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Assessment of monocyte activation and systemic inflammation markers in HIV-positive opioid users

A Kholodnaya[1]; K So-Armah[2]; D Cheng[3]; N Gnatienko[4]; G Patts[3]; J Samet[5]; M Freiberg[6] and D Lioznov[7]

[1]Infectious Diseases and Epidemiology, Saint Academician I.P. Pavlov First St. Petersburg State Medical University, St Petersburg, Russian Federation. [2]Clinical Addiction Research and Education Unit, Boston University School of Medicine, Boston, MA, USA. [3]Biostatistics & Epidemiology Data Analytics Centre, Boston University School of Public Health, Boston, MA, USA. [4]Boston Medical Center, Boston, MA, USA. [5]Clinical Addiction Research and Education Unit, Boston University School of Public Health, Boston, MA, USA. [6]Cardiovascular Medicine Division, Vanderbilt University Medical Center, Nashville, TN, USA. [7]Department of Infectious Diseases and Epidemiology, Academician I.P. Pavlov First St. Petersburg State Medical University, St Petersburg, Russian Federation

Background: With increased life expectancy for treated HIV-positive patients non-AIDS events and substance use have become especially relevant sources of morbidity and mortality. Chronic inflammation is thought to be a driver of non-AIDS events. We hypothesise that opioid use increases intestinal permeability and bacterial translocation from the gut into blood and leads to increased systemic inflammation and increased morbidity and mortality. Our primary objective was to investigate the association between opioid use and soluble CD14 (sCD14), a biomarker of monocyte activation that indicates the presence of components of gram-negative bacteria in blood. We also assessed the association of opioid use with inflammation (interleukin-6 [IL-6]) and altered coagulation (D-dimer).

Methods: We analysed data from the Russia ARCH study – an observational cohort of 351 HIV-positive antiretroviral therapy-naive individuals followed over two years. Plasma levels of sCD14 (primary outcome), IL-6 and D-dimer (secondary outcomes), HIV viral load and CD4 count were evaluated at baseline, 12 and 24 months. Data on opioid use (the main independent variable) were collected through self-report. Participants were categorised into three groups according to their history of opioid use: (1) current opioid use – last opioid use within past 30 days (n = 121); (2) prior opioid use – no use in past 30 days (n = 186); 3) never opioid use (n = 44). Linear mixed effects models (adjusting for age, gender, body mass index, HIV viral load, years since first HIV-positive test, alcohol consumption, diarrhoea and use of NSAIDs) were used to evaluate the associations between opioid use and the biomarkers. Variables representing concomitant liver disease (i.e. liver fibrosis, hepatitis C, hepatitis B) were explored as potential effect modifiers.

Results: In adjusted models, compared to never opioids users, sCD14 levels were significantly higher among current users (adjusted mean difference 259.5 ng/mL [95% CI 77.0 to 441.9], $p = 0.008$) but not prior users (adjusted mean difference 116.7 [−54.4 to 287.7], $p = 0.170$). IL-6 and D-dimer were higher among those with current and prior opioid use (Table 1).

Conclusions: Opioid use in HIV-positive participants is associated with an increase in monocyte activation and higher inflammatory response. The underlying mechanism for this association is not known. However, it is possible that opioid use may lead to intestinal permeability and chronic systemic inflammation.

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Impact of CMV on liver progression in HIV/HCV/CMV co-infected patients in a large cohort of HIV-infected patients

S Vita[1]; P Lorenzini[2]; M Lichtner[3]; M Giulia[4]; C Mastroianni[5]; A Bandera[6]; A Di Biagio[7]; C Pinnetti[8]; A Calcagno[9]; A Castagna[10]; A Antinori[11]; A d'Arminio Monforte[12]; on behalf of Icona Foundation Study Group

[1]Public Health and Infectious Disease, SM Goretti Hospital, Rome, Italy. [2]Clinical Department, National Institute of Infectious Diseases Lazzaro Spallanzani, Rome, Italy. [3]Public Health and Infectious Disease, Sapienza University of Rome, Polo Pontino, Rome, Italy. [4]Department of Health Sciences/Clinic of Infectious Diseases, University of Milan, Rome, Italy. [5]Public Health and Infectious Disease, Sapienza University of Rome, Rome, Italy. [6]Azienda Socio Sanitaria Territoriale di Monza, San Gerardo Hospital, University of Milano-Bicocca, Rome, Italy. [7]Clinic of Infectious Diseases, Ospedale Policlinico San Martino, Genova, Italy. [8]Division of Infectious Diseases, National Institute of Infectious Diseases Lazzaro Spallanzani, Rome, Italy. [9]Department of Medical Sciences, University of Turin, Amedeo di Savoia Hospital, Turin, Italy. [10]Infectious Diseases Department, IRCCS San Raffaele, Milan, Italy. [11]HIV/AIDS Department, National Institute of Infectious Diseases Lazzaro Spallanzani, Rome, Italy. [12]Department of Health Sciences, ASST Santi Paolo e Carlo, S. Paolo Hospital, University of Milan, Milan, Italy

