A Switch to Raltegravir Does not Lower Platelet Reactivity in HIV Infected Individuals; A Randomized Controlled Trial

Wouter A. van der Heijden[1], Marjolein Bosch[1], Monique Keuter[1], Reinout van Crevel[1], Andre J van der Ven[1], Quirijn de Mast[1]

[1]Department of Internal Medicine, Radboud university medical center, Nijmegen, The Netherlands

Introduction

- Platelets not only play a pivotal role in hemostasis, but also in inflammation and immunity[1]
- HIV infection is associated with platelet hyperreactivity and increased platelet-monocyte aggregation[2]
- In a cross-sectional study *Tunjungputri et. al* showed reduced platelet reactivity and platelet-monocyte aggregation in individuals treated with a raltegravir-based regimen[2]

Objective

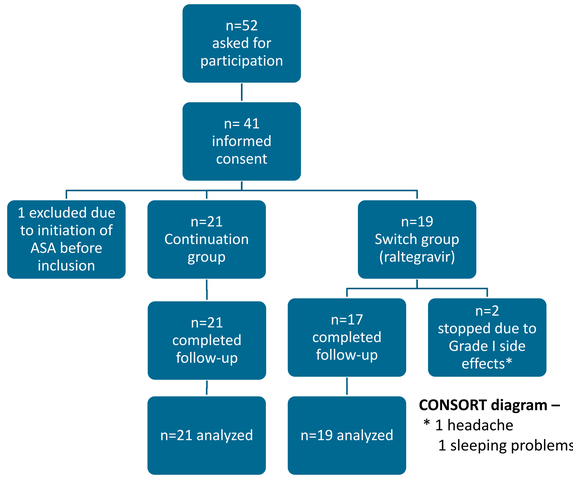
- To investigate whether switching a non-nucleoside reverse transcriptase inhibitor (NNRTI)- or protease inhibitor (PI)-based regimen to a raltegravir-based regimen reduces platelet reactivity and/or platelet-monocyte aggregates

Methods

- An investigator initiated, single-center, prospective randomized, open-label, blinded endpoint (PROBE) trial
- 40 adult virologically suppressed *(<40 copies) HIV-infected individuals receiving a standard backbone of two NRTI's with either a NNRTI or a boosted PI were enrolled.
- Participants were randomized (1:1) to continue the same ART regimen or to switch to raltegravir for 10 weeks
- Platelet function was assessed using a flow-cytometry-based assay measuring p-selectin expression and fibrinogen binding upon ex vivo stimulation
- Platelet-monocyte aggregation and soluble markers of inflammation and platelet activation were measured

Results

- No significant differences in platelet reactivity, platelet-monocyte complexes or soluble markers between the groups were observed at week 10 (see figures below)



Patient characteristics	Switch (n=19)	Continuation (n=21)	
Age	48.1 ± 8.9	50.5 ± 9.9	NS
Female sex	1 (5.2%)	0 (0%)	NS
Body mass index (kg / m^2)	26.3 (SD:4)	24.7 (SD:3)	NS
Current smoker	4 (21.1%)	6 (28.5%)	NS
Prior cardiovascular event	3 (15.8%)	1 (4.8%)	NS
Viral load (<80 copies/mL)	19 (100%)	21 (100%)	NS
Nadir CD4 (10^6 cells/L)	294	265	NS
CD4 count (10^6 cells/L)	760	650	NS
eGFR (ml/min /1.73m^2)	81 ±12	82 ±10	NS
HIV exposure(years)	10	9	NS
cART exposure (years)	7	6	NS

Conclusions

- A switch to a raltegravir-based regimen in virally suppressed HIV-infected individuals reduces neither platelet reactivity nor platelet-monocyte aggregation
- No changes in hsCRP or monocyte activation were observed in this trial

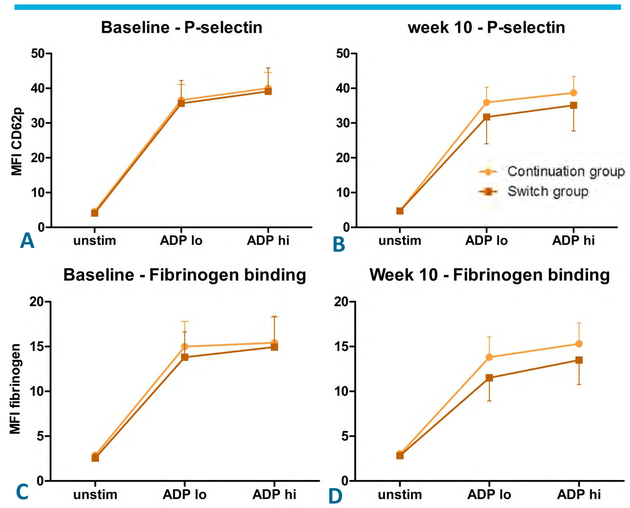


Figure 1 – Platelet reactivity by flow cytometry - P-selectin expression in median fluorescence intensity (MFI) after ex vivo stimulation with different concentrations of the platelet agonist adenosine diphosphate (ADP; lo: 7.81µM, hi: 125µM) at baseline (A) and after 10 weeks (B). Fibrinogen binding after ex vivo stimulation with ADP at baseline (C) and 10 weeks (D). No significant differences detected between groups. Data are expressed as means with SEM.

