Hot News

A Third Pathogenic and Lymphotropic Human Retrovirus

Human gamma retrovirus XMRV (xenotropic murine leukemia-related virus) was originally discovered in a subset of prostate cancers linked to an ineffective ribonuclease L (RNaseL)-mediated antiviral pathway (Urisman, et al. PLoS Pathog. 2006;2:e25). Surprisingly, the recent discovery of infectious XMRV in peripheral blood of a majority of chronic fatigue syndrome (CFS) patients (Lombardi, et al. Science. 2009;326:585-9) confirms and extends the clinical relevance of this third pathogenic human retrovirus, in addition to HTLV-1 (delta retrovirus) and HIV (lentivirus).

Chronic fatigue syndrome is characterized by persistent or relapsing debilitating fatigue, musculoskeletal pain, and neurocognitive difficulties, as well as immunological abnormalities (Reeves, et al. BMC Med. 2005;3:19; Devanur, et al. Clin Virol. 2006;37:139-50). Due to its unknown etiology, no clinical or biomarkers for diagnosis and no effective treatments are currently available for the estimated 15-20 million CFS patients worldwide. Although it is tempting to assume a causal link between XMRV and CFS, it is unclear if primary XMRV infection might subsequently trigger the other viral (herpes-, arbo- and enterovirus) and nonviral infections which have been epidemiologically linked to CFS onset. However, currently available molecular techniques and large databases, including longitudinal samples, should rapidly reveal if XMRV infection is, at least temporally, related to disease onset or rather precedes it by several years or decades, similar to HIV-1 and HTLV-1. Both hypotheses might in fact be correct since CFS is generally characterized by a sudden onset reminiscent of acute (viral?) infection, whereas prostate cancer mainly affects the elderly and might be accompanied by a steady decline in (antiretroviral) immune function over time.

If XMRV is a not a mere environmental trigger but a major factor, or even the main etiological agent in CFS pathogenesis, diagnostic tests and possibly specific treatment will finally be available to millions of patients worldwide. If the retroviral link revealed by Lombardi, et al. turns out to be "druggable", CFS will automatically upgrade from a neglected disease to a "hot target" for the pharmaceutical industry. The million dollar question is in fact if specific "XMRV/CFS" treatment would simply drain from the vast arsenal of HIV antiretrovirals or focus on immunomodulators or novel drug classes.

What might nearly three decades of research in HTLV and HIV teach us about this newcomer? First, the sequence data presented by Lombardi, et al., albeit limited, seems to suggest that XMRV, much like HTLV-1 (Van Dooren, et al. Mol Biol Evol. 2004;21:603-11), may be a slowly evolving retrovirus, indicating viral propagation might occur mainly through host cell replication rather than through HIV-like, reverse transcriptase-mediated, cell-to-cell spread. Second, the demonstration by Lombardi, et al. of infectious XMRV in lymphocytes and plasma suggests the same transmission routes as HIV and HTLV: maternofetal (including breast feeding), sexual, and exposure to blood products. However, previously described outbreaks of "epidemic" CFS, e.g. in a symphonic orchestra, a school, and a convent, challenge an HIV-like epidemiological spread. It remains to be established whether the degree of genetic variability is sufficient to allow the reconstruction of transmission chains, as is frequently done for HIV-1 (Lemey, et al. AIDS. 2005;19:1649-58). Third, XMRV infects prostate cancer cells but is also lymphotropic. According to Lombardi, et al., both B-cells and T-cells can be infected, similar to HTLV-1, which can use several ubiquitously expressed receptors (glucose transporter 1, and others), in contrast to CD4-restricted HIV infection. Likewise, CD4 or CD8 T-cell subsets are not quantitatively different in CFS patients (Tirelli, et al. Scand J Immunol. 1994;40:601-8), but altered NK cell levels and function have been repeatedly reported. Thus, considering the pathogenic profile, molecular evolution, and broad cellular tropism, including pan-lymphotropism, XMRV seems to display HTLV-1-like characteristics.

