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HIV JournalView



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Looking Beyond HIV Viral Loads

A review of:

Predictive value of plasma HIV RNA level on rate of CD4 T-cell decline in untreated HIV infection.
Benigno Rodríguez, Ajay K. Sethi, Vinay K. Cheruvu, Wilma Mackay, Ronald J. Bosch, Mari Kitahata, Stephen L. Boswell, W. Christopher Mathews, David R. Bangsberg, Jeffrey Martin, Christopher C. Whalen, Scott Sieg, Suhrida Yadavalli, Steven G. Deeks, Michael M. Lederman. *Journal of the American Medical Association.* September 27, 2006;296(12):1498-1506.

One of the most interesting articles published in the month of September was one from Benigno Rodríguez et al, which appeared in the Sept. 27 issue of the *Journal of the American Medical Association*. For over a decade now, clinicians have known that patients with high baseline HIV RNA loads tend to experience faster disease progression than those who have lower viral loads. Being able to use *baseline* viral load information to predict the speed of CD4+ T-cell decay over time would be useful for estimating the appropriate timing of

STUDY SNAPSHOT

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| Design: | Retrospective, repeated-measures analysis to determine the accuracy of using baseline HIV-1 RNA measurements for predicting CD4+ T-cell loss over time. |
| Population: | Two cohorts of untreated individuals with chronic HIV-1 infection: one involving 1,289 individuals treated at four U.S. medical teaching institutions, and one involving 1,512 individuals included in the MACS cohort. |

antiretroviral therapy initiation. There is, however, a great deal of overlap between fast and slow progressors, and it is extremely difficult to use a single or a few HIV RNA thresholds in an individual patient to predict the rate of CD4+ T-cell loss over time in the absence of treatment.

In this paper, Rodríguez and his collaborators specifically examined the question of just how well a baseline viral load can predict a decline in

CD4+ cell count over time. They looked at two cohorts of untreated, HIV-infected individuals: one involving several U.S. teaching institutions and a second confirmatory cohort that included individuals from the Multicenter AIDS Cohort Study (MACS), an ongoing, multi-site, prospective study in the United States of the natural and treated histories of HIV in men who have sex with men. The investigators determined that, at best, the baseline viral load predicts only 8% to 10% of the variability of CD4+ T-cell decay.

The Bottom Line

The most important implication of this study, which has yet to be confirmed in other settings, is the limited utility of applying baseline viral load measurements to guide decisions about the initiation of antiretroviral therapy.

In fact, even the current HIV treatment guidelines recognize the limited role that baseline viral load plays in the decision to start therapy.¹ The critical factor in deciding when to start antiretroviral therapy is the absolute CD4+ cell count. The current maximum threshold for the initiation of antiretroviral therapy in the developed world is 350 cells/mm³; however, I would not be surprised if this threshold swings back to a higher number in the future.

Another important implication of this study is that it shows us just how much we do not understand about the mechanisms that drive the CD4+ T-cell loss that characterizes HIV infection and lies at the heart of its pathogenesis. Although we are 25 years into the HIV/AIDS epidemic, this issue still remains as one of the biggest mysteries of the disease. We know that genetic factors play a significant role in immunologic decline, because particular sequence variations in the genes encoding human leukocyte antigen (HLA) receptors and CCR5 receptors are associated with fast or slow disease progression. We also know that the massive destruction of CD4+ T cells in the intestinal mucosa that occurs after primary infection with HIV is probably very important in predicting the subsequent course of the disease. Likewise, chronic immune activation plays a significant role in the destruction of CD4+ T cells during the chronic phase of the disease. When CD4+ T cells become activated, they are programmed to die in a process known as programmed cell death. HIV infection is characterized by permanent CD4+ T-cell activation and thus continuous CD4+ T-cell death. In fact, in one study, markers of CD4+ T-cell activation were a better prognostic predictor of HIV disease progression than viral load.

This article has generated considerable discussion among clinicians and researchers and has reactivated an old discussion in the field of HIV between virologists, who strictly consider HIV infection and AIDS to be a viral disease, and immunologists, who tend to place more stress on the role of the immune system in HIV pathogenesis. Hopefully studies like this will focus the attention of researchers on non-virological factors as potential therapeutic targets for the treatment of HIV infection.

