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Acquired Immuno Deficiency Syndrome

Editorial

# Ready for New HIV Challenges in Post-ART Era?

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In 90's the introduction of antiretroviral therapy for HIV treatment changed gradually HIV infection in a chronic disease. The consolidated use of highly active antiretroviral treatment (HAART)substantially affect HIV RNA plasma viremia levels, leading circulating virus below the current analytical cut off limits, and, in the major part of cases, to CD4+ T cells recovery. However, it is not ableto eliminate HIV-1, which persists as a latent infection in anatomical and functional reservoirs, such as resting memory CD4+ T cells [1]. Moreover, HAART is unable to reduce or clock the persistent immune dysfunction, inflammation and coagulation abnormalities, which are commonly observed in HAART-treated patients and that are strongly predictors of risk for non-AIDS morbidity and mortality [2,3].

In the last years the cases such as the "Berlin patient" [4,5] and the "Mississipi Baby" [6] revived hopes for a cure against HIV both in researchers and patients, opening novel challenges both for the identification new interventions for virus eradication as well as the epistemological approach for designing and evaluating the efficacy of such interventions. These cases, although not conclusive, have revived the interest of researchers and scientific word to rethink the fight against HIV with a new point of view: a cure may be possible.

In the absence of an effective vaccine or other preventive therapy, the research against HIV/AIDS is moving now to looking for therapeutic interventions capable to generate a *cure* for HIV both eliminating the chronic symptoms and co-morbidities in infection without eliminate the virus (*functional cure*), and both eradicating virus from host with or without effective HAART (structural or sterilizing cure) [7].

In the current guidelines for clinical development of new HIV antiviral drugs, early studies, including short period of functional mono therapy followed by optimization of the treatment in treatment naïve subjects and confirmatory *head-to*-head studies (by "add-on" or "substitution" design) aimed at comparing the investigational product to the standard cART with direct antiviral properties [GUIDELINE ON THE CLINICAL DEVELOPMENT OF MEDICINAL PRODUCTS FORTHE TREATMENT OF HIV INFECTION Doc. Ref. EMEA/CPMP/EWP/633/02Revision 2, 2009] are foreseen. New drug efficacy is evaluated using generally accepted surrogate markers such as HIV RNA viral load and CD4+ T-cell counts [GUIDELINE ON THE CLINICAL DEVELOPMENT OF MEDICINAL PRODUCTS FORTHE TREATMENT OF HIV INFECTION Doc. Ref. EMEA/CPMP/EWP/633/02Revision 2, 2009]. The comparison with the standard antiviral therapy is performed measuring the capability of reducing HIV plasma viremia up to levels the limit of quantification of the validated RT PCR test and containing the immunological deplation measured by CD4+ T lymphocytes decay. Although relevant parameters for the monitoring of cART efficacy, the use of these outcomes in studies aimed at individuating benefits of treatment optimization and/or eradication with concomitant cART appears quite limited.

In the development of new therapeutics for functional or sterilizing cure of HIV, the identification and validation of novel efficacy biomarkers represent a major scientific and regulatory need. In the absence of robust surrogate markers, clinical studies of novel therapeutic agents having as objective HIV eradication (therapeutic immunizations or drugs) should directly demonstrate their effects on the persistence of virus not only in its circulating form in infected cells. The lonely detection of HIV RNA plasma viremia, which in effective cART quickly goes to levels below the limit of detection of assays currently in use, may not provide information on the persistence

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of viral reservoir and the interruption of antiretroviral therapy backbone, is not advisable at the current state of knowledge [8-10]. In addition, the same cART backbone could be also essential, acting in synergy with the novel tested treatment.

Is the scientific word really ready for this new challenge? Which parameters may directly or not detect the persistence of HIV or HIV-unrelated morbidities? Detection of HIV gene/protein expression or ultra-sensitive HIV RNA plasma viremiais unable to reveal latent virus as well as immunological responses may persist years after virus exposition. Evaluation of blood HIV proviral DNA may represent a good solution, because of its role as a prognostic factor for therapy efficacy is known [11] and since it is already methodologically accepted as parameter for diagnosis of HIV in infants, where common assays for HIV (ELISA and a confirmatory WB, if appropriate) cannot be used due to the presence of persisting maternal HIV antibody against HIV proteins in the child up to 15-18 months of age [12].

A consensus for the evaluation of the efficacy of a functional cure may be also generated on the basis of available data on the major non-AIDS co-morbidities (such as cardio-vascular diseases, malignancies, or accelerated aging) observed also in successfully HAART-treated patients [2,13]. Epidemiological data of the same pathologies in HIV-uninfected subjects and the common use in medical practice of prognostic risk factors may be of help to both meliorate the management of HIV patient and to evaluate potential new interventions affecting these co-morbidities [14].

A not trivial question is demanded to HIV researchers, but *"guttacavatlapidem" (Lucrezio)….*

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