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AIDS Rev. 2016;18:166-7

Hot News

New Strategies for a Comprehensive Fight Against HIV Infection using Monoclonal Antibody Therapy

Highly active antiretroviral therapy (ART) has allowed a long-term control of viral replication and HIV infection has been transformed into a chronic disease. However, ART is not able to eradicate the virus, and high levels of inflammation and immune-activation are observed despite prolonged ART. Consequently, a number of comorbidities, such as cardiovascular diseases and cancer, are gaining relevance in patients living with HIV. Moreover, the toxicities associated with continued exposure to ART cause several metabolic disturbances with clinical relevance, and the cost of treatment is a heavy burden for the national health systems. In this scenario, new therapeutic strategies aiming at viral eradication are being actively pursued.

The identification of monoclonal antibodies capable of generating a broad and powerful immune response against a wide range of HIV strains has been one of the great challenges since the discovery of this infection. These antibodies are being evaluated as part of the HIV vaccine development, but also as potential drugs to control HIV replication.

3BNC117 has been identified as a broad and potent neutralizing antibody to HIV-1 that targets the CD4 binding site on the viral envelope spike. This antibody has demonstrated to prevent infection in animal models, but also suppress viremia in HIV-1-infected individuals. Recently, results from a phase I clinical trial have been published, showing that a single dose of this antibody stimulates patient´s immune response (Schoofs, et al. Science. 2016;352:997-1001). A single 3BNC117 infusion was administered to 15 viremic individuals and 12 individuals on ART with no detectable viremia or low-level viremia (< 20 to 100 copies/ml) and then they were monitored over a six-month period. All but one of the 15 viremic patients showed increased breadth and/or potency neutralizing response against a number of different autologous HIV strains. In comparison to viremic subjects, the neutralizing activity was significantly less pronounced in the group of 12 ART-treated individuals and control groups. Therefore, this study concluded that 3BNC117-mediated immunotherapy enhances host humoral immunity to HIV-1.

Antibodies also have the potential to guide host immune effector cells to kill HIV-1-infected cells. In the same issue of Science, Lu, et al. report that 3BNC117 treatment is not only able to block new infections, but it also accelerates infected cell clearance (Lu, et al. Science. 2016;352:1001-4). Using a humanized mouse model, they observed that 3BNC117 could also target CD4 T-infected cells and decrease their *in vivo* half-lives by a FcyR-dependent mechanism. This observation might explain why post-exposure prophylaxis with neutralizing antibodies is more effective than ART in humanized mice. These findings have relevant implications in the development of HIV prevention therapies and for the reduction or elimination of the viral reservoir. Hence, the impact of 3BNC117 administration on the latent infection in patients receiving ART is currently being evaluated. A comprehensive approach including ART in combination with different effective strategies will probably be necessary to reduce and finally eliminate the viral reservoir. The use of neutralizing antibodies such 3BNC117 seems to be a good candidate for this approach.

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HIV: Test and Treat, Please!

Despite the fact that HIV infection can still not be eradicated from carriers, tremendous advances in antiretroviral therapy have led to achieving sustained suppression of HIV replication in most treated individuals. This translates into huge benefits for both patients and their sexual partners. This message was emphasized during the last IAS Conference, held in Durban, South Africa, at the end of July 2016. In parallel with this major AIDS event, two major publications were released: the updated recommendations on HIV therapy and the PARTNER study.

The new guidelines on antiretroviral therapy (Gunthard, et al. JAMA. 2016;316:191-210) address both treatment of infected adults and prevention of HIV acquisition in exposed individuals. There is no doubt that antiretroviral therapy must be offered to all HIV-infected persons with detectable viremia, regardless of CD4 count. The preferred recommended regimens

are those based on two nucleoside reverse transcriptase inhibitors plus one integrase inhibitor.

Daily tenofovir/emtricitabine (Truvada®) is the preferred regimen as pre-exposure prophylaxis to prevent HIV infection in persons at high risk. When indicated, post-exposure prophylaxis should be started as soon as possible after presumed exposure.

Long-acting antiretroviral agents administered intramuscularly, such as cabotegravir and rilpivirine, may be a good alternative therapeutic option in some patient populations. Agents with new mechanisms of action (i.e. BMS-663068, an attachment inhibitor, or BMS-955176, a maturation inhibitor) are in late-stage clinical development.

If the cost of antiretroviral medications continues to decline and becomes affordable for anyone, pushing "test and treat" strategies may allow to achieve the 90-90-90 WHO goal for 2020, meaning that 90% of infected individuals worldwide have been diagnosed, that 90% of them are on antiretroviral treatment, and that 90% of the latter depict undetectable virus replication. Only in this way, the HIV/AIDS pandemic may begin to be controlled, halting the stable two million new HIV infections still occurring per year.

The PARTNER study (Rodger, et al. JAMA. 2016; 316:171-81) is a prospective observational study of 1,166 HIV-serodiscordant couples conducted at 14 European countries. All HIV-positive index cases had undetectable viremia (< 200 HIV RNA copies/ml) taking antiretroviral therapy and reported condomless sex. Up to one third of men who had sex with men (MSM) admitted other partners during the study period, whereas it was reported by only 4% of heterosexual HIV-serodiscordant couples. The median number of condomless sexual acts was around three per month in the study population.

Although 11 HIV-negative partners became infected during a median follow-up of 16 months, phylogenetic analysis excluded in all cases that infection had been transmitted by the HIV-positive index partner. Thus, all 11 were infected by other sexual partners. Moreover, only one out of 11 newly HIV-infected persons was heterosexual, the rest being MSM. These findings highlight that suppressive antiretroviral therapy is very effective in halting HIV transmission. Furthermore, it indirectly supports the need for pre-exposure prophylaxis only for MSM engaged in high-risk practices with multiple partners, some of whom may not be aware of their HIV status and therefore be viremic and infective. In contrast, in heterosexual stable couples willing to have children, antiretroviral therapy of the HIV-positive partner may provide a unique opportunity to have natural sex, pursuing pregnancies without risk for the spouse and babies, as previously shown by others (Barreiro, et al. J Acquir Immune Defic Syndr. 2006;43:324-6).

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