

Response to Antiretroviral Therapy: Immunological Aspects and Emerging Problems

Ivano Mezzaroma

Department of Clinical Medicine, Sapienza–University of Rome, Italy

As immunologists, our research interests are mainly related to primary and acquired immune deficiencies. Regarding HIV-1 infection, our researches initially addressed the immunological mechanisms underlying the immune reconstitution during cART and the discordant response to antiretroviral therapies. Antiretroviral therapy in HIV-1-infected individuals has a broad spectrum of clinical outcomes. In the majority of patients, plasma viral load becomes undetectable and CD4⁺ T-cells increase over time. However, in a number of subjects a discrepancy between plasma viral load and the CD4⁺ T-cell recovery is observed. CD4⁺ T-cell count cannot increase despite full plasma viral load suppression (immunologic non responder). Defective immune reconstitution may depend on several factors including previous therapeutic failure, duration of antiretroviral therapy, low CD4⁺ T-cell count at the initiation of cART, advanced stage of disease, low adherence to therapy, and previous treatment interruptions. There is no definitive evidence that age, viral strain/clade, or host genetic factors play a role in this different response to cART. The increased T-cell activation/apoptosis has been associated with a lack of effective immunologic response. Viral replication in lymphoid tissues, despite undetectable plasma viral load, has been proposed as the underlying mechanism of cellular activation. However, this “paradoxical response” probably can be associated with other events. Insufficient CD4⁺ T-cell repopulation may be due to a thymus failure or a defect in bone marrow function. The toxic effect of antiviral drugs on T- and B-cell precursors, the stage of disease, and the low number of CD4⁺ T-cells before cART may also account for this insufficient T-cell renewal. Indeed, an imbalance in the production of cytokines such as TNF, IL-2 and IL-7 may also be a crucial event for the induction of reduced immune reconstitution. From a clinical point of view, we posed a particular attention at the treatment of multi-drug experienced patients: this is an important concern in the management of HIV-1 disease; partially solved by the availability of new drugs acting at different phases of viral replication, as in this setting the discordant response is quite frequent. Taking in account that immune recovery during cART is linked both to the activity of antiviral drugs, as well as to the regenerative capability of thymus and bone marrow, we focused our efforts on the study of the central mechanisms underlying lack of immunological response in the presence of a complete control of HIV-1 replication under cART. In this field we have studied the role exerted by the damage of the bone marrow functions due to HIV-1 infection and its relationship with the recovery of the immunological response. Hematological abnormalities frequently occur in patients infected with HIV-1. Increasing evidence indicates that bone marrow suppression results from viral infection of accessory cells, with impaired stromal function and alteration of hematopoietic growth factor network. We investigated the effects of antiretroviral therapy on cytokine and chemokine production by hematopoietic and stromal cells in HIV-1-infected subjects before and during cART. Compared with uninfected controls, an altered cytokine and chemokine production by bone marrow cells has been observed: this altered pattern is characterized by decreased IL-2 and elevated TNF- α , MIP-1 α , MIP-1 β , and RANTES levels, along with a defective bone marrow clonogenic activity. Antiretroviral therapy determined an amelioration of stem cell activity and a restoration of

stromal cell pattern, in parallel with the normalization of functional and morphologic characteristics of stromal cells. We also demonstrated that an altered clonogenic capability and a defective stromal cell function characterize the bone marrow of HIV-infected subjects with low CD4⁺ T cell counts during cART. In fact, the altered pattern of inflammatory cytokines in bone marrow may impair hemato-lymphopoiesis in HIV-1 infected subjects who do not experience reconstitution of CD4⁺ T cells despite suppression of virus replication while receiving cART (so called immunological non-responders). Moreover, we analyzed these aspects at peripheral blood level, studying T cell phenotypes and their functions involved in immune recovery during cART. The reduced expression of IL-7R α associated with the persistent immune activation and the alteration of Treg frequencies in part explains the low level of CD4⁺ T cells observed in patients with discordant response.

A more recent field of research is related to the chronic side effects occurring with the use of different antiretroviral drugs described in HIV-1 infected population under cART. An increasing number of clinical studies suggest that subjects infected with HIV-1 have a significant increase in cardiovascular risk as well as in renal impairment and bone mineral density alterations, for a number of reasons not yet fully clarified. Among these, a key role is played by HIV-1 itself as well as by the immune hyper activation and the chronic inflammation that characterize HIV-1 infection. Furthermore, alterations in lipid and glucose metabolisms, associated or not with cART use are well described. Initially, the metabolic toxicity has been described mainly in patients treated with protease inhibitors (PIs). The metabolic abnormalities are the underlying mechanism by which PIs use results in an increase in cardiovascular events, directly related to the time of exposure to this class of drugs. Recently, other studies showed that there is an increased risk of myocardial infarction in patients treated with abacavir, whereas tenofovir use is mainly linked with renal impairment and bone mineral density decrease. These aspects are important tools in the management of HIV-1 infected subjects. Clarify these points and understand the mechanisms underlying these problems would allow us to a more accurate selection of patients to who administer different schemes of cART.

***Corresponding author:** Ivano Mezzaroma, Department of Clinical Medicine, Sapienza–University of Rome, Italy, E-mail: ivano.mezzaroma@uniroma1.it

Received August 05, 2011; **Accepted** October 17, 2011; **Published** October 20, 2011

Citation: Mezzaroma I (2012) Response to Antiretroviral Therapy: Immunological Aspects and Emerging Problems. J AIDS Clinic Res S2:e001. doi:[10.4172/2155-6113.S2-e001](https://doi.org/10.4172/2155-6113.S2-e001)

Copyright: © 2011 Mas CM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credit ed.