comparison of CD4 counts and HIV RNA measurements for the "early treated" individuals were restricted to the period following treatment cessation, and before any ART was re-initiated, and the corresponding ART-free period for the "deferred" group. CD4 data were analysed using piecewise linear mixed models. Individuals were included if they seroconverted at or after January 1996, were ≥ 15 years at SC, and identified during primary HIV infection (PHI). Those with ≥ 2 CD4 < 350 cells/ μ l or AIDS within the first 6 months following SC were excluded.

Results: Of the 348 early treated individuals, 147 received ART of limited duration: <6 months (38), 6-12 months (40) and >12 months (69). CD4 loss was steeper for the first 6 months following ART cessation but the subsequent rate of loss was similar to the corresponding rate for the 675 individuals in the "deferred" group ($p=0.26$). Although those treated >12 months appeared to experience higher CD4 levels following ART cessation, those treated ≤ 12 months had comparable CD4 levels 6 months after cessation to those in the deferred group. There was no difference in HIV RNA set-points between the early and deferred groups ($p=0.43$). AIDS rates were similar but death rates were higher in the deferred group ($p=0.05$), mainly due to an increased number of non-AIDS deaths in this group.

Conclusions: Transient ART, initiated within 6 months of HIV SC, seems to have limited beneficial effects on CD4 cell count levels and no effect on viral load set-point. However its long-term effects are still inconclusive and need further investigation.

1. Introduction

Background

•Beneficial immunologic/virologic effects of HAART in both primary and chronic HIV-1 infection

•Strong prognostic value of "early" CD4/viral load levels.

•Treatment guidelines: "Immediate treatment is **probably** justified for individuals identified in acute infection".

•Limited/contradicting evidence regarding long-term effects of HAART in primary infection.

•Adverse events due to long-term exposure to HAART.

The question regarding the optimal time of HAART initiation and its duration, for individuals identified soon after SC, remains.

Objectives

- Compare two groups of HIV infected individuals:

•"Early treatment" group: initiated HAART (≥ 30 days) within the first 180 days after SC

•"Deferred treatment" group: initiated HAART later or remained HAART free for the whole follow-up

in terms of: CD4 cell counts, viral load levels, clinical outcomes (AIDS, death) focusing on the period between treatment cessation and ART resumption ("early" group) or SC and ART initiation ("deferred" group)

- Investigate the effects of "early" HAART's duration.

2. Methods

Patients & Methods

Study population derived from CASCADE (N=9,810)

Inclusion criteria

Age at SC ≥ 15 years (N=9,742), SC on or after 1996 (N=3,572),

SC window < 180 days/Lab evidence/SC illness (N=1,755)

Follow-up ≥ 180 days (N=1,355)

Exclusion criteria

Initiation of HAART which lasted for <30 days within the first 180 days

after SC (N=21), AIDS development (N=21) or two CD4 measurements

<350 cells/ μ l (N=97) within the first 180 days after SC, <2 CD4 or viral load measurements (N=193)

Statistical Methods

Follow-up censored at ART initiation ("deferred" group) or re-initiation ("early" group). Piece-wise linear mixed models for CD4 evolution with random intercept and slopes. Simple two sample comparisons for viral-load at "set-point". Log-rank tests and Cox models for time to clinical events analyses

3. Results

Study sample size after inclusion/exclusion criteria: N=1023

•**Early group:** N=348 (34%). Of them, 147 stopped all ART drugs after being on HAART for <6 (38), 6-12 (40) and >12 months (69).

•**Deferred group:** N=675 (66%). Of them 226 initiated HAART during chronic infection

Heterosexual contact was the most common mode of infection (~71%) whereas the median age at SC was ~32 years in both groups

Figure 1. Cross-sectional median CD4 levels by time since seroconversion – stratified by group and ART period [during first HAART and following its cessation (T1) for "early treated" individuals]. Numbers indicate individuals contributing measurements at each time point.

