Abstracts from the current global iterature: Discordant virological and immunological response in anti-retroviral therapy

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Clinical outcome of HIV-infected patients with discordant virological and immunological response to antiretroviral therapy

A. Zoufaly, M. an der Heiden, C. Kollan, J. R. Bogner, G. Fätkenheuer, J. C. Wasmuth, M. Stoll, O. Hamouda, J. van Lunzen literature and the ClinSurv Study Group. J Infect Dis 2011;203:364-71.

Background: A subgroup of human immunodeficiency virus type 1 (HIV-1)–infected patients with severe immunodeficiency show persistently low CD4+ cell counts despite sustained viral suppression. It is unclear whether this immuno-virological discordance translates into an increased risk for clinical events. *Materials and Methods*: This study was a data analysis from a large multicenter cohort incorporating 14,433 HIV-1–infected patients in Germany. Treatment-naive patients beginning antiretroviral therapy (ART) with CD4+ cell counts <200 cells/μl who achieved complete and sustained viral suppression <50 copies/ml (n = 1318) were stratified according to the duration of immuno-virological discordance (failure to achieve a CD4+ cell count ≥200 cells/μl). Groups were compared by descriptive and Poisson statistics. The time-varying discordance status was analyzed in a multivariable Cox model. *Results*: During a total of 5038 person-years of follow-up, 42 new AIDS events occurred. The incidence rate of new AIDS events was highest in the initial 6 months of complete viral suppression (immuno-virological discordance group, 55.06; 95% confidence interval (CI) 30.82-90.82; and immune responder group, 24.54; 95% CI, 10.59-48.35) and decreased significantly by 65% per year in patients with immuno-virological discordance (incidence risk ratio, 0.35; 95% CI, 0.14-0.92; P = 0.03). Immuno-virological discordance and prior AIDS diagnosis were independently associated with new AIDS events (hazard ratio, 3.10; 95% CI, 1.09-8.82; P = 0.03). *Conclusion*: Compared with immune responders, patients with immuno-virological discordance seem to remain at increased risk for AIDS. Absolute risk is greatly reduced after the first 6 months of complete viral suppression.

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Skewed T-cell maturation and function in HIV-infected patients failing CD4+ recovery upon long-term virologically suppressive HAART

Giulia Marchetti, Lidia Gazzola, Daria Trabattoni, Francesca Bai, Giuseppe Ancona, Laurenzia Ferraris, Luca Meroni, Massimo Galli, Mario Clerici, Andrea Gori, Antonella d'Arminio Monforte. AIDS 2010;24:1455-60.

Objective: Analysis of functionally defined T-cell differentiation in HIV-infected patients with low CD4+ on virologically suppressive HAART is crucial to design clinically efficacious treatments. *Materials and Methods*: We cross-sectionally investigated the maturation (CD45RA/CCR7, CD7) and function (antigen-specific enzyme-linked immunosorbent spot assay (ELISPOT),

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interleukin-2 (IL-2)/interferon-γ–producing cells) of CD4+ and CD8+ T cells in 34 HIV-infected immunological nonresponders (INRs): CD4+ cell count less than or equal to 200 cells/μl, HIV-RNA 50 copies/ml or less, as compared to 20 full responders (CD4+ >500 cells/μl, HIV-RNA <50 copies/ml). *Results*: We describe skewed T-cell maturation in INRs with outgrowth of effector memory CD45RA − CCR7 − CD4+/CD8+ and Th2-committed CD7 − CD4+, and reduced unprimed-naive T cells ($P = 0.001$). Functionally, INRs display reduced Gag-specific ELISPOT ($P = 0.04$) and IL-2–secreting CD8+ ($P = 0.08$), while showing CMV-specific responses comparable to full responders. *Conclusion*: CD4 lymphopenia on HAART results in skewed, senescent T-cell maturation profile, inefficient T-helper function, and poor HIV-specific CD8+ response. This delineates a functional/phenotypic T-cell pattern that correlates with unfavorable clinical outcome.

