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Treatment Interruption in Early Starters in the Netherlands (TRIESTAN): successful for at least 36 weeks

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1. Introduction

Between 1996-2000, many HIV-1 positive patients initiated HAART (highly active antiretroviral therapy) at a CD4+ T-lymphocyte count (CD4 count) >350 cells/mm^3, which is higher than advised in current guidelines.

Many of these patients and their clinicians now consider stopping HAART, often because of emerging toxicity. In addition, patients would be relieved of adherence to strict dosing regimens which may affect the quality of life.

TRIESTAN is a prospective, non-randomised, multi-centre study in which we evaluated the safety, efficacy and benefit of discontinuing HAART in such patients.

2. Methods

All patients who had initiated HAART at a CD4 count >350 cells/mm^3 were identified from the Dutch ATHENA national observational cohort. Exclusion criteria were a CD4 count <500 cells/mm^3 or HIV-RNA in plasma (pVL) >50 copies/ml in the 6 months prior to inclusion in the current trial, antiretroviral experience before HAART, >1 change of regimen because of virological failure, and prior non-Hodgkin's lymphoma or Kaposi's sarcoma. Eligible patients were offered the choice to either interrupt or continue HAART. All patients in the study were followed at week 0-1-4-8-12 and every 12 weeks thereafter. Follow-up ended 144 weeks after inclusion or 6 months after therapy was restarted.

The primary outcome was the safety and efficacy of discontinuation of HAART. Safety was evaluated by determining the proportion of patients who fell <300 cells/mm^3 while off HAART , the proportion of patients with a new AIDS diagnosis or death and the number of patients who developed an acute retroviral syndrome . Efficacy was evaluated by determining the time that patients who discontinued

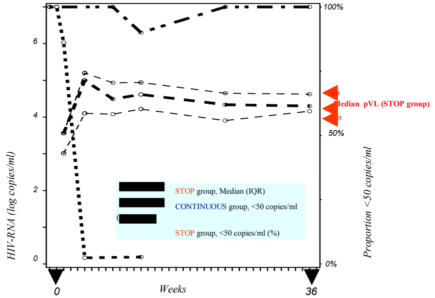
3. Baseline characteristics

		Stop HAART n=46	Continuous HAART n=25
Sex (male)		39 (85%)	22 (88%)
Age, median (IQR)		44 (39-48)	44 (36-51)
Region of origin	Netherlands	30 (65%)	21(84%)
	other	16 (35%)	4 (16%)
Mode of transmission	heterosexual	7 (15%)	3 (12%)
	homosexual	33 (72%)	22 (88%)
	IVD	3 (7%)	0 (0%)
	other/unknown	3 (7%)	0 (0%)
Year of start HAART	before 1998	24 (52%)	6 (24%)
	1998-2000	17 (27%)	15 (60%)
	2001-2002	5 (11%)	4 (16%)
CD4 cells at start HAART (IQR, cells/mm3)		496 (430-720)	510 (440-637)
Median HIV-RNA at start HAART (IQR, log10/ml)		4.7 (4.4 -5.2)	4.7 (4.1-5.0)
HIV-RNA category	unknown	0 (0%)	1 (0%)
	<100.000 copies/ml	27 (59%)	18 (72%)
	>100.000 copies/ml	19 (41%)	6 (24%)
Median duration HAART before T0* (IQR, months)		70 (49.3-78.9)	57.2 (42.4-73.4)
Median number regimens before T0* (IQR)		3 (2-4)	1 (1-2)

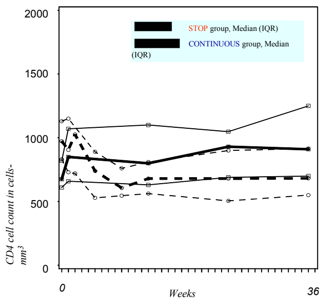
T0* Time at wich HAART is stopped

4. Results: plasma HIV-RNA

At the time of analysis, 18 of the 46 patients (39%) in the STOP group had reached week 36. Figure 1 shows the course of the HIV-RNA in plasma over the first 36 weeks. The median pVL of the 18 patients with measurement available at week 36 was 4.3 log copies/ml (IQR: 4.2-4.6). This figure is lower than the median pVL at start of HAART.



5. Results: CD4 cell count and disease progression



Of the 18 patients who had reached week 36, none had reached a CD4-cell count <300 cells/mm^3 while off HAART. The median CD4 count at week 36 was 680 cells/mm3 (IQR: 570-880).

Moreover, no new AIDS diagnoses occurred while patients were off HAART. All patients, including those who had not yet reached week 36 at the time of analysis, were alive.

6. Results: restart of HAART

Four patients had restarted HAART at the time of this report. Patients had chosen to reinitiate therapy after 2, 3 (two patients) and 5 months off HAART, respectively. All patients restarted for personal reasons: three patients restarted because they felt uncomfortable not taking pills and the fourth felt that the frequency of blood sampling in the study was too low.

7. Results: Plasma drug levels

In the STOP-group, 61% of the patients used a non-nucleoside reversed transcriptase inhibitor (NNRTI), 21% a protease inhibitor (PI) and 18 % a triple nucleoside containing regimen. Plasma drug levels were determined at week 0 and week 1. All PI plasma drug levels available at week 1 were undetectable and all available pVL< 50 copies/ml .

Plasma drug levels of patients taking a NNRTI were available at week 0 and week 1 in 24 of the 28 patients(86%). 15 of the 24(63%) complete sets drug levels were below lower limit of detection(LLD) at week 1. We could not find an association between the plasma drug levels of NNRTI at week 0 and 1 PVL at week 1 was available in 24(86%) of the 28 patients using NNRTI. All were < 50 copies/ml HIV-RNA at week 1 except one. In this patient plasma drug levels of efavirenz were 0.67 and <0.0 mg/l at week 0 and week 1 respectively and pVL were <50 copies/ml and 3649 copies/ml at week 0 and week 1 respectively.

8. Adverse events

We defined acute retroviral rebound syndrome (ARVS) as a peak in the pVL within 4 months after stopping HAART, that was higher than the baseline pVL, with a simultaneous occurrence of one or more of the following complaints: fever, malaise, lymfadenopathy, headache, sore throat, mucocutaneous events, diarrhoea, weight loss or nausea. We recorded hospitalisation in this period and scored the grade of the complaints based on information in the medical file of the patients.

Of the 46 patients who had stopped, 13 patients reported one or more complaints (28%). Of these patients, 11(24%) had mild complaints and 2 moderate complaints. In total, 8 patients (17%) had fever . Of the 13 patients who had complaints, only 6 (13%) were classified as 'possible ARVS' using the definition above. None of these patients were hospitalised or restarted HAART.

7. Conclusions

We conclude that it is safe to temporarily discontinue HAART in patients who started therapy at a CD4 >350 cells/mm^3 during the first 36 weeks:

- CD4$^+$ T-lymphocyte count did not decline below 300 cells/mm^3
- No AIDS-defining events occurred
- 13% of the patients stopping HAART experienced a (mild) self-limiting acute retroviral rebound syndrome

We conclude that it is efficacious to discontinue HAART in this group:

- Patients could remain without HAART at least 36 weeks
- No patients restarted HAART due to a decline of CD4$^+$ T-lymphocyte count

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