

# PREDICTIVE FACTORS OF THROMBOCYTOPENIA IN PATIENTS RANDOMIZED TO INTERMITTENT OR CONTINUOUS ANTIRETROVIRAL THERAPY IN THE ANRS 106 - WINDOW TRIAL

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## ABSTRACT

**Background:** The benefit of antiretroviral (ARV) therapy on HIV-related thrombocytopenia has been well reported. We addressed the predictive factors of thrombocytopenia in the setting of an intermittent, time-guided ARV treatment trial.

**Methods:** Sub-study of the ANRS-106 Window trial: 403 HIV+ patients (pts) under stable HAART (CD4 count >450/mm<sup>3</sup> and HIV-RNA <200 cp/ml for at least 6 months) randomized to either continuous (CT) or intermittent 8 weeks off – 8 weeks on therapy (IT) for 96 weeks. Cases of thrombocytopenia (platelet count <150x10<sup>3</sup>/µL) were reported throughout the study period. Only first occurrence is considered. Uni- and multivariate logistic regression models were used to define predictors of thrombocytopenia.

**Results:** Twelve pts withdrew consent before or at week 0. Baseline characteristics of the 391 pts included in the analysis were : 80% of male pts, with a median [IQR] age of 42 years [36; 48]; 8% had AIDS and 1% a history thrombocytopenic purpura (TP). Forty-five (12%) pts were infected by either HBV or HCV. Median CD4 was 741/µL [605; 915] with a median platelet count of 243x10<sup>3</sup>/µL [206; 283]. Ninety-five percent of pts were on a triple or more-drug regimen, including AZT and/or ddI in 68%.

Thrombocytopenia (<150x10<sup>3</sup>/µL) were reported in 69 pts: 50 IT (25.4%), 19 CT (9.8%) with a median time [IQR] of occurrence of 9 [8;40] and 40 [9;74] weeks in IT and CT arm, respectively. Significant platelet decrease (<50x10<sup>3</sup>/µL) was observed in 11 (9 and 2 in the IT and CT arm, respectively), two of them (IT arm) having mild hemorrhagic symptoms.

In univariate analysis, factors associated with thrombocytopenia, were : IT strategy with odds ratio estimates (OR) and [95%CI]=3.13 [1.77, 5.55], history of TP : OR=7.27 [1.19, 44.38], baseline CD4 : OR (by decrease of 100/µL)=1.25 [1.06-1.46] and low baseline platelet counts (by decrease of 50x10<sup>3</sup>/µL) : OR=3.20 [2.24-4.58].

No influence of age, CDC stage, AZT and/or ddI-based regimen or viral hepatitis co-infection was observed. In multivariate analysis, factors associated with increased risk of thrombocytopenia were IT strategy: OR=3.98 [2.10-7.57] p=0.0001, history of TP : OR=29.91 [1.71- 524.55] p=0.02 and a low platelet count : OR (by decrease of 50x10<sup>3</sup>/µL)=3.45 [2.33-5.09] p=0.0001.

**Conclusions:** Our study shows that in pts undergoing IT, there is a significant risk of thrombocytopenia in case of a history of TP and low baseline platelet count. These patients should be discouraged to undertake IT.

## BACKGROUND

ANRS 106 Window is an open-label, non-inferiority study involving 403 adults with CD4 cell counts of 450/µL or greater and plasma HIV1-RNA levels less than 200 copies/mL, randomly assigned to switch to an 8-week off, 8-week on regimen (IT) or to continue their antiretroviral regimen (CT). The primary endpoint was the proportion of patients reaching a confirmed CD4 cell count less than 300/µL.

Over 96 weeks, the proportion of pts meeting this endpoint was non-inferior in the intermittent group (3.6% versus 1.5%, upper bound of the 95%confidence interval of the difference : 5.6%). No AIDS-defining event was recorded. At week 96, the median decrease from baseline in the CD4 cell count was greater in the IT arm (-155 versus -8 cells/µL) whereas the proportion of pts with plasma HIV1-RNA levels less than 400 copies/ml were 81% and 90% in the IT (8 weeks after treatment resumption) and CT arm, respectively (P=0.02).

The deleterious effect of HIV on platelet count in ART-naïve patients is well known, mediated by both megakaryocytes infection and peripheral platelet destruction by IgG platelet antibodies or immune circulating complexes ; the benefit of antiretroviral therapy on HIV-related thrombocytopenia has also been well reported.

Few studies however underlined the risk of thrombocytopenia occurring during antiretroviral therapy interruption phases, either time- or CD4-guided.