In sharp contrast to the formidable advance in HIV-1/AIDS treatment, no effective treatment is currently available for the severe and mostly fatal neurodegenerative (HAM/TSP) and leukemic (ATLL) diseases associated with HTLV-1 infection. This renewed attention for non-HIV pathogenic retroviruses might eventually benefit an equally large (10-20 million) population of HTLV-1-infected individuals. However, much unlike HIV-1/AIDS and HTLV-1-associated illnesses, adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropic spastic paraparesis (HAM/TSP), where disease onset takes years or decades, respectively, CFS is generally characterized by a sudden onset, most often accompanied by flu-like syndromes. Finally, with a prevalence of 3-4% in the healthy population (Lombardi, et al.), XMRV may turn out to be the most common of the human pathogenic retroviral triumvirate, although larger epidemiological studies are obviously required.

Considering the dramatic and opposite effects of the clinical impact of HIV/HTLV-1 vs. HIV/HTLV-2 coinfection (Casoli, et al. AIDS Rev. 2007;9:140-9), XMRV might not be a mere bystander in coinfection with either HIV or HTLV, and hence screening of both asymptomatic and patient cohorts might actually yield surprising results.

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Dynamics of Transmitted HIV-1 Drug Resistance – The San Francisco Model

Transmission of drug resistance in the context of HIV-1 treatment is an important threat for the efficient control of the HIV-1 pandemic. The recent initiation of antiretroviral therapy (ARV) programs in Africa highlights the importance of studying this problem in more depth. In a recent issue of Science (Smith, et al. Science. 2010;327:697-701) a mathematical analysis was presented of the transmission of HIV-1 drug-resistant strains in the San Francisco community of men who have sex with men (MSM). The model is able to track the accumulation of resistance against multiple drug classes. By setting parameters for the model with detailed data on the San Francisco's MSM community, the authors tried to understand and predict the evolutionary dynamics of wild-type and multiple ARV-resistant strains in this population. The initial conditions of the model were calibrated to match the epidemiological conditions in San Francisco in 1987 when zidovudine (AZT) was introduced. Then, the model was used to simulate the evolutionary history of ARV resistance in San Francisco and to predict its future dynamics.

The model estimated the overall level of transmitted drug resistance (TDR) in 2008 at 14%, which is in agreement with the most recent empirical estimates of 13-16% (Truong, et al. AIDS. 2006;20:2193-7). The simulation of the next five years (2008-2013) predicts that single-class resistance to nucleoside reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI) will remain at current levels (< 2%), but nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance will increase to a level depending on the use of NNRTI in the drug regimens and on adherence to therapy. These results are in contrast with recent results from Europe, where the overall prevalence of TDR between September 2002 and December 2005 was found to be 8.4%, and the prevalence of NNRTI resistance declined after an initial increase (Vercauteren, et al. Retrovirology. 2008;5:12; Vercauteren, et al. J Infect Dis. 2009;200:1503-8). On the other hand, recent data have confirmed that the emergence of drug resistance at the population level is more frequent against NNRTI than against PI (UK Collaborative Group on HIV Drug Resistance. Clin Infect Dis. 2010;50:1275-85).

An important result from the modeling was the identification of the strongest determinants of TDR. These included, in decreasing order of importance, the length of the untreated asymptomatic period (faster disease progression prompted earlier treatment and therefore more TDR); the transmissibility of wild-type strains of HIV from both untreated and treated individuals (a higher transmissibility of the former decreased while of the latter increased TDR); and the degree of viral suppression in treated patients and the relative transmissibility of drug-resistant strains. These predictions have implications that point beyond the San Francisco epidemic. In Africa, the asymptomatic period might be shorter, which could facilitate TDR according to the model results. The authors also caution that emerging NNRTI resistance could have particularly severe consequences in resource-limited countries, where first-line regimens are based on NRTI/NNRTI combinations and second-line treatments are hardly available. In addition, the strong effect of per-act transmissibility from untreated wild-type infections might imply that groups with higher transmission probabilities (e.g. MSM vs. heterosexuals, populations with low vs. high rates of circumcision) might experience less TDR. In this context, it calls for an explanation why the San Francisco MSM community shows especially high levels of transmitted drug resistance. The study has also found that NNRTI-resistant viruses were capable of sustained transmission in the majority of the simulations. However, the strains resistant to other drug classes were typically unable to persist by continued transmission; their presence in the population must therefore have depended on new repeated *de novo* emergence of drug resistance.

