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Hot News

A New HIV Paradigm: Dual Antiretroviral Regimens as Maintenance Therapy

Since the advent of triple combination antiretroviral therapy in 1996, the prognosis of HIV-infected persons has improved drastically. The clinical benefits of HAART derive from producing sustained viral load suppression and CD4 gains. The major drawbacks of the first HAART regimens were common adverse events and high pill burden, which resulted in difficult drug adherence and led to frequent discontinuations and selection of drug resistance.

Improvements in drug development have resulted in more potent, convenient and tolerable agents, including single-tablet regimens. As a result, HAART has become an unprecedented success in medical therapeutics, blunting both disease progression and transmission. The benefit of current HIV paradigms of "test and treat" and "treatment as prevention" has permitted focusing efforts on the next step, which is HIV cure. In this scenario, claims for moving back to dual antiretroviral therapy may be viewed as paradoxical. However, in real life, difficulties for accessing good antiretroviral regimens are frequent, largely due to high prices. Moreover, concerns exist on adverse events and drug adherence under any indefinite treatment.

The release at CROI 2017 of results from two large trials, LAMIDOL (Joly, et al. Abstract 458) and SWORD (Llibre, et al. Abstract 44LB), which have tested simpler antiretroviral regimens as maintenance HIV therapy, represent an important contribution. In patients with undetectable viremia for > 6 months under triple combinations, a switch to dolutegravir plus either lamivudine or rilpivirine kept suppressed viremia in ≥ 95% of patients one year later. These results are better than those obtained by switching to dual regimens based on boosted protease inhibitors (i.e., lopinavir, atazanavir or darunavir) that were penalized with more frequent side effects and/or potential for drug interactions.

In other diseases with a subacute and/or chronic course, such as tuberculosis, psoriasis, some cancers or autoimmune disorders, induction-maintenance strategies are well established. The first treatment shot kills the new pathological event (attack phase) whereas the second (remission phase) adapts to consolidate the response and halt rebounds. This principle of therapeutics is generally achieved by using drug regimens with less toxicity after the initial upfront treatment. For example, four drugs for two months followed by isoniazid-rifampin for an additional four months are recommended for tuberculosis. Likewise, secukinumab is given weekly for the first month in psoriasis followed by monthly subcutaneous administration.

Ultimately, the newest dual antiretroviral regimens could save money and improve patients' quality of life by reducing side effects and pill burden. Adapting the principle of induction-maintenance to HIV therapeutics represents an important step. This strategy fits better the goal of precision medicine that pursues adjusting therapy to each individual. This is especially important for managing chronic illnesses such as HIV infection.

The risks of suboptimal antiretroviral therapies derive from viral escape with HIV replication in compartments such as the brain, where drugs may not reach appropriate concentrations and may favor selection of drug resistance, as has been shown with protease inhibitor monotherapy (Imaz, et al. AIDS Res Human Retroviruses. 2014;30:984-7; Antinori, et al. AIDS. 2015;29:1811-20; Donath, et al. Med Microbiol Immunol. 2016;205:575-83). Therefore, a longer follow-up of patients simplified to dolutegravir plus either lamivudine or rilpivirine is warranted.

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When is Early Antiretroviral Therapy Early Enough for HIV Remission?

Several strategies to reduce and control the HIV reservoir are being evaluating to achieve the great challenge of HIV remission or functional cure. Some of these are based on immune and gene therapy, or in the use of agents with latency reversing properties. Moreover, acute HIV infection and the impact of early antiretroviral treatment (ART) initiation is another key issue of current research. It has been demonstrated that ART initiation during acute HIV infection minimizes the establishment of the latent HIV reservoir. Therefore, early ART initiation might delay viral rebound following treatment interruption and might potentially induce a post-treatment controller state. In this regard, new interesting data were presented at CROI 2017, recently held in Seattle.

