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Development of thrombocytopenia and risk of AIDS and serious non-AIDS events in Europe

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BACKGROUND

Thrombocytopenia (TCP) is common in HIV+ individuals and may reflect underlying activated coagulation and inflammatory pathways.[1-3]

Associations between TCP and increased mortality have been reported,[4] but little is known about the relationship between TCP and clinical outcomes in treated HIV+ cohorts.

HYPOTHESIS

We hypothesise that patients with lower platelet counts have enhanced inflammation/ coagulation which will lead to an increase in serious non-AIDS defining events (NADEs) but not of AIDS defining events (ADEs).

STUDY AIMS

- To describe the prevalence of TCP in EuroSIDA and the factors associated with its development
- To assess whether the risk of fatal and non-fatal NADEs or ADEs are affected by measures of platelet count

MATERIAL AND METHODS

Inclusion Criteria

Patients aged >16 with at least one platelet count after 1/1/2005 (when platelets were routinely collected in EuroSIDA) with prospective follow up data and CD4 count or viral load measured within 6 months of baseline (defined as the first platelet measurement).

TCP: platelet count $\leq$100 x 10^9/L

NADEs[5]: pancreatitis, end-stage liver/renal disease, malignancies, cardiovascular events (excluding stroke).

Statistical analyses

Incidence rates and multivariate Poisson regression were used to identify factors associated with the development of TCP during prospective follow-up.

Multivariate Poisson regression was also used to assess the relationship between current platelet count or proportion of follow-up (%FU) with TCP and the incidence of ADEs and NADEs.

We also carried out sensitivity analyses requiring a repeated platelet count $\leq$100 x 10^9/L (at least 3 months apart) to confirm TCP and recalculating incidence rates for fatal and non-fatal ADEs and NADEs after lagging platelets by 6 months prior to clinical events.

RESULTS

Of 18,791 patients enrolled in EuroSIDA, 11,234 met the inclusion criteria. 561 (5.0%) had TCP at baseline (**Figure 1**).

After a median FU of 4.6y (43,745 PYFU), 944 patients developed TCP (IR 20.4/1,000 PYFU, 95% CI 19.1-21.7). These patients were more likely to come from Southern Europe, be IDUs, smokers and anaemic, as well as have positive hepatitis C antibody test, lower CD4, higher VL and lower baseline platelet counts.

There were 919 NADEs and 614 ADEs. Crude incidence of ADEs and NADEs increased as current platelet decreased or as %FU with TCP increased, although those with highest platelet counts had a slighter higher incidence of ADEs/NADEs (**Figure 2**).

Patients who developed TCP or had more % FU with TCP had significantly increased incidence of either NADEs or ADEs, but the association with NADEs was stronger. Those with the highest platelet counts have also a significantly higher risk of both ADEs and NADEs (**Table 1**).

Among NADEs, the adjusted incidence of malignancies (455 events), but not of cardiovascular events (245 events) was significantly higher in patients with current TCP and more %FU with TCP (**Figure 3**).

Sensitivity analyses rendered consistent results (data not shown).

CONCLUSIONS

- TCP was more strongly associated with NADEs than ADEs.
- Among NADEs, a lower platelet count precedes the diagnosis of cancer, but not of cardiovascular events.
- Studies to assess whether activated coagulation pathways may herald the development of cancer during treated HIV infection are warranted.

REFERENCES

1. Marks *et al*. Risk factors for thrombocytopenia in HIV-infected persons in the era of potent antiretroviral therapy. JAIDS 2009; 52:595-9
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4. Johannessen *et al*. Predictors of mortality in HIV-infected patients starting antiretroviral therapy in a rural hospital in Tanzania. BMC Infect Dis 2008;8:52
5. Mocroft A *et al*. Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. JAIDS 2010; 55:262-70