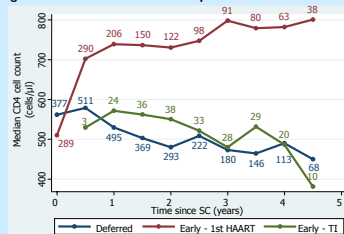
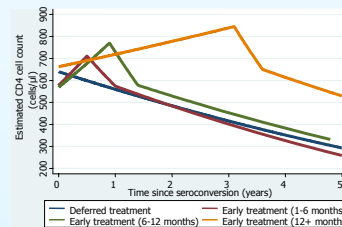


Figure 2. Predicted average CD4 cell count trends by group ("early" and "deferred" treatment) and duration of "early" HAART.



CD4 cell count evolution

A steep decrease in CD4 cell counts is observed during the first 6 months after HAART's cessation followed by a less steep slope thereafter (Figure 2). Ultimate rates of CD4 loss were similar between "early" and "deferred" groups ($p=0.26$). Individuals receiving "early" HAART for ≤ 12 months appear to reach comparable CD4 levels as those still untreated within ~6 month of stopping treatment. Individuals treated for >12 months however, appear to maintain higher CD4 levels after treatment cessation compared to untreated individuals (Figures 1, 2).

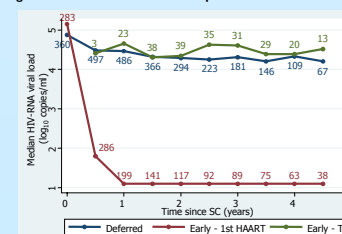
Viral load levels evolution

Viral load levels of "early" treated individuals, return to levels which are comparable to those in the "deferred" treatment group, 6 months after the cessation of "early" HAART (Figure 3). "Set-point" levels do not differ by group ($p=0.43$) nor by duration of "early" HAART ($p=0.57$) (Figure 4).

Clinical events

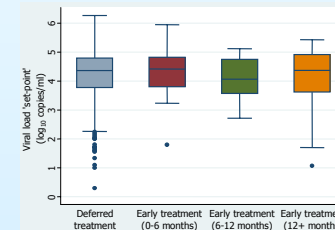
There were no deaths within the period from SC to HAART initiation ("deferred" group) or re-initiation ("early" group).

Figure 3. Cross-sectional median HIV-RNA levels by time since seroconversion – stratified by group and ART period [during first HAART and during its cessation (T1) for "early treated" individuals]. Numbers indicate individuals contributing measurements at each time point.



AIDS rates within the same period were also similar: 6/348 (1.7%) and 11/664 (1.6%) for "early" and "deferred" groups, respectively ($p=0.78$). Considering the whole follow-up irrespectively of ART status, AIDS rates remained similar ["Early": 13/348 (3.7%), "Deferred" : 20/675 (3.0%); $p=0.95$] but death rates were significantly higher in the "Deferred" group [12/675 (1.78%) vs. 2/348 (0.57%) in the "Early" group; $p=0.05$]. It should be noted though that the vast majority of deaths in the "Deferred" group (9/12) were non-AIDS related.

Figure 4. Viral load "set-point" (average of all viral load measurements/individual taken > 1 year after SC and while both groups were off ART and "early treated" individuals had stopped HAART for at >6 months) and duration of "early" HAART.



4. Conclusions

•Similar ultimate rates of CD4 decline for "early" and "deferred" groups.

•Although those treated >12 months appeared to maintain higher CD4 counts following ART cessation, those treated ≤ 12 months had CD4 counts 6 months after cessation comparable to those in the "deferred" group.

•No difference in viral load "set-point" levels

•Similar AIDS rates but higher death rates (mainly non-AIDS) in the "deferred" treatment group

Transient ART, initiated within 6 months of HIV SC, seem to have limited beneficial effects on CD4 cell count levels and no effect on viral load set-point. Long-term effects are still inconclusive.

CASCADE collaborators

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