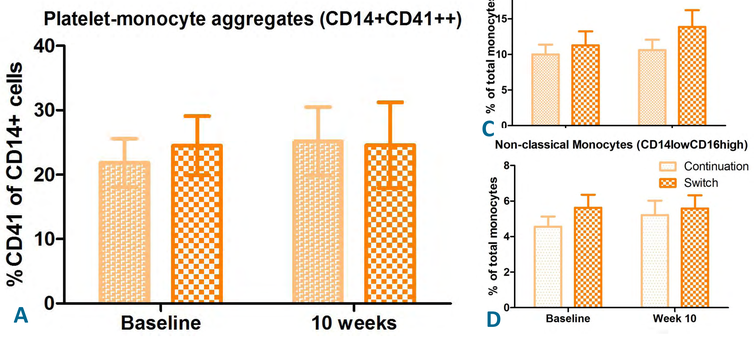


Figure 2 – Platelet-monocyte aggregation (above) and monocyte subsets (right) – Cells were gated on size, granularity and CD14 positivity subsequently the percentage of CD41 positive cells were recorded (A). No differences between groups were observed. Secondly monocyte subsets were assessed, without differences between groups at week 10 (B,C,D). Data are expressed as means with SEM. No significant differences were found between groups. CD14: CD16: Fc fragment of IgG, low affinity III receptor; CD41: integrin alpha chain 2b

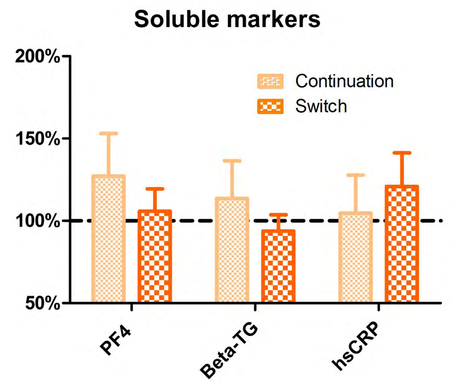


Figure 3 – Soluble markers of platelet activation and inflammation (above)– Platelet factor 4 (PF4; median: 9.46 ng/mL (IQR 5.1-14.0)), β-thromboglobulin (beta-TG; median: 22.7 ng/mL (IQR 16.7-36.8) and high sensitive C-reactive protein (hsCRP; median: 383 ng/mL (IQR: 184-1005) were measured by ELISA in citrated plasma. Data is depicted as percentual change compared to baseline (mean, SEM). No differences between groups were observed after treatment.

Discussion

- Both platelet hyperreactivity and platelet-leukocyte interaction are known risk factors for cardiovascular disease (CVD)[3,4]
- Other strategies focusing on the reduction of platelet activation should be explored to reduce the excess risk for CVD in HIV infection[5]
- Speculatively, strategies focusing on reduction of immune activation could prove effective in reducing platelet hyperreactivity

References:

1. Semple JW, Italiano JE, Jr., Freedman J. Platelets and the immune continuum. Nature reviews Immunology. 2011;11(4):264-74.
2. Tunjungputri RVDV, Andre; Schonsberg, Anna; Mathan, Till; Koopmans, Peter; Roest, Mark; Fijnheer, Rob; Groot, Philip; de Mast, Quirijn. Reduced platelet hyperreactivity and platelet-monocyte aggregation in HIV-infected individuals receiving a raltegravir-based regimen. 2014.
3. Freedman JE, Loscalzo J. Platelet–Monocyte Aggregates Bridging Thrombosis and Inflammation. Circulation. 2002;105(18):2130-2.
4. Hauguel-Moreau M, Boccara F, Boyd A, Salem JE, Brugier D, Curjol A, et al. Platelet reactivity in human immunodeficiency virus infected patients on dual antiplatelet therapy for an acute coronary syndrome: the EVERE2ST-HIV study. European heart journal. 2017.
5.Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, et al. HIV infection and the risk of acute myocardial infarction. JAMA internal medicine. 2013;173(8):614-22.

Wouter A. van der Heijden
Geert Grooteplein Zuid 8, 6525 GA Nijmegen, The Netherlands
☎ +31-24-3619610 ✉ Wouter.vanderHeijden@radboudumc.nl

Disclosures.
This work was supported by an unrestricted grant from MSD.
WH received a travel grant from MSD
Clinicaltrials.gov: NCT62383353

Radboudumc university medical center