Hot News

Pre-Exposure Prophylaxis for HIV Upfront

The recent publication of two trials, CAPRISA (Abdoool-Karim, et al. Science. 2010;329:1168-74) and iPrEX (Grant, et al. N Engl J Med. 2010;363:2587-99) last year has raised in an unprecedented manner the interest for pre-exposure prophylaxis (PrEP) as a way to confront the HIV pandemic. CAPRISA examined nearly 900 heterosexually active women in South Africa and demonstrated that use of the topical vaginal tenofovir reduced the risk of HIV acquisition by 39% overall, rising to 54% in those women with high gel adherence.

The iPrEX trial examined nearly 2,500 men who have sex with men (MSM) in South America, South ot been adequately studiedtrial to show that daily oral tenofovir/emtricitabine (Truvada®) could reduce the risk of HIV infection by 44% overall, increasing to 73% in the subset of men with sustained good drug adherence.

These trial results have been greeted with huge enthusiasm, especially in the wake of disappointing results from several prior studies, but also have raised numerous questions about who could potentially benefit, the long-term risks of these interventions, and cost and access issues. Moreover, antiretroviral use for preventing contagion in HIV seronegatives at risk must be considered in the context of other interventions that may equally help to reduce HIV acquisition (Table 1).

While Truvada® has not been approved so far for HIV prevention, doctors may prescribe drugs for off-label use, and some individuals engaged in high-risk behaviorsmight consider the use of the drug as PrEP right away. For these reasons, on January 28, 2011 the CDC released new guidance intended to offer instructions and cautions for people interested in using PrEP now, while awaiting more extensive clinical trial data regarding longer-term use, and other at-risk populations. The CDC guidance is available at: http://www.cdc.gov/nchhstp/newsroom/PrEPMSMGuidanceGraphic.html.

Briefly, the CDC guidelines for PrEP recommend: (i) confirming that the person seeking PrEP is at substantial, ongoing, high risk for acquiring HIV infection; (ii) testing for HIV, including, if symptomatic, acute HIV infection that may not be detectable with a standard antibody test since using just two antiretroviral drugs could lead to resistance if HIV is present, and repeating HIV testing every three months while on PrEP; (iii) screening for and treating other sexually transmitted diseases (syphilis, gonorrhea, hepatitis B and C, etc.), and repeating STD testing every six months while on PrEP; (iv) testing for kidney function (creatinine clearance) because tenofovir may produce renal injury in some individuals, and monitoring kidney function after three months and then annually while on PrEP; (v) screening for and, if uninfected, vaccinating against hepatitis B; if infected, consider the dual use of Truvada® for treatment since tenofovir and emtricitabine are active against HBV as well as HIV; (vi) providing PrEP as part of a comprehensive prevention approach along with risk-reduction counseling and condoms, and assessing risk behavior every three months while on PrEP; and (vii) stressing the importance of and offering support for drug adherence.

It should be kept in mind that the iPrEX trial did not provide evidence that using Truvada® only

Table 1. Effectiveness of different strategies to reduce sexual HIV contagion

Intervention	Reduction	Reference	Comments
Condom	80%	Weller, et al. Cochrane Database Syst Rev. 2002	Meta-analysis
Circumcision	65%	Wawer, et al. Lancet. 2009	More effective for male than female
Vaccine RV144	31%	Rerks-Ngarm, et al. New Engl J Med. 2009	No effect on viral load once infected
PrEP TDF topical gel (microbicides)	39%	CAPRISA. Science. 2010	Heterosexual women in South Africa
PrEP Truvada® oral	44%	iPrEX. New Engl J Med. 2010	MSM, international

PrEP: pre-exposure prophylaxis; TDF: tenofovir; MSM: men who have sex with men.

before or after sex is effective. Pre-exposure prophylaxis has the potential to contribute to effective and safe HIV prevention for MSM engaged in high-risk behaviors, but its maximal cost-effectiveness will be obtained when taking into consideration some vital aspects: (i) targeting MSM at high-risk for HIV acquisition; (ii) being delivered as part of a comprehensive set of prevention services, including risk-reduction and medication adherence counseling, ready access to condoms, and diagnosis and treatment of STDs; and (iii) being accompanied by monitoring of HIV status, side effects, adherence, and risk behaviors at regular intervals. Finally, all these efforts to help to reduce HIV acquisition must be accompanied by appropriate information and education about safer lifestyles, intended to reduce sexual promiscuity and particularly high-risk sexual practices.

