Systemic inflammation markers after simplification to atazanavir/ritonavir plus lamivudine in virologically suppressed HIV-1-infected patients: ATLAS-M substudy

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Background: Biomarkers of systemic inflammation predict non-AIDS events and overall mortality in virologically suppressed HIV-1-infected patients.

Objectives: To determine whether switching to a dual antiretroviral maintenance therapy was associated with modification of biomarkers of systemic inflammation as compared with continuation of successful standard triple therapy.

Methods: In this substudy of the randomized ATLAS-M trial, we compared in virologically suppressed patients the impact at 1 year of simplification to a dual therapy with atazanavir/ritonavir plus lamivudine versus maintaining atazanavir/ritonavir plus two NRTI triple therapy on markers of systemic inflammation. Plasma levels of interleukin-6, C-reactive protein (CRP), soluble CD14 (sCD14) and D-dimer were quantified by ELISA at baseline and at 48 weeks.

Results: A subset of 139 of 266 randomized patients with available samples was analysed: 69 in the triple therapy arm and 70 in the dual therapy arm. The baseline biomarker levels were comparable between randomization arms. No significant differences in changes from baseline to week 48 were observed between arms (dual therapy versus triple therapy): IL-6, #0.030 versus #0.016 log10 pg/L; CRP, #0.022 versus #0.027 log10 pg/mL; sCD14, #0.016 versus +0.019 log10 pg/mL; and D-dimer, #0.031 versus +0.004 log10 pg/mL. A history of cancer was associated with higher baseline levels of IL-6 (#P = 0.002) and CRP (#P = 0.049). No relationship was observed between baseline biomarker level and persistent residual viraemia, HIV-1 DNA load, plasma lipids and other potential explanatory variables.

Conclusions: Simplification with atazanavir/ritonavir plus lamivudine does not affect plasma markers of systemic inflammation in virologically suppressed patients. The association between these findings and clinical outcomes requires further evaluation.

Introduction

Combination ART (cART) maintenance strategies have been proposed to reduce long-term drug toxicity, adverse effects and treatment costs in HIV-1-infected subjects.1,2 Within this context, the randomized ATLAS-M trial demonstrated the virological efficacy and safety of treatment simplification in virologically controlled HIV-1-infected patients to a dual regimen based on a boosted PI, i.e. atazanavir/ritonavir, plus lamivudine as a single NRTI, as compared with continuing a triple atazanavir/ritonavir-based therapy.3 Consistently, this dual therapy demonstrated non-inferior efficacy with respect to standard triple therapy in the SALT trial.4
The impact of this simplification strategy on systemic inflammation has not yet been assessed.

Individuals with HIV-1 infection have elevated concentrations of soluble biomarkers of inflammation, monocyte activation and coagulation that decrease but do not normalize with cART, although the sources of this excess systemic inflammation are only partially known.

The plasma levels of these biomarkers have been found to predict severe non-AIDS events and overall mortality, even in patients on fully suppressive cART. Thus, the quantification of these biomarkers may provide prognostic information in virologically suppressed patients.

Although in the ATLAS-M study there were no differences in plasma virological suppression between arms, dual therapy and triple therapy could impact the systemic inflammation differently through several mechanisms that have been hypothesized to be contributors to residual inflammation, including low-level HIV-1 replication in sanctuary sites (that may not be captured by HIV-1 levels in plasma), microbial translocation subsequent to HIV-1-related damage to the gastrointestinal tract, as well the potential direct effects of antiretrovirals on inflammatory pathways. In this substudy, of the ATLAS-M trial: 77.3% were male, mean age was 43 years (95% CI 42, 45), mean CD4 cell count was 660 (95% CI 615, 704), median time since HIV-1 diagnosis was 4.41 years (IQR 1.83, 9.58) and median time of cART exposure was 2.44 years (IQR 1.36, 5.00). As per the ATLAS-M trial inclusion criteria, all subjects had HIV-1 viral load <50 copies/mL; however, 35.2% displayed an undetectable viraemia and 64.8% had detectable residual viraemia. The current subset included 70 patients who were randomized to the dual therapy arm and 69 patients randomized to maintain the triple therapy.

The patients included in the two arms were similar for the main characteristics (see Table 1) and did not differ from those of the entire cohort (data not shown).

The baseline levels of the biomarkers in the dual therapy arm and the triple therapy arm were comparable: IL-6, 3.28 (95% CI 3.19, 3.36) versus 3.28 (95% CI 3.17, 3.38) log10 pg/L (P = 0.954); CRP, 6.48 (95% CI 6.33, 6.62) versus 6.50 (95% CI 6.39, 6.60) log10 pg/mL (P = 0.812); sCD14, 6.08 (95% CI 6.06, 6.11) versus 6.11 (95% CI 6.07, 6.14) log10 pg/mL (P = 0.241); and D-dimer, 5.50 (95% CI 5.45, 5.54) versus 5.48 (95% CI 5.43, 5.53) log10 pg/mL (P = 0.553).