Background: CMV seropositivity has been linked with severe non-AIDS events/deaths and subclinical carotid artery disease in HIV-infected individuals [1,2]. CMV/HCV/HIV co-infected women have been shown to display higher CMV IgG levels versus HIV mono-infected [3]; likewise HIV/HCV/CMV co-infected patients have higher HCV viral load, suggesting a persistent interaction between viruses. We evaluated prevalence and impact of CMV-Ab on liver progression and AIDS events in HIV/HCV/CMV co-infected subjects in the ICONA cohort.

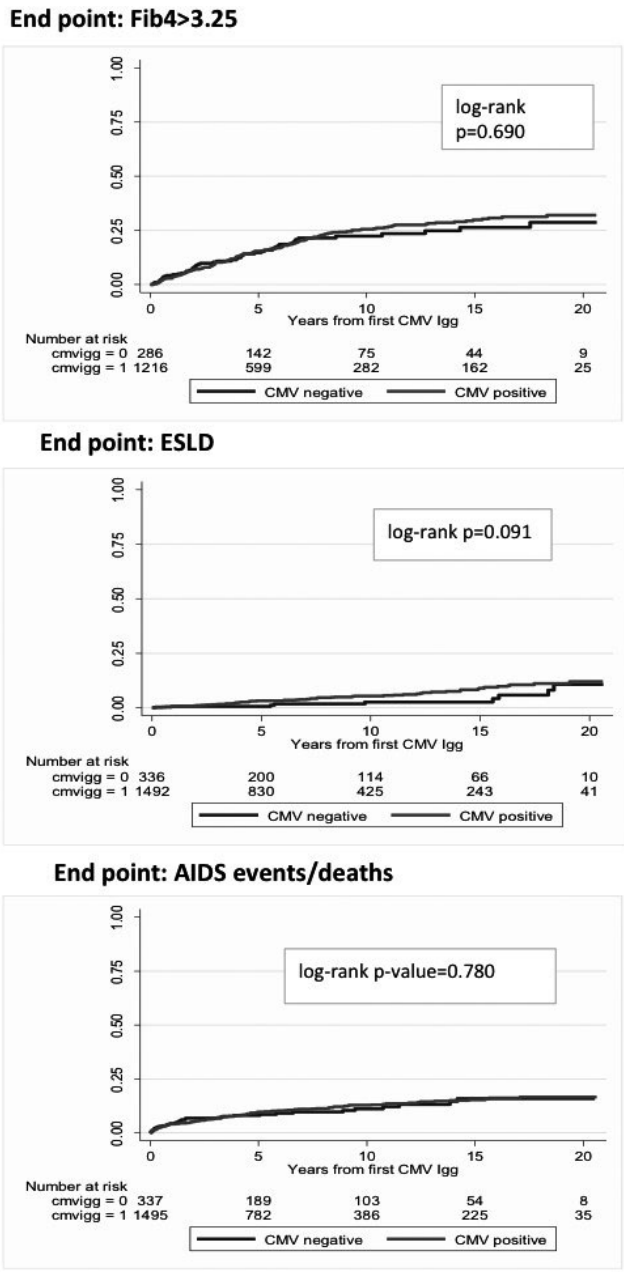
Materials and methods: We included patients from ICONA with ≥1 CMV-IgG and HCV-Ab available, at least one follow-up visit and no end stage liver disease (ESLD) at baseline. Three different endpoints: (1) first of two consecutive Fib-4 ≥ 3.25, 2) ESLD, 3) AIDS-defining event/death. Subjects were followed from first CMV available test (baseline) to first event/last observation/first negative HCV-RNA. Three separate Cox regression models were used.

Results: Eight thousand and ninety-eight patients had known baseline CMV IgG serostatus, of these 1994 (25%) were HCV-Ab positive and included in the analysis; 82% (1633) were HIV/CMV/HCV co-infected, while 18% (361) were HIV+/CMV-/HCV+. Two populations differed at

Abstract P227 – Table 1. Association between opioid use category and plasma concentrations of sCD14, IL6 and D-dimer. Linear mixed effects model

	sCD14 adjusted mean difference (95% CI)	IL-6 adjusted ratio of means[a] (95% CI)	D-dimer adjusted ratio of means[a] (95% CI)
Current opioid use (within past 30 days)	259.5 (77.0 to 441.9) $p = 0.008$	2.130 (1.576 to 2.879) $p < 0.001$	2.062 (1.519 to 2.799) $p < 0.001$
Prior opioid use	116.7 (−54.4 to 287.7) $p = 0.170$	1.333 (1.005 to 1.767) $p = 0.046$	1.682 (1.257 to 2.250) $p = 0.001$
Never opioid use	Reference group	Reference group	Reference group

We did not detect interaction effects from liver disease.
[a]represents the ratio of means after back transformation from natural log scale.