Carmen de Mendoza
Infectious Diseases Department
Hospital Carlos III
Madrid, Spain

HIV Cure Following CCR5 Δ32 Stem Cell Transplantation – An Update

An HIV-infected patient underwent stem cell transplantation in Germany with a graft containing CCR5Δ32/Δ32 cells in February 2007 because of a relapse of acute myeloid leukemia. Antiretroviral therapy was discontinued on the day of transplantation. The patient had a second relapse 13 months later and received a second stem cell transplant from the same donor. Replacement of host stem cells with donor-derived cells homozygous for the CCR5 gene variant Δ32 (CCR5Δ32/Δ32) apparently resulted in the HIV viral reservoir being reduced over time, strongly suggesting that the patient was cured of HIV (Hutter, et al. N Engl J Med. 2009;360:692-8).

A recent report (Allers, et al. Blood [in press]) has updated the current status of this individual. The patient's systemic recovery of CD4+ T-cells after the stem cell transplantation and discontinuation of antiretroviral therapy was similar to that of ten control patients who also had stem cell transplants, but who were not infected with HIV. This is quite impressive, given that it would have been expected that the long-lived viral reservoir would lead to HIV rebound and disease progression during the process of immune reconstitution. The expansion of activated CD4+ T-cells after stem cell therapy usually enriches targets for HIV infection in HIV-infected patients, causing HIV to rebound after stem cell transplantation. However, this individual's CD4+ T-cell numbers returned to normal and HIV remained undetectable. Moreover, the patient's donor-derived CD4+ T-cells gradually increased in the gastrointestinal mucosa, and his mucosal CD4+ T-cell numbers normalized relative to those of the HIV-uninfected stem cell transplantation control patients. In addition, HIV remained undetectable in the gut tissue, which is the largest component of the lymphoid organ system.

The patient's peripheral and mucosal CD4+ T-cells remained susceptible to infection with X4 HIV strains; thus, exogenous HIV reinfection still appears to be a risk, and host cells that survived the chemo-irradiation therapies remained potential sources for the rebound of X4 variants. However, host-originating CD4+ T-cells appeared to be completely removed from the patient's immune system during immune reconstitution; HIV was undetectable in the brain during a neuropathologic examination, and no CCR5 expression could be detected in liver tissue sections, indicating the replacement of microglial and Kupffer cells by donor-derived cells. Finally, another interesting finding is that the patient has experienced a steadily decline of HIV antibody titers over time.

Altogether, these results support that the patient remains without any evidence of HIV infection. Although a bone marrow transplant from a CCR5Δ32/Δ32 donor is not a practical approach for HIV cure for the millions who have HIV, this case represents the first proof-of-concept that HIV infection can be cured, and that hopefully there might be other strategies that can be more practically deployed. No doubt, this patient has contributed to the renewed interest for HIV eradication.

Jose M. Benito
Infectious Diseases Department
Hospital Carlos III
Madrid, Spain

New Department of Health and Human Services Antiretroviral Treatment Guidelines 2011

On January 10, 2011, the U.S. Department of Health and Human Services (DHHS) announced the latest revision of its guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. The recent update does not introduce major changes related to when to start antiretroviral therapy or what drugs to use, but it includes new recommendations related to CD4 count and viral load testing, as well as for treatment of HIV-infected individuals with hepatitis B or tuberculosis.

The previous revision of the guidelines in December 2009 shifted the recommended CD4 threshold for initiating antiretroviral therapy from

350 to 500 cells/mm^3. Of note, half of the panel issuing the guidelines thought treatment should be started even sooner. The latest update, however, does not make any changes with regard to when to start treatment.

The CCR5 antagonist maraviroc plus zidovudine/lamivudine was added as an "acceptable" option for first-line therapy; other nucleoside reverse transcriptase inhibitor backbones, could be acceptable, but they have not been adequately studied in combination with maraviroc. On the other hand, ritonavir-boosted saquinavir was downgraded from "alternative" to "acceptable with caution", due to the potential for electrocardiographic PR and QT prolongations.

With regard to monitoring, the DHHS panel now recommends that people on antiretroviral therapy with a high CD4 count and no other health issues can generally get their T-cells measured less often, every 6-12 months. They also said that since viral load "blips" or transient, low-level increases are common, changes should only be considered a reflection of treatment failure if confirmed above 200 copies/ml.

Turning to coinfections, the panel offered more specific advice for the treatment of HIV/HBV coinfection, especially for people who are resistant to or unable to take tenofovir marking that entecavir could be the election, but taking into account that entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients.

For tuberculosis, they now recommend that antiretroviral therapy should be initiated generally within 2-4 weeks if patients have less than 200 CD4$^+$ T-cells/mm^3, but at least within eight weeks of starting tuberculosis treatment if they have higher CD4 counts.

Pablo Labarga
Infectious Diseases Department
Hospital Carlos III
Madrid, Spain