AF6 The HACART Study: Predictors of immuno-virologic outcomes and immuno-virologic discordance among adults on HIV antiretroviral therapy in Nigeria

Chuka J. Anude, Emeka Eze, Henry C. Onyegbutulem, Man Charurat, Mary-Ann Etiebet, Samuel Ajayi, Patrick Dakum, Oluyemisi Akinwande, Chris Beyrer, Alash'le Abimiku, William Blattner. JAIDS doi: 10.1097/01.qai.0000413826.88167.93.

Background: Patient retention and positive immuno-virologic outcomes are the key goals of any HIV treatment program. Information on predictors of immuno-virologic failure and discordance and their associations with clinical, demographic, socioeconomic, and behavioral risk factors are not well described in Nigeria, as HIV viral load testing is not routinely offered in public HIV treatment programs. *Materials and Methods*: The HIV AIDS Care and Anti-Retroviral Therapy (HACART) study was a large multi-center observational clinic-based cohort study of 2585 initially ART-naive adults who started HAART between April 2008 and February 2009. A total of 628 out of 1780 patients alive and active at 12 months were randomly selected for in-depth analyses. *Results*: Virologic suppression rate (<400 copies/mLl) was 76.7%, immunologic recovery rate (CD4 change from baseline ≥50 cells/mm^3) was 77.4%, and immuno-virologic discordance rate was 33%. In multivariable logistic regression controlling for adherence, the risk of virologic failure was significantly associated with age <30 years (OR 1.76; 95% CI: 1.09-2.84), anemia (hemoglobin <10 g/dl) (OR 1.60; 95% CI: 1.04-2.48), residential distance 51-100 km (OR 0.41; 95% CI: 0.20-0.87), and post-secondary education (OR 0.53; 95% CI: 0.32-0.90). The risk of immunologic failure was associated with male gender (OR 1.65; 95% CI: 0.01-2.67) and age <30 years (OR 1.71; 95% CI: 1.19-2.63). The risk of immuno-virologic discordance was associated with age <30 years (OR 1.64; 95% CI: 1.06-2.53) and post-secondary education (OR 0.61; 95% CI: 0.38-0.98). *Conclusion*: Although favorable immuno-virologic outcomes can be achieved in this large ART program in Nigeria, immuno-virologic discordance was observed in a third of the patients. Baseline anemia assessment and management (anti-malarials, anti-helminthics, hematinics, etc.) may help improve virologic outcomes. Intensifying treatment preparation and nutritional activities, and focusing on young patients, males, and persons with less than post-secondary education may help obtain favorable immuno-virologic outcomes.

Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort

Steven F. L. van Lelyveld, Luuk Gras, Anouk Kesselring, Shuangjie Zhang, Frank De Wolf, Annemarie M. J. Wensing, Andy I. M. Hoepelman; on behalf of the ATHENA national observational cohort study. AIDS 2012;26:465-74.

Objective: We investigated the risk of AIDS and serious non-AIDS–defining diseases (non-ADDs) according to the degree of immunological recovery after 2 years of virological successful antiretroviral therapy (HAART). *Design*: Retrospective observational cohort study including HIV-infected patients treated with HAART resulting in viral suppression (<500 copies/ml). *Materials and Methods*: Patients were grouped according to their CD4 cell count after 2 years of HAART: CD4 cell count less than 200 cells/μl (group A), 200–350 cells/μl (group B), 351-500 cells/μl (group C), or more than 500 cells/μl (group D). Analysis was done to assess predictors for poor immunological recovery and the occurrence of a composite endpoint [death, AIDS, malignancies, liver cirrhosis, and cardiovascular events (CVEs)], non-ADDs, CVEs, and non-AIDS–defining malignancies (non-ADMs). *Results*: Three thousand and sixty-eight patients were included. Older age, lower CD4 cell nadir, and lower plasma HIV-RNA at the start of HAART were independent predictors for a poor immunological recovery. The composite endpoint, non-ADDs, and CVE were observed most frequently in group A (overall log rank, $P < 0.0001$, $P = 0.002$, and $P = 0.01$,

respectively). In adjusted analyses, age was a strong independent predictor for all endpoints. Compared with group A, patients in group D had a lower risk for the composite endpoint (hazard ratio 0.54; (95% confidence interval (CI) 0.33-0.87); Patients in group B had a lower risk for CVEs (hazard ratio 0.34 (95% CI 0.14-0.86)). *Conclusion*: Poor immunological recovery despite virological successful HAART is associated with a higher risk for overall morbidity and mortality and CVEs in particular. This study underlines the importance of starting HAART at higher CD4 cell counts, particularly in older patients.

