

Factors Associated with Time to CD4 Count < 350 After a Treatment Interruption (TI) Following Effective Antiretroviral Therapy (ART) +/- Interleukin-2 (IL-2): Results of a Pilot Study (ACTG A5102)

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ABSTRACT

BACKGROUND

RESULTS

One uncontrolled trial (AIDS 2004; 18: 439-446), one small randomized trial (AIDS 2004; 18: 2381-2389) and one larger randomized trial (CID 2005; 40: 594-600) utilizing the CD4+ T-cell count as the threshold to stop and restart antiretroviral therapy (ART) have recently been published, all with results supporting further studies of a therapeutic strategy that initiates and stops antiretroviral therapy at specific CD4 thresholds (Figure 1a). We were interested in interventions that could safely prolong the TI (Figure 1b). We conducted a prospective randomized study evaluating the use of IL-2 as an intervention aimed at prolonged the time off therapy.

OBJECTIVES

To recognize factors, including the use of IL-2, that would identify individuals who could be maintained off ART for longer periods of time.

DESIGN

We evaluated the associations between time to CD4 < 350 cells/mm³ during TI and several biological markers both at baseline and during TI utilizing a Cox proportional hazard model using one predictive variable at a time.

47 HIV+ subjects on potent ART with CD4+ T-cell counts > 500 cells/mm³ and HIV-1 RNA levels < 200 copies/ml were randomized to Arm A (ART + three 5-day cycles of IL-2 @ 4.5 million units SC BID every 8 weeks-n=23) or Arm B (ART only-n=24) for 18 weeks (Step 1). 21 of the subjects were on a PI-based therapy. At the end of Step 1, all study subjects with CD4 count > 500 cells/mm³ underwent a TI maintained until the CD4 count decreased to < 350 cells/mm³ (Step 2). At the time of the analysis, the median follow up time on TI was 78 weeks (distribution of subjects by Step shown in Figure 1c)

STUDY POPULATION

Patients were eligible for A5102 if they had never experienced virologic failure on a HAART regimen defined by DHHS and at screening their plasma HIV RNA levels was < 200 copies/ml with CD4+ T-cell count > 500 cells/mm³.

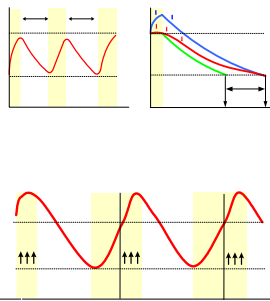


Figure 1.

- A. Intermittent or "pulse" therapy concept. ART is stopped and restarted at specific thresholds. The duration of the times off and on antiretroviral therapy varies in each individual.
- B. The impact of spontaneous interventions on an intermittent ART strategy: discontinuation. Therapy has to be restarted at time X. Line A (green): Spontaneous CD4 decay after ART discontinuation. Line B (red): Intervention's (red arrows) affect/s the slope of the CD4 decay after treatment discontinuation. ART to be restarted at time Y. The benefit of the intervention is the difference between Y and X. Line C (blue): Intervention's that increase/s the CD4 before treatment interruption without affecting the slope of the CD4 decay. ART to be restarted at time Y. The benefit of the intervention is the difference between Y and X.
- C. A5102 Steps and Disposition. The yellow area represents periods of time where the participants receive antiretroviral therapy. The duration of these phases is indicated above. The white area represents variable periods of time where the subject is not receiving antiretroviral therapy. The numbers represent the number of participants in each step at the time of analysis (14 subjects off study).

Figure 2- Median CD4 count

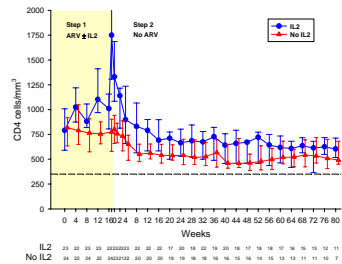


Figure 3-Time CD4 Decline to < 350

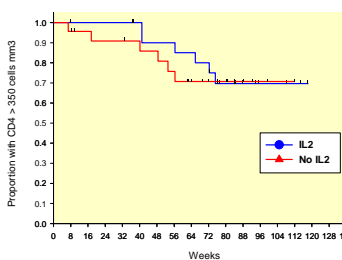
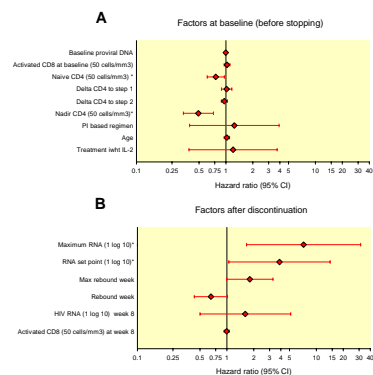


Figure 4- Factors associated with time to CD4 < 350 mm³



Results: At the time of the analysis, the median follow up time on TI was 78 weeks. The CD4+ T-cell count was significantly higher in the IL-2 group during the TI for 20 weeks and remained higher thereafter (Figure 2).
•The positive effect of IL-2 on maintaining a higher CD4+ count during TI persisted for 72 weeks (Figure 3).
•Of the baseline variables evaluated, only high naïve CD4+ count before the initiation of HAART and higher naïve CD4 count at entry were associated with sustained CD4+ T cell counts and longer TI (Figure 4A)
•**After TI**, a higher viral set point (closely linked to maximum RNA level) was associated with a shorter time to CD4+ T-cell count < 350 cells/mm³ (Figure 4B).
•IL-2 was well tolerated with no unexpected toxicities.

DISCUSSION

The effect of IL-2 administration while on ART on preserving the CD4+ count during TI was evident for 72 weeks with most subjects in both study arms remaining off ART for more than 1 year. Implications of our results for TI strategies include the potential advantage of starting ART earlier (when the CD4+ count is higher) and evaluating interventions that could decrease HIV-1 RNA rebound during the TI (such as immunomodulators that could dampen T-cell activation).