Hot News

Welcome to "Hot News", a section of AIDS Reviews written by the editors and invited experts which focuses on recently reported information believed to be of both impact and higher interest to the readership.

New Guidelines for the Use of Antiretroviral Therapy as Prophylaxis after Non-occupational Exposure to HIV

The Centers for Disease Control, in conjunction with the Food & Drug Administration, the National Institutes of Health, and the U.S. Health Resources and Services Administration has recently updated its guidelines for the use of antiretroviral therapy as prophylaxis after non-occupational exposure to HIV (MMWR 2005).

The previous guidelines (1998) concluded that the panel was unable to recommend for or against antiretroviral prophylaxis since they did not find sufficient evidence about its efficacy. New data from human, animal, and laboratory studies are the basis for the current recommendations.

The evidence of possible benefits from non-occupational postexposure prophylaxis (nPEP) comes from animal transmission models using SIV and HIV, perinatal clinical trials with abbreviated regimens for reducing mother-to-child HIV transmission, and different observational studies which have assessed occupational and sexual HIV exposure.

The risks from the use of nPEP have been also assessed. After extensive review, the panel concluded that the availability of nPEP will not lead to increases in risky behavior, severe side effects, or toxicities, and the occasional selection of drug-resistant viruses is rare.

Recommendations for the use of antiretroviral nPEP are divided in three arms. Firstly, persons who have had non-occupational exposure to blood, genital secretions, or other infected body fluids of persons known to be HIV-infected, when the exposure represents a substantial risk for transmission, and when the person seeks care within 72 hours of exposure. In this situation, the advice is 28 days of HAART. If the source person is available for an interview, it is important to obtain information about his or her antiretroviral history and viral load, in order to select one or another regimen for nPEP.

The sooner nPEP is provided, the more likely it is to interrupt transmission. No evidence indicates that any specific antiretroviral combination of drugs is optimal for use as nPEP. However, certain regimens are preferred: efavirenz and lamivudine or emtricitabine with zidovudine or tenofovir (as a non-nucleoside regimen) and lopinavir/ritonavir and zidovudine with either lamivudine or emtricitabine (as a protease inhibitor regimen). Other alternative regimens are possible, including new PIs such as atazanavir or fosamprenavir. No evidence indicates that a three-drug HAART regimen is more likely to be effective than a two-drug regimen. The recommendation for a three-drug regimen is based on the assumption that the maximal suppression of viral replication afforded by HAART will provide the best chances of preventing infection in a person who has been exposed.

Secondly, for persons who have had non-occupational exposure to potentially infected body fluids of a person of unknown HIV infection status, when there is a substantial risk for HIV transmission, and if the person seeks care within 72 hours, no recommendations are made. Evaluation of the risk and benefits on a case-by-case basis must be done by the clinician in charge, with attention to potential adherence of the person exposed to a treatment with a significant rate of side effects. If the source person is available, a rapid HIV test could be of great help.

Finally, for persons who seek care more than 72 hours after potential non-occupational HIV exposure, or persons with any exposure that did not represent a substantial risk for HIV transmission, nPEP is not recommended, regardless of the HIV status of the source. However, on the basis of currently available data, it is not possible to confirm that nPEP will be completely ineffective if initiated more than 72 hours after exposure. Therefore, after exposures that confer a serious risk for transmission, even if the exposed person seeks care after 72 hours, clinicians might consider the administration of nPEP.

In summary, the 2005 CDC guidelines for the use of antiretroviral therapy as prophylaxis following non-occupational exposure represent a substantial advance in the field in comparison with prior guidelines from 1998. Accumulated data about efficacy and

benefits of nPEP have permitted changing the recommendations. However, antiretroviral therapy cannot replace behaviors that help avoid exposure, and prophylaxis should not be recommended for people who have frequent exposures to HIV.