Reduced thymic output is a major mechanism of immune reconstitution failure in HIV-infected patients after long-term antiretroviral therapy

Taisheng Li, Ning Wu, Yi Dai, Zhifeng Qiu, Yang Han, Jing Xie, Ting Zhu, Yanling Li. Clin Infect Dis (2011) 53:944-51. doi: 10.1093/cid/cir552 First published online: September 29, 2011.

Background: Approximately 20% of human immunodeficiency virus type 1 (HIV-1)–infected adults do not normalize their CD4+ T lymphocytes after long-term effective highly active antiretroviral therapy (HAART). The mechanistic basis for this failure is unclear. *Materials and Methods*: Seventy-four patients were followed up regularly for 3-7 years. Patients with undetectable plasma viral load (<50 copies/ml) for over 12 months were further classified into two groups: (1) immunological nonresponders, whose CD4+ T-cell count was <200/μl or <20% compared with baseline and (2) immunological responders, whose CD4+ T-cell count was > 300/μl or > 30% compared with baseline. *Results*: Compared with 17 immunological responders, 13 immunological nonresponders had a lower magnitude of naive CD4+ T-cell increase, a lower percentage of recent thymic immigrants (CD31+%), and a higher percentage of activated CD8+ T cells. Furthermore, unlike CD4+ T cells, which increased along with the decrease of viral load, the percentage of recent thymic immigrants (CD31+%) had little change in the majority of patients. These data were fit into a mathematical model, from which we deduced that the initial rate of CD4+ T-cell restoration is associated significantly with the percentage of recent thymic immigrants (CD31+%). *Conclusions*: Our data indicate that the failure to restore CD4+ T-cell count following HAART was associated primarily with a defect in recent thymic immigrants, which suggests the existence of thymus exhaustion.

Immunologic failure despite suppressive antiretroviral therapy is related to activation and turnover of memory CD4 cells

Michael M. Lederman, Leonard Calabrese, Nicholas T. Funderburg, Brian Clagett, Kathy Medvik, Hector Bonilla, Barbara Gripshover, Robert A. Salata, Alan Taege, Michelle Lisgaris, Grace A. McComsey, Elizabeth Kirchner, Jane Baum, Carey Shive, Robert Asaad, Robert C. Kalayjian, Scott F. Sieg, Benigno Rodriguez. J Infect Dis (2011) 204:1217-26. doi: 10.1093/infdis/jir507.

Background: Failure to normalize CD4+ T-cell numbers despite effective antiretroviral therapy is an important problem in human immunodeficiency virus (HIV) infection. *Materials and Methods*: To evaluate the potential determinants of immune failure in this setting, we performed a comprehensive immunophenotypic characterization of patients with immune failure despite HIV suppression, persons who experienced CD4+ T-cell restoration with therapy, and healthy controls. *Results*: Profound depletion of all CD4+ T-cell maturation subsets and depletion of naive CD8+ T cells was found in immune failure, implying failure of T-cell production/expansion. In immune failure, both CD4+ and CD8+ cells were activated, but only memory CD4+ cells were cycling at increased frequency. This may be the consequence of inflammation induced by *in vivo* exposure to microbial products, as soluble levels of the endotoxin receptor CD14+ and interleukin 6 were elevated in immune failure. In multivariate analyses, naive T-cell depletion, phenotypic activation (CD38+ and HLA-DR expression), cycling of memory CD4+ T cells, and levels of soluble CD14 (sCD14) distinguished immune failure from immune success, even when adjusted for CD4+ T-cell nadir, age at treatment initiation, and other clinical indices. *Conclusions*: Immune activation that appears related to exposure to microbial elements distinguishes immune failure from immune success in treated HIV infection.