Dr. Ananworanich presented results from the RV411 study (Colby, et al. CROI 2017; Abstract 124), an offshoot of the RV254/SEARCH 10 trial, which includes more than 450 patients from Bangkok who were diagnosed during acute HIV infection within a

few days/weeks after exposure (between Fiebig stages I and IV) and in whom ART was immediately started. In the RV411 study, eight patients initiated ART in Fiebig stage I, defined as HIV-RNA$^+$, p24$^-$ and IgM$^-$. These patients maintained HIV RNA levels < 20 copies/ml, with a median CD4 of 561 cells/mm^3, on ART for a median of 2.8 years before undergoing treatment interruption. After that, they were closely monitored every 3-7 days. All patients experienced viral rebound at a median time of 26 days after treatment interruption. The highest median viral load was 5,169 copies/ml after four days from the first detectable viral load. No symptoms related with acute retroviral syndrome or new drug resistance mutations at viral rebound or treatment failure were seen after ART resumption.

These findings represent an important piece of knowledge in the hard race towards HIV remission. The results obtained in this study suggest that even when ART is initiated very early during the first stages of HIV infection and viral suppression is maintained long-term, there is no significant delay in the time to viral rebound after treatment interruption. Therefore, even in the context of an extremely small HIV reservoir size, something more than early ART initiation will be needed to achieve the goal of a functional cure for HIV infection.

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Hepatitis A Outbreaks in European Homosexual Men

Hepatitis A virus (HAV) is a small RNA, non-enveloped agent predominantly transmitted via the fecal/oral route through person-to-person contact or contaminated food and water. The mean incubation period is 28 days (range: 15-50). Acute hepatitis A is always self-limited and very rarely fatal. Moreover, it never progresses to chronicity. Acutely infected persons are most likely to transmit HAV before the onset of jaundice, when viral particle concentration in stool is highest.

Transmission through sexual contact, particularly in men who have sex with men (MSM) as well as through sharing of needles and syringes has also been described. Hepatitis A is a vaccine-preventable disease, although universal childhood HAV vaccination is not mandatory in most Western countries. In adults, HAV vaccination is generally recommended in MSM and injecting drug users (IDU) as well as in travelers to endemic regions in Latin America, Africa, and Asia. In the European Union and North America virtually all HAV infections are directly or indirectly imported, and cause local outbreaks around restaurants, kindergartens, residencies, etc.

Outbreaks of acute hepatitis A have been reported during the last year among MSM and household contacts in several European countries, including the United Kingdom, Germany, Portugal and Italy. During the last semester of year 2016, 37 cases of acute hepatitis A with two unique IA genotype strains were reported in the UK, primarily among MSM. Epidemiological and laboratory investigations supported that they were imported from Spain, with secondary sexual transmission in the UK (Beebeejaun, et al. Euro Surveill. 2017;22:30454). Since November 2016, 38 cases of hepatitis A have been notified in Berlin; 30 reported in MSM. Phylogenetic analysis revealed sequences linked to cases in other German cities and to clusters in other European countries (Werber, et al. Euro Surveill. 2017;22:3045). More recently, hospital admissions due to acute hepatitis A have been on the rise among HIV-infected MSM in Milan and Lisbon, with profiles similar to those previously reported in Central Europe.

The magnitude and particular features of the current outbreak of hepatitis A in Europe highlights the interconnectedness of MSM and the need to increase coverage of hepatitis A vaccination in this group. Although HIV infection does not seem to increase susceptibility to hepatitis A, and liver enzyme elevations tend to be milder in this group, a high rate of concomitant sexually transmitted infections (e.g. syphilis, chlamydia, gonorrhea) have been reported.

Although the HAV vaccination schedule consists of two intramuscular doses separated at least six months apart, a recent study has shown that three-dose vaccination schedules provide greater anti-HAV IgG titers and more durable protection (Cheng, et al. J Infect Dis. 2017;215:606-13). The shortage of HAV vaccines in many non-endemic countries is currently a major obstacle for halting the ongoing HAV outbreak.

In summary, MSM are in particular risk for HAV infection and there is a need to provide proper information and education on safer sexual behavior, including personal hygiene measures before and after sexual contacts. HAV vaccination should be reinforced in this population, as well as post-exposure prophylaxis to close contacts (active and passive immunization is effective if administered within two weeks after exposure). Finally, it is important to exclude other sexually transmitted diseases in acute transmitted diseases in acute hepatitis A episodes in MSM.

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