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RNA Helicase Involvement in HIV-1 Rev Export

The replication of HIV-1 is regulated in a temporal manner by its viral mRNA expression. Control of HIV-RNA expression is complex and involves the interplay of ***cis***-acting viral transactivators and cellular proteins. The nucleocytoplasmic transport of unspliced and singly spliced viral RNA is brought about by the viral protein Rev. Nuclear export of Rev involves the Ran-CRM1 export pathway, but this is not the only requirement for efficient transport, as recently discovered by Kuan-The Jeang and Lawrence Kleiman's teams who have reported the involvement of a DEAD box RNA helicase, DDX3, in the Rev/CRM1 transport pathway (Yedavalli, et al. Cell 2004; 119:381-92).

DEAD box RNA helicases are thought to play important roles in directing RNA-protein rearrangements by unwinding RNA helices. DDX3 is important and limiting for HIV replication, suggesting that it might represent a new target for chemotherapeutic intervention. One of the major problems in HIV treatment is the selection of drug-resistant viruses. Drugs interfering with cellular targets (such as DDX3, which is essential for viral replication) will not lead to drug-resistant viruses. However, intervening with cellular functions is usually harmful for the cell. Interestingly, DDX3 expression was upregulated in Tat-expressing cells, and Tat is a viral transcriptional transactivator, suggesting that infected cells will be more susceptible to drugs interfering with DDX3 than uninfected cells. It would be of great interest to study the impact of DDX3 inhibition on cellular function.

On the other hand, the same authors found that DDX3 directly interacts with Rev. This interaction could as well be targeted for anti-HIV therapeutic development, and is likely to be less toxic than drugs directly interfering with DDX3 function.

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Is Tenofovir + Emtricitabine Superior to Zidovudine + Lamivudine?

Study 934 is a phase III, multicenter trial designed to compare a regimen of tenofovir (TDF), emtricitabine (FTC) and efavirenz (EFV) to Combivir® (lamivudine + zidovudine) and EFV in treatment-naive HIV-positive patients. Results from the analysis of 487 patients have recently been released, showing a statistically significant difference favoring TDF/FTC in the percentage of patients who achieved and maintained HIV-RNA < 400 copies/mL at 48 weeks. Overall, 84% of patients in the TDF/FTC arm compared to 73% of patients in the Combivir® arm achieved and maintained HIV-RNA < 400 copies/mL at week 48 using the TLOVR algorithm requested by the FDA (p = 0.002; 95% CI, +4.3% to +18.6%). Similarly, 80% of patients in the TDF/FTC arm compared to 71% of patients in the Combivir® arm achieved and maintained HIV-RNA < 50 copies/mL at week 48 (p = 0.027; 95% CI, +1.2% to +16.1%).

Patients receiving TDF/FTC had a significantly greater increase from baseline in the CD4 count at week 48 compared to those receiving Combivir® (189 *vs.* 158 cells/mm^3, p = 0.002). The incidence of adverse events leading to permanent discontinuation of the study regimen was 4% in the TDF/FTC arm and 9% in the Combivir® arm (p = 0.019), and the most common of these adverse events were anemia (0 *vs.* 6%), nausea (< 1 *vs.* 2%), vomiting (0 *vs.* 1%) and fatigue (0 *vs.* 1%) in the TDF/FTC and Combivir® arms, respectively. Thus, the main factor driving the much poorer performance of Combivir® versus TDF/FTC in study 934 was the higher rate of anemia in patients exposed to Combivir®. Given that a significant proportion of patients in this trial had low CD4 counts at baseline, this risk was particularly enhanced. In fact, in the subset of patients with CD4 counts > 200 cells/mm^3, there were no significant differences in efficacy or safety when comparing both treatment arms.

In August 2004, the FDA granted accelerated marketing approval of Truvada® – FTC and TDF in a fixed-dose combination in one tablet, to be taken once a day in combination with other antiretroviral agents. In December 2004, Gilead and Bristol-Myers Squibb announced the establishment of a joint venture to develop and commercialize a once-daily fixed-dose combination of TDF, FTC and EFV. All these improvements in drug presentations are much appreciated and should improve the patient's treatment adherence.

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