Abstract P228 – Figure 1. KM analysis for the three endpoints: Fib-4 index ≥3.25, end stage liver disease, AIDS events/death.

baseline only for CD8 count (median 823 in CMV- vs. 903 in CMV+, $p = 0.007$) and nadir CD4 (<200 70.4% in CMV- vs. 76.4% in CMV+, $p = 0.007$). No differences were observed for liver-related parameters (AST, ALT, Fib-4, APRI). When considering Fib-4 index ≥3.25 endpoint on 1490 subjects with baseline Fib-4 < 3.25, ESLD events were recorded on 13,741 PYFU (IR 0.5 per 100 PYFU [95% CI 0.4 to 0.7]). No differences were found according to CMV infection (Figure 1). Protective factors for Fib-4 progression were female sex and homosexual as mode of HIV transmission versus IVDU, while older age and higher Fib-4 index at baseline were associated with higher risk of the outcome. AIDS-defining events or AIDS-related death occurred in 207 patients (180 and 27 respectively) over 12,973 PYFU (IR 1.6 per 100 PYFU [95% CI 1.4 to 1.8]). Patients with CMV infection presented not significant higher risk respect those without infection. Females, CDC stage C and baseline Fib-4 > 3.25 were associated with higher risk of the outcome, while reduced risk was associated to baseline CD4 > 500 cells/mm^3 and nadir CD4 > 200 cells/mm^3.

Conclusion: In our study population of HCV/HIV co-infected subjects, CMV IgG positivity does not seem to be associated with a higher risk of liver and AIDS progression. The current use of DAA could allow us to evaluate the impact of HCV eradication in this specific population.

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The importance of serological testing and risk factors of measles, mumps, rubella and VZV among HIV-infected adults in Istanbul, Turkey during measles outbreak in Europe

O Altuntas Aydin[1]; S Senoglu[1]; H Kumbasar Karaosmanoglu[1]; Z Yesilbag[1] and A Aydin[2]

[1]Infectious Diseases and Clinical Microbiology, University of Health Sciences, Bakirkoy Dr Sadi Konuk Training and Research Hospital, Istanbul, Turkey. [2]Neurosurgery, University of Health Sciences, FTR Training and Research Hospital, Istanbul, Turkey

Background: Measles, mumps, rubella (MMR) and varicella zoster virus (VZV) infection can cause serious diseases and complications in HIV/AIDS patients. Due to successful vaccination programmes measles has become neglected in Turkey. Even though welcoming more than 3 million immigrants from Syria in the last seven years, measles outbreak has not been encountered in our country. However, recent outbreaks of measles are ongoing in Europe, especially in Italy, France, Romania and Turkey's neighbourhood Greece [1]. The objective of this study was to determine of MMR and VZV seronegativity and the risk factors associated being seronegative in HIV-infected adults in Istanbul, Turkey.

Materials and methods: All HIV-infected patients in our cohort who had MMR and VZV serological tests performed between January 2016 and May 2018 were retrospectively identified. Sera were tested for MMR and VZV IgG using commercial immunoassays. Age, gender, CD4 cell counts, MMR and VZV IgG serological results were evaluated from the records. Statistical analyses were performed by using SPSS Statistics v.21.0. Categorical variables were compared using chi-square test and Fisher's exact test.

Results: MMR and VZV IgG serologies were available in 415 of 712 patients in active follow-up (58.2%). Out of 415 naive patients 88.6% were men and median age was 35.6 years (range 18 to 67). Seronegativity was found in 3.9% for measles, 4.8% for rubella, 8.2% for mumps and 3.4% for VZV. Among 18.7% measles, 23.5% mumps, 35% rubella and 7.1% varicella IgG seronegative patients CD4 cell count was less than 200/mm^3. Being born after 1983 is strongly associated with seronegativity against measles ($p = 0.00$) and a nadir CD4 cell count below 200/mm^3 is independently associated with rubella seronegativity ($p = 0.013$).

Conclusions: There is high need for MMR vaccination in HIV-infected patients in Turkey born in 1983 or later. Measles continues to spread across Europe as the vaccination coverage in many European countries is suboptimal. Systematic measles antibody screening and vaccination should be performed in HIV-infected individuals to prevent serious disease and complications in the era of vaccination.