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Hot News

HIV Pre-Exposure Prophylaxis – Is it just about pills?

The increasing use of antiretrovirals for averting HIV infection before potential exposure is under debate. Whereas there is no doubt about the benefit of using Truvada® (tenofovir plus emtricitabine) to reduce HIV acquisition in uninfected persons who have sex with HIV-infected stable partners, concerns are rising about the increasing rate of sexually transmitted infections in subjects engaged in sex with multiple partners, due to misinterpreted self-security. This fact accounts for the rising incidence of syphilis and acute hepatitis C (including re-infections), particularly among men who have sex with men (Sanchez et al. J Viral Hepat 2013; 33: 1357-62; Ingiliz et al. J Hepatol, in press).

As pointed out by Jean-Michel Molina at the HIV Glasgow Conference in October 2016, a lesson has to be taken from the implementation of PrEP in France, namely that easy access to Truvada® for PrEP must be complemented with counselling and education if we really want to impact positively on public health. Recent studies have shown that the use of pre-exposure prophylaxis might be associated with risk compensation, thus limiting or hampering the efficacy of PrEP (Alaei K, et al. AIDS 2016; 30: 2753-2756) as well as increasing the incidence of sexually transmitted infections (Kojima N. AIDS 2016; 30:2251-2). These data show that a merely pharmacological approach to HIV prevention is not enough, and that behavioural interventions are needed for maximizing the results of PrEP programs while avoiding the pitfall of increasing sexually transmitted infections. And the best way to do so is promoting sexual public health, including the use of condoms and avoiding particularly risky sexual practices, often associated with alcohol abuse and drugs (chemsex) (Daskalopoulou et al. Lancet HIV 2014; 1: e22-e31). Therefore, government efforts in sexual public health should include adequate support, counselling and education, besides expanding access to PrEP.

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Reactivation of Hepatitis B in HIV Patients Treated for Hepatitis C

Two billion people have been exposed to HBV and exhibit serological markers of past infection such as anti-HBc and/or anti-HBs. However, around 240 million suffer from chronic hepatitis B, as defined by the presence of serum HBsAg for longer than six months. In addition, a small proportion of patients exposed to HBV may harbor detectable viremia (serum HBV DNA) in the absence of HBsAg, which is named "occult hepatitis B".

The persistence of hepatitis B cccDNA within the nucleus of infected hepatocytes after initial exposure, even in persons that once cleared the virus, accounts for late HBV rebounds. Under certain circumstances, such as immunosuppression or viral interference, hepatitis B reactivation may occur over time, leading to liver enzyme flares, and is occasionally life threatening. Reactivation of hepatitis B is a well-known complication during chemotherapy for hematological malignancies (i.e. with doxorubicin or cyclophosphamide) and immunosuppressant therapy (i.e. with rituximab or everolimus) for cancer, transplantation, or immunological conditions, including rheumatoid arthritis or inflammatory bowel disease. Based on this information, HBV screening and antiviral prophylaxis before initiation of chemotherapy or immunosuppressant therapy is currently recommended (Voican, et al. Ann Oncol, in press).

A different warning for the risk of hepatitis B reactivation has recently emerged from patients treated with oral direct-acting antivirals (DAA) for hepatitis C (de Monte, et al. J Clin Virol. 2016;78:27-30; Wang, et al. Clin Gastroenterol Hepatol, in press). Given that these agents produce a drastic blocking of HCV replication, they provide the opportunity for open replication of other hepatotropic viruses until then under competition for hepatocytes. This is the situation for individuals coinfected with HBV and HCV (Soriano, et al. Curr HIV/AIDS Rep. 2015;12:344-52). In October 2016 the FDA alerted about this risk of hepatitis B reactivation using DAA with a "boxed warning", the most prominent concern, added to the drug labels, recommending HBV screening and monitoring during and after treatment in all patients receiving DAA for hepatitis C. A total of 24 cases of HBV reactivation were reported to FDA up to July 2016, two of which died and another required liver transplantation. Of note, HBV reactivation had not

been reported as an adverse event in clinical trials because patients with HBV coinfection were uniformly excluded from trials.

Although most cases of HBV reactivation during DAA therapy for hepatitis C tend to present as liver enzyme elevations at 4-8 weeks of treatment and occur in HBsAg-positive patients, HBV DNA rebound may occasionally occur in patients with resolved HBV infection (HBsAg-negative and anti-HBc-positive), especially when immunity is compromised such as in the elderly and HIV-infected persons. Failure to do screening of HBV serologic markers before beginning DAA may lead to misinterpretation of liver enzyme flare-ups, considering it as DAA hepatotoxicity, and wrongly discontinuing DAA therapy prematurely. At present, all chronic hepatitis C patients scheduled for treatment with DAA should be screened for HBsAg and anti-HBc. In those with any positive HBV marker, serum HBV DNA should be tested at baseline and during DAA therapy. Preemptive antiviral prophylaxis during DAA treatment using entecavir or tenofovir should be considered in the subset of HBV/HCV-coinfected patients with detectable HBV DNA.

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Risk of HIV Escape using Sub-Optimal Antiretroviral Dual or Monotherapy

Budget constrictions have pushed some researchers to explore whether antiretroviral therapy with one or two drugs instead of the well-established triple-drug regimens may be able to maintain undetectable viremia in HIV-infected individuals, at least used as simplification in patients already with viral suppression under standard triple therapy. With the advent of co-formulations and the improved safety of the newest antiretroviral agents, there is no other reason than cost to justify moving from triple to dual or monotherapy.

A recent publication has highlighted the risk of sub-optimal antiretroviral therapies (Lorenzo-Redondo, et al. Nature. 2016;530:51-6). Deep sequencing of HIV-1 DNA was performed in blood and inguinal lymph nodes from three HIV-positive individuals at different time points during the first six months of antiretroviral therapy. In contrast with prior studies made using bulk sequencing, the authors found an evolution of viral sequences over time, reflecting ongoing HIV replication but without selecting drug resistance mutations. This paradoxical finding was explained by a dynamic model of HIV-1 persistence in sanctuary sites where drug pressure could not be enough to completely block virus replication. Currently, triple drug therapy is the best way to maximize the chances of adequate tissue penetrance and distribution of antiretroviral drugs to fully suppress HIV-1 replication.

The persistence of HIV-1 replication in sanctuary sites despite undetectable viremia in plasma largely accounts for the increased risk of cardiovascular disease and lymphoma (Totonchy, et al. Curr Opin Virol. 2016;20:71-7) seen in HIV-1 patients on apparently successful antiretroviral therapy. Since HIV-1 escape along with immune activation and inflammatory phenomena are more pronounced when using mono or dual therapies, it is time to defend standard triple drug regimens against administrative budget pressures and constrains which may harm the patients. This has been recently highlighted by data from a large German cohort of patients on protease inhibitor monotherapy that demonstrated viral escape in the central nervous system in half of these patients (Donath, et al. Med Microbiol Immunol. 2016;205:575-83).

Finally, in the recently published large multicenter, international PROTEA study (Girard et al. HIV Med 2017; 18: 5-12) patients on antiretroviral therapy with HIV-RNA <50 copies/mL at baseline, were randomized to switch to DRV/r monotherapy (n=137) or stay on triple therapy (DRV/r plus two nucs, n=136). The monotherapy arm showed lower efficacy than the triple arm (75% vs 85%, respectively), particularly in patients with CD4 counts <200 cells/μL. Moreover, one patient in the monotherapy arm was hospitalized with HIV encephalitis and elevated cerebrospinal fluid HIV-RNA.

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