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.

Anti-HIV Yoghurt?

Microbicide gels to prevent vaginal HIV infection are becoming a realistic goal, although testing their clinical effectiveness is difficult, considering the need for clinical studies in large, high-risk populations (Dhawan and Mayer, J Infect Dis 2006;193:36-44). Several such gels are entering clinical studies, some of them using potent antiviral agents. The current prospects are, however, that these gels will be expensive and have to be applied before each incidence of high-risk sexual intercourse. Will this be feasible in the developing world? Cost studies will need to be done. In addition, cultural restrictions may prevent women from applying microbicides immediately before high-risk sexual intercourse. If feasible, vaginal microbicides will only prevent sexual transmission. Preventing mother to child transmission (MTCT) during breastfeeding presents a different challenge involving a different kind of mucosal transmission. There are so far no specific studies addressing this problem, other than advising against breastfeeding. In many countries, the dangers of formula feeding are larger than the risk of vertical transmission. Even though successful treatments exist to reduce MTCT during pregnancy and delivery, transmission during breastfeeding can undo all these benefits.

An intriguing new approach towards both problems was recently published by the group of Ramratnam (Pusch, et al. J Acquir Immune Defic Syndr 2005;40:512-20). They genetically engineered *Lactococcus lactis* to produce the antiviral agent cyanovirin, with the intention to use such strains to prevent vaginal and oral transmission. Natural vaginal isolates of lactobacilli can be engineered to secrete heterologous anti-HIV proteins (Chang, et al. Proc Natl Acad Sci USA 2003;100:11672-7). Lactobacilli are also involved in the production of yoghurt and cheese. Some "probiotic" yoghurts contain vast amounts of *Lactococcus lactis*, and probiotic yoghurt producers advertise health claims of such fermented drinks, a market now worth six billion Euros (Abbott A., Nature 2004;427:284-6). While the science behind these drinks is questionable, no serious adverse events have been reported so far. Mucosal retention after oral administration or direct application of lactobacilli has a half-life of approximately six hours to seven days, depending on the strain used. This could result in attractive schemes for both vaginal and oral protection against HIV infection. Genetic engineering of bacteria presents a new challenge in anti-HIV research. While cyanovirin has not yet proven its efficiency in clinical research, several peptides and proteins have proved clinically beneficial as antiviral drugs, and might be good candidates for such an approach.

I look forward to the development in these lines of HIV research and let us hope that if this is a promising field, fear of genetic modification of bacteria in a clinical situation can be overcome. An encouraging communication in this respect is the prospect of a clinical trial of a transgenic bacteria delivering drugs to fight Crohn's disease (Baker M. Nature Biotechnology 2005;10:605-45).

Anne-Mieke Vandamme
Katholieke Universiteit Leuven
Laboratory for Clinical and Epidemiological Virology
AIDS Reference Laboratory
Rega Institute and University Hospitals
Leuven, Belgium

News on the Pathogenesis of HIV Infection

Once again, the Retrovirus Conference, held this year in Denver, was a meeting point for the latest research on different aspects of HIV infection, from basic science to clinical issues. Regarding pathogenesis, several sessions were devoted solely to this important aspect, in which studies in non-primate animal models and in humans were presented. From their findings, it is clear now that the majority of CD4+ T-cell depletion following acute SIV/HIV infection occurs in the gut-associated lymphoid tissue (GALT). The vast majority of CD4+ T-cells in this location are infected and destroyed during the acute phase of infection and this occurs in both the pathogenic and nonpathogenic animal models, i.e. SIV-infected macaques and sooty mangabeys or African green monkeys, respectively. The difference between both models is that after the acute phase, GALT-associated CD4+ T-cells are restored in the natural host, whereas they remain very low throughout

the course of chronic viral infection in rhesus macaques that ultimately develop AIDS.

The main difference between these two outcomes seems to depend on the level of immune activation. In fact, in the natural host, there is only limited immune activation and proliferation of CD4+ T-cells, whereas in rhesus macaques there is a heightened immune activation and proliferation of GALT-associated T-cells. Intriguingly, in one of the studies with sooty mangabeys, two of the animals developed an extreme, mucosal CD4+ T-cell depletion that was also reflected in peripheral blood, but these animals did not develop AIDS-defining conditions. The absence of progression could be due to the low level of immune activation and, as a consequence, to a preservation of enough immune competence in the residual CD4+ T-cells to be sufficient to prevent the progression to AIDS. Thus, a new concept arose from these studies – immune activation seems to be the main factor that differentiates nonpathogenic and pathogenic SIV/HIV infections.