When we compared biomarker level changes between baseline and week 48 within each treatment arm, we found no significant changes from baseline (see Figure 1).

Statistical analysis

Plasma levels of IL-6, CRP, sCD14 and D-dimer were log 10-transformed to approximate a normal distribution. Comparisons between and within treatment arms were made using the parametric unpaired and paired sample t-tests, as appropriate. IL-6 levels below the assay detection limit (18% and 16% of samples tested at baseline and week 48, respectively) were set to the lower level of detection.

Residual viraemia was categorized as detectable (1–49 copies/mL) or undetectable (< 1 copy/mL). Linear regression analysis was used to assess the factors associated with the biomarker levels.

All analyses were performed using the IBM-SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA).

Results

This substudy analysed 139 of 266 patients randomized in the ATLAS-M trial: 77.3% were male, mean age was 43 years (95% CI 42, 45), mean CD4 cell count was 660 (95% CI 615, 704), median time since HIV-1 diagnosis was 4.41 years (IQR 1.83, 9.58) and median time of cART exposure was 2.44 years (IQR 1.36, 5.00). As per the ATLAS-M trial inclusion criteria, all subjects had HIV-1 viral load <50 copies/mL; however, 35.2% displayed an undetectable viraemia and 64.8% had detectable residual viraemia. The current subset included 70 patients who were randomized to the dual therapy arm and 69 patients randomized to maintain the triple therapy.

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When we compared biomarker level changes between baseline and week 48 within each treatment arm, we found no significant changes from baseline (see Figure 1).

No significant difference in log10 change from baseline to week 48 was observed between arms (dual therapy versus triple therapy): IL-6 (pg/L), −0.030 (95% CI −0.098, +0.038) versus −0.016 (95% CI −0.108, +0.076) (P = 0.812); CRP (pg/mL), +0.022 (95% CI −0.074, +0.118) versus +0.027 (95% CI −0.076, +0.131) (P = 0.943); sCD14 (pg/mL), −0.016 (95% CI −0.042, +0.010) versus +0.019 (95% CI −0.015, +0.035) (P = 0.106); and D-dimer (pg/mL), −0.031 (95% CI −0.068, +0.006) versus +0.004 (95% CI −0.035, +0.043) (P = 0.198).

We have also performed subgroup analyses to explore the effect of removing specific drugs from the standard triple regimen. When patients were stratified according to the baseline regimen containing abacavir (100% combined with lamivudine) or tenofovir (98.3% combined with emtricitabine), we found no difference in change in any markers within or between dual and triple therapy arms (all P > 0.05). At week 48, the virological profile was comparable to that observed at baseline: most of the patients...
maintained HIV-1 RNA <50 copies/mL (97.8%), with 35.3% of them showing undetectable residual viraemia. Using linear regression, a history of cancer, including Burkitt lymphoma, Kaposi sarcoma, cervical cancer, breast cancer and Hodgkin’s lymphoma was associated with higher baseline levels of IL-6 [mean log10 difference +0.435 (95% CI +0.165, +0.705); P = 0.002] and higher baseline levels of CRP [mean log10 difference +0.374 (95% CI +0.001, +0.746); P = 0.049]. No relationship was observed between baseline biomarker level and residual viraemia, HIV-1 DNA load, plasma lipids and other potential explanatory variables (Table S1, available as Supplementary data at JAC Online).

**Discussion**

Despite complete virological suppression on cART, HIV-1-infected patients show a residual inflammatory response that has been related to long-term clinical consequences.7–11 Therefore, additional information regarding the effects of ART strategies on inflammatory biomarkers is required.

Here, we showed that the changes at 1 year of inflammation, monocyte activation and coagulation marker levels in patients on atazanavir/ritonavir with two NRTIs were comparable after simplification to a dual therapy with atazanavir/ritonavir with lamivudine, as compared with continuation of the previous effective triple therapy.
The levels of the biomarkers at baseline were similar to that previously reported in HIV-1-infected patients with HIV-1 RNA <50 copies/mL.6,10

Moreover, we found minimal and no significant changes between baseline and week 48 within study arms. This is consistent with a previous longitudinal study that showed a plateau phase following an initial decrease in inflammatory biomarker levels within the first year after cART-induced HIV suppression.6

Only few data exist regarding the effect of specific antiretrovirals on inflammation; most focus on differences between abacavir and tenofovir, given the association of abacavir with higher inflammation markers and with cardiovascular risks in some
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Author contributions

S. B. and F. L. performed the experiments, analysed the data and finalized the drafting of the paper. A. D. L. and S. D. G. contributed to article drafting. All other authors were responsible for collection of data and samples. All authors critically reviewed and subsequently approved the final version.

Supplementary data

Table S1 is available as Supplementary data at JAC Online.
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