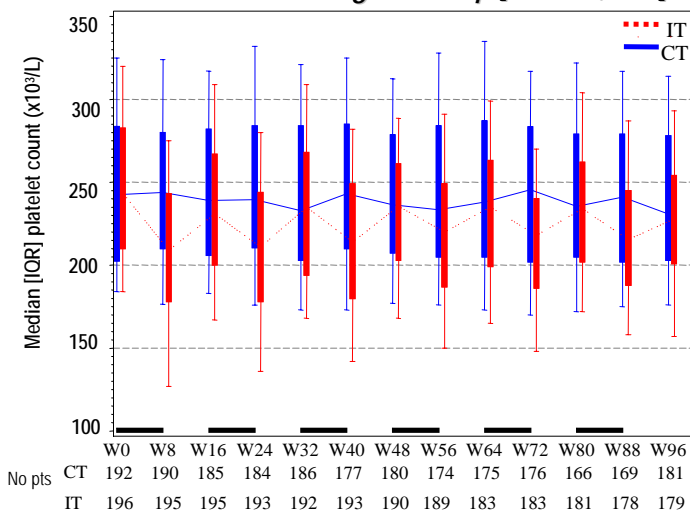
In this ANRS-106 Window trial substudy, we describe the median platelet count in the setting of a fixed-scheduled intermittent ART and assess the predictive factors of thrombocytopenia, defined as a platelet count below 150x10<sup>3</sup>/µL.

## BASELINE CHARACTERISTICS

|                                       | Thrombocytopenia <150x10 <sup>3</sup> /µL during follow-up<br>N = 69 (18%) | Overall study population<br>N = 391 |
|---------------------------------------|--|-------------------------------------|
| Male                                  | 57 (83%)   | 312 (80%)                           |
| Age                                   | 42 [37 ; 47]   | 42 [36 ; 48]                        |
| CDC stage C                           | 7 (10%)  | 32 (8%)                             |
| History of ITP                        | 3 (4%)   | 5 (1%)                              |
| HBV coinfection                       | 2 (3%)   | 10 (3%)                             |
| HCV coinfection                       | 10 (14%)   | 39 (10%)                            |
| Nadir CD4 count (µL)                  | 271 [197 ; 343]  | 280 [204 ; 371]                     |
| Baseline CD4 count (µL)               | 661 [557 ; 816]  | 741 [605 ; 915]                     |
| Platelet count (x10 <sup>3</sup> /µL) | 198 [168 ; 231]  | 243 [206 ; 283]                     |
| Haemoglobin (g/dL)                    | 14.5 [13.3 ; 15.3]   | 14.4 [13.5 ; 15.2]                  |
| > 3 ARV in regimen                    | 69 (100%)  | 373 (95%)                           |
| AZT in baseline regimen               | 32 (46%)   | 175 (45%)                           |
| ddl in baseline regimen               | 22 (32%)   | 127 (32%)                           |

## RESULTS

### Platelet count during follow-up [Median, IQR]



Dark lines on X-axis represent off-therapy periods

Severe thrombocytopenia (<50x10<sup>3</sup>/µL) episodes occurred in 11 pts (9 IT, 2 CT), 5 of whom switched to continuous therapy for these events. Only two patients experienced mild haemorrhagic symptoms (menometrorrhagia in one case and haematoma at blood venous puncture sites in the other).

No evidence of link between thrombocytopenia and other blood cell lineages abnormal counts (i.e. WCC, RCC) was observed.

## Univariate analysis

| Probability of having a platelet count <150x 10 <sup>3</sup> /µL | OR – CI <sub>95%</sub> | p      |
|--|------------------------|--------|
| Treatment arm (IT versus CT)                                     | 3.13 [1.77 – 5.55]     | 0.0001 |
| Baseline platelet count (step : -50x10 <sup>3</sup> /µL)         | 3.20 [2.24 – 4.58]     | 0.0001 |
| Baseline CD4 count (step : -100/µL)                              | 1.25 [1.06 – 1.46]     | 0.007  |
| History of ITP (yes versus no)                                   | 7.27 [1.19 – 44.38]    | 0.03   |
| Nadir CD4 count (step : -50/µL)                                  | 1.11 [0.97 – 1.26]     | 0.14   |
| HBC or HCV coinfection (yes versus no)                           | 1.61 [0.77 – 3.35]     | 0.21   |
| CDC stage (C versus A/B)   | 1.34 [0.56 – 3.24]     | 0.51   |
| Sex (woman versus man)   | 0.80 [0.41 – 1.58]     | 0.52   |
| Age (step : +10 years)   | 1.05 [0.79 – 1.40]     | 0.76   |
| Baseline haemoglobin (step : -0.5 g/dL)                          | 0.99 [0.83 – 1.18]     | 0.91   |
| AZT or ddI in baseline ARV regimen (yes versus no)               | 1.00 [0.58 – 1.76]     | 0.99   |

## Multivariate analysis

| Probability of having a platelet count <150x10 <sup>3</sup> /µL | OR – CI <sub>95%</sub> | p      |
|---|------------------------|--------|
| Treatment arm (IT versus CT)                                    | 3.98 [2.10 – 7.57]     | 0.0001 |
| Baseline platelet count (step : -50x10 <sup>3</sup> /µL)        | 3.45 [2.33 – 5.09]     | 0.0001 |
| History of ITP (yes versus no)                                  | 29.91 [1.71 – 524.55]  | 0.02   |
| Baseline CD4 count (step : -100/µL)                             | 1.17 [0.98 – 1.41]     | 0.09   |

## CONCLUSION

Our study shows that in pts undergoing IT, there is a significant risk of thrombocytopenia in case of a history of TP and low baseline platelet count. These patients should be discouraged to undertake IT.

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