In humans, a severe depletion of CD4+ T-cells in GALT and MALT (mucosal-associated lymphoid tissue) during the acute phase of HIV infection has also been demonstrated. This CD4+ T-cell depletion persists throughout the chronic phase of infection. Furthermore, there is little reconstitution of CD4+ T-cells at the gastrointestinal (GI) tract following the use of HAART and there is no correlation with peripheral blood CD4+ T-cell counts. This lack of mucosal CD4+ T-cell restoration under successful HAART can be explained by continuous infection of CD4+ T-cells at this level, even in the context of suppressed plasma viremia. The level of infection in the GI tract in patients on HAART is at least tenfold higher than in peripheral blood. This finding might explain the absence of both CD4+ and CD8+ HIV-specific T-cell responses in the gut.

In other compartments, such as lung mucosa, maintenance of CD4+ T-cells and low virus replication levels has been noticed. The preservation of CD4+ T-cells in this tissue correlates with maintenance of HIV-specific T-cell responses and low cellular proviral load. Further studies are needed to better delineate the role of HIV-specific responses in the maintenance of CD4+ T-cells and how this is linked to what is observed in peripheral blood.

Finally, supporting the influence of the GI-tract CD4+ T-cell depletion on HIV disease progression, studies in long-term non-progressors have shown a maintenance of these cells associated with a suppression of viral replication in the gut-associated mucosa. Interestingly, initiation of HAART during primary HIV infection can reconstitute gut-associated CD4+ T-cells and lead to better control of virus replication in this tissue. In summary, the current evidence suggests that the GI tract is the main organ supporting viral replication and CD4+ T-cell depletion in HIV infection. Immune activation is the main driving force for inducing both CD4+ T-cell depletion and disease progression.

José M. Benito
Service of Infectious Diseases
Hospital Carlos III
Madrid

48-Weeks Results of the RESIST Trials

The one year results of the RESIST trials were reported at the last Retrovirus Conference, held in Denver in February, 2006. Tipranavir is a non-peptidic protease inhibitor (PI) recently approved in several countries for the treatment of HIV infection. The drug has been designed to be active against PI-resistant viruses. RESIST trials 1 and 2 are prospective, multicenter studies in which heavily antiretroviral-experienced patients were randomized to be rescued with TPV/r or a comparative PI (CPI/r), in all cases with an optimized backbone of other antiretroviral drugs. The two studies record the largest number of pretreated, HIV-infected patients so far evaluated in the context of a clinical trial. A total of 1483 individuals have been recruited in RESIST 1 and 2, 746 on TPV/r and 737 on CPI/r. Of note, nearly half of the patients in the comparator arm were on lopinavir/r.

Table 1. Proportion of patients with treatment response (>1 log reduction in plasma HIV-RNA) in the RESIST trials at 48 weeks, stratified by baseline CD4 count and viral load

	TPV/r	CPI/r
CD4 count (cells/mm^3)		
> 350	41.3%	21.8%
200-350	40.9%	18.4%
50-200	33.8%	16%
< 50	18.4%	6.3%
Plasma HIV-RNA (copies/ml)		
< 10,000	54.1%	33.3%
10,000-100,000	33.5%	15.7%
> 100,000	25.7%	7.6%

Risk of treatment failure was 34% lower in TPV/r *versus* CPI/r ($p < 0.001$). Moreover, treatment response was more durable on average on TPV/r than on CPI/r. The virologic response (> 1 log reduction in plasma HIV-RNA) at 12 months according to baseline parameters is recorded in the table 1.

According to these results, initiating TPV/r in antiretroviral-experienced patients with lower baseline viral loads or higher CD4 counts will significantly improve the chances of virologic response.

Pilar Garcia-Gasco
Service of Infections Diseases
Hospital Carlos III
Madrid, Spain

Three-Year Final Results of the NEFA Simplification Trial

The NEFA trial was a randomized study in which 460 HIV-infected patients taking two nucleoside analogs plus at least one protease inhibitor, and having undetectable plasma HIV-RNA for longer than six months were randomized to switch to nevirapine (n = 155), efavirenz (n = 156), or abacavir (n=149). The results at one year had been reported earlier (Martinez, et al. N Engl J Med 2003;349: 1036-46). At the last Retrovirus Conference, the three-year final results were reported. Overall, 11% in the nevirapine arm, 15% in the efavirenz arm, and 23% in the abacavir arm reached the protocol-defined end-points (death, progression to AIDS, or virologic failure) on an intent-to-treat basis. The significantly greater benefit of nevirapine over the other two arms was mainly driven by a higher incidence of side effects with efavirenz and a greater rate of virologic failure with abacavir.

Nuria Simarro
Service of Infections Diseases
Hospital Carlos III
Madrid, Spain