The model of Smith, et al. tracked broad classes of drug resistance, but did not implement individual resistance mutations, specific treatment regimens, or the sexual contact network over which HIV-1 is spreading. This level of detail requires stochastic, individual-based modeling (Phillips, et al. HIV Med. 2007;8:536-46). Such models are needed to follow the accumulation of individual mutations in the complex evolution of drug resistance at the population level, and also to understand the patterns of transmission over the sexual network. For example, in the future it will be important to investigate the clustering of transmitted drug resistance in the transmission

network. This will help to understand whether TDR is propagated efficiently from rare cases of *de novo* emergence to form large clusters of transmission, or if frequent emergence and inefficient spread generate a greater number of small drug resistance transmission clusters that do not propagate much further in the transmission network. Finally, individual-based models with explicitly implemented resistance mutations and drugs offer the possibility to assess the maximum potential efficacy of available treatments to suppress virus replication in both the currently untreated and treated infected populations. This "epidemic management potential", including the threat of drug resistance, would be the most direct measure of the success of epidemic control strategies, and a target for maximization.

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Test and Treat For Prevention of New HIV Infections

A new and potentially important prevention strategy for HIV infection is "test and treat", in which positive testing is followed by treatment (Montaner, et al. Lancet. 2006;368:531-6). HIV testing can reduce new infections as individuals aware of their HIV status can reduce their risk behavior (Marks, et al. AIDS. 2006;20:1447-50). Treatment of infected individuals can prevent new infections as antiretroviral drugs suppress the viral load, which is the key factor driving transmission of HIV (Quinn, et al. N Engl J Med. 2000;342:921-9). Granich, et al. explored this "test and treat" approach in a key mathematical modeling study (Granich, et al. Lancet. 2009;373:48-57). Most importantly, they predicted that annual voluntary HIV testing followed by immediate start of antiretroviral drugs for those individuals who test positive regardless of their CD4 count, could reduce the HIV pandemic to one incident case of HIV per 1,000 people within a decade. However, the mathematical model made several assumptions which may not be practical in a clinical setting. These challenges are outlined below.

Achieving universal HIV testing can be a challenge in daily practice (Dieffenbach, et al. JAMA. 2009;301:2380-2), although not impossible as shown in Kenya where large numbers of individuals are tested for HIV (Alsop. Lancet. 2010;375:1242). Moreover, several studies have reported that many patients are not retained in care after a positive HIV test (Roden, et al. PLoS Med. 2007;4:e298), and can therefore not benefit from antiretroviral treatment.

Another challenge of universal HIV testing is the window phase of antibody based HIV tests. This phase denies identification of subjects in the brief and highly infectious, acute stage of infection (Pilcher, et al. AIDS. 2007;21:1723-30). Studies from Quebec (Brenner, et al. J Infect Dis. 2007;195:951-9) and Switzerland (Yerly, et al. AIDS. 2001;15:2287-92) have reported that the acute stage contributes to a disproportionately high number of new HIV infections. However, it has not been established if the acute stage also plays an important role in onwards transmission in generalized epidemics.

Another challenging assumption is starting treatment regardless of the CD4 count. This assumption suggests that some patients may start treatment at a high CD4 count when they do not yet require antiretroviral drugs (Hammer, et al. JAMA. 2006;296:827-43). Providing antiretrovirals at high CD4 T-cell counts may not be achievable in resource-poor settings due to financial constraints. For instance, some hospitals in Uganda place new patients on waiting lists as they do not have the resources to provide antiretrovirals to all them (McNeil. At Front Lines, AIDS War Is Falling Apart. New York Times. May, 10, 2010).

Finally, the mathematical model did not include loss of sexual inhibition. Any efficacious HIV prevention strategy can lead to behavioral disinhibition, in which a reduced fear of HIV leads to increased risk behavior. Previous modeling has shown that increased risk behavior can lead to a loss of any prevention achieved through expanded access to antiretrovirals (Velasco-Hernandez, et al. Lancet Infect Dis. 2002;2:487-93). Additionally, expanded access to drugs in a test and treat program may lead to an increased rate of drug resistance, which can then be transmitted to others (Vercauteren, et al. J Infect Dis. 2009;200:1503-8).

In summary, Granich, et al. made a very important contribution to the use of "test and treat" as a prevention strategy. Future mathematical modeling should include further refinements as described above. The efficacy of this approach for prevention of new HIV infections should be thoroughly investigated in a clinical setting. Moreover, surveillance of HIV drug resistance is recommended in regions where "test and treat" programs are established.

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