Figure 1

Flow chart for the study

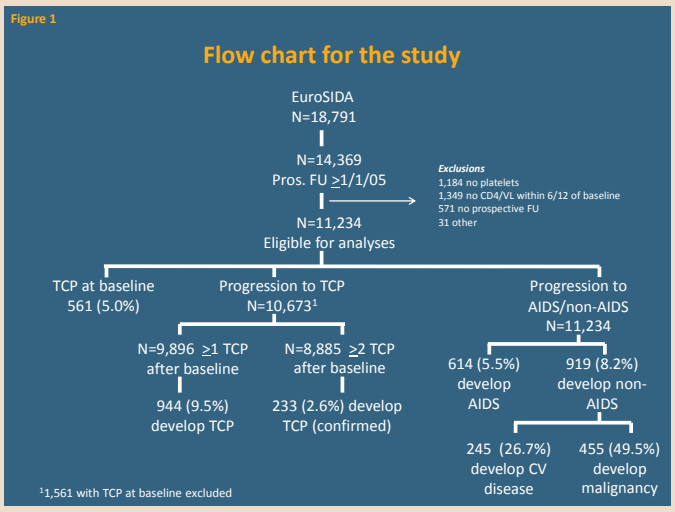


Figure 2

Crude incidence rates of ADEs and NADEs Relationship with current platelet count and % follow-up with TCP

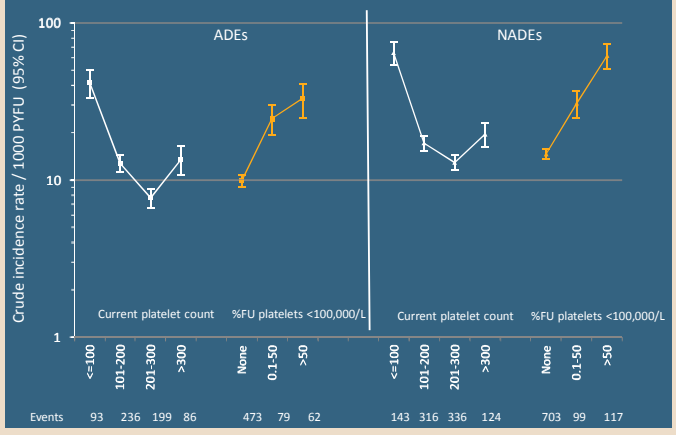


Table 1

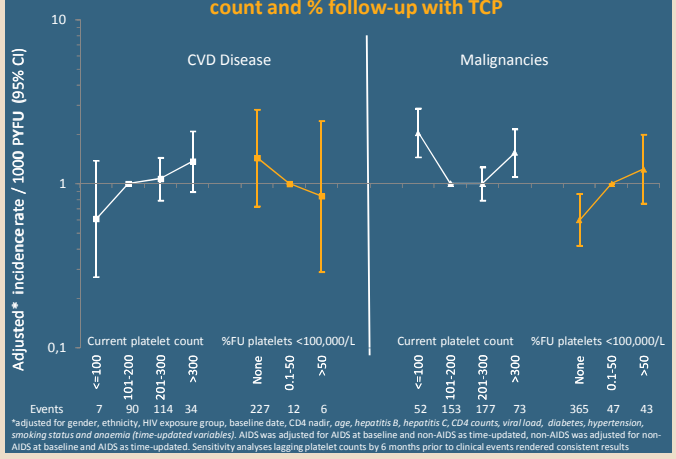
Adjusted* incidence rate ratios of ADEs and NADEs per current platelet count and proportion of follow-up time with thrombocytopenia

Clinical Outcome	Current platelet count (X 1,000/µL)				% follow up with TCP (platelets < 100,000/µL)		
	≤100	101-200	201-300	>300	0	0.1-50%	>50%
ADEs IRR (95% CI)	1.37 (1.04-1.82)	Ref	0.89 (0.72-1.11)	1.35 (1.01-1.81)	0.70 (0.52-0.95)	Ref	0.85 (0.56-1.28)
NADEs IRR (95% CI)	2.59 (2.06-3.24)	Ref	0.95 (0.80-1.12)	1.34 (1.05-1.71)	0.59 (0.47-0.76)	Ref	1.57 (1.15-2.14)

*adjusted for gender, ethnicity, HIV exposure group, baseline date, CD4 nadir, *age, hepatitis B, hepatitis C, CD4 counts, viral load, diabetes, hypertension, smoking status and anaemia (time-updated variables)*. AIDS was adjusted for AIDS at baseline and non-AIDS as time-updated, non-AIDS was adjusted for non-AIDS at baseline and AIDS as time-updated. Sensitivity analyses lagging platelet counts by 6 months prior to clinical events rendered consistent results

Figure 3

Association between CVD events, malignancies, current platelet count and % follow-up with TCP



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The EuroSIDA Study Group

The multi-centre study group of EuroSIDA (national coordinators in parenthesis)

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