Unfortunately, the success of targeting pathways distinct from the HIV virus itself has been very limited thus far. Interleukin-2, which is a cytokine that increases CD4+ T-cell production, has been in development for almost two decades and has yet to make it as a promising therapeutic. Interleukin-2 is approved in some European countries for compassionate use in patients with discordant responses (for example, in those with virologic suppression, but poor CD4+ cell count

Main Results:

Individuals who presented with higher baseline HIV-1 RNA levels experienced greater subsequent CD4+ cell count declines. This trend was observed across several categories of baseline HIV-1 RNA load, yet only 4% to 6% of the variability in CD4+ cell count loss was explained by these baseline values. The use of multiple HIV-1 RNA measurements or the analysis of individuals with only high baseline viral loads slightly improved the correlation between baseline HIV-1 RNA and CD4+ cell count decline ($R^2 = 0.09$).

Significance:

Baseline viral load only minimally predicts the rate of CD4+ T-cell decline in untreated individuals, suggesting that other factors, as yet undefined, play a more significant role in driving CD4+ T-cell loss.

increases). Hopefully, in the next couple of years, we will see the results of large, randomized trials that are addressing whether CD4+ cell count improvements associated with the use of interleukin-2 produce better clinical outcomes.

Delays in the Diagnosis of Lung Cancer Among HIV-Infected Patients Are Linked to Increased Mortality

A review of:

Delayed diagnosis and elevated mortality in an urban population with HIV and lung cancer: implications for patient care. Malcolm V. Brock, Craig M. Hooker, Eric A. Engels, Richard D. Moore, Maura L. Gillison, Anthony J. Alberg, Jeanne C. Keruly, Stephen C. Yang, Richard F. Heitmiller, Stephen B. Baylin, James G. Herman, Julie R. Brahmer. *Journal of Acquired Immune Deficiency Syndromes*. September 2006;43(1):47-55.

Lung cancer in HIV-infected patients has particular characteristics that make it somewhat different from the types of lung cancer observed in the general population. There is a predominance of adenocarcinoma and a relatively lower frequency of small-cell lung cancer. As in the general population, the disease tends to occur in individuals who smoke, and the prevalence of smoking happens to be very high among HIV-infected individuals. Frequently, these cancers develop in HIV-infected patients with relatively high CD4 + cell counts and occur before the development of any opportunistic infections.

Another important study published in September comes from Johns Hopkins University where clinicians assessed their experience with lung cancer in patients with

HIV infection. Based on 92 biopsy-proven cases of lung cancer in HIV-infected individuals, compared with 4,973 cases in HIV-indeterminate individuals, the investigators showed that lung cancer in the HIV-infected population:

1. is very aggressive (stage III/IV disease: 87% versus 70%; $P < .001$),
2. tends to occur at a younger age (age < 50 years: 65% versus 11.5%; $P < .001$), and
3. results in poor overall survival in comparison with the population without HIV infection (median overall survival: 6.3 versus 9.4 months; $P < .001$).

The main factors for this worse prognosis were black race, which is probably a surrogate for poor access to medical care, and advanced lung cancer staging. When these variables were controlled for in a multivariate analysis, HIV status was no longer predictive of a poorer outcome (hazard ratio [HR]: 1.04; 95% confidence interval [CI]: 0.83-1.32).

STUDY SNAPSHOT

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| Design: | Retrospective study evaluating the clinical diagnosis of lung cancer in HIV-infected individuals. |
| Population: | Ninety-two HIV-infected individuals and 4,973 HIV-indeterminate individuals (comparator group) diagnosed with lung cancer at Johns Hopkins Hospital between 1986 and 2004. |
| Main Results: | HIV-infected individuals with lung cancer presented at a younger age and with more advanced cancer. Mortality was higher in HIV-infected versus HIV-uninfected individuals (HR: 1.57; 95% CI: 1.25-1.96), with 92% dying from lung cancer. Advanced cancer staging and black race correlated with worse survival; HIV infection was not associated with increased mortality after correcting for these factors (HR: 1.04; 95% CI: 0.83-1.32). Chest radiographs were unreliable for detecting lung cancer. |
| Significance: | HIV-infected individuals have a shorter survival time following lung cancer diagnosis due to more advanced lung cancer presentation than HIV-uninfected individuals. Clinicians should be more wary of lung cancer in HIV-infected individuals and should not over-rely on chest radiographs for early detection. |

Significant delays in diagnosis certainly contributed to the very advanced presentations: Most patients (87%) presented with advanced disease and many (69%) had metastases in other organs. As this study proves, the advanced disease stage is the main factor affecting long-term prognosis.

The Bottom Line

The main clinical implication of this study is that clinicians should be aware of the difficulties in diagnosing early-stage lung cancer in HIV-infected patients. As such, health care providers should have a low threshold for considering a further diagnostic workup for patients with unexplained pulmonary or systemic symptoms and abnormal chest x-rays, especially if they are smokers. The workup options include a computed tomography (CT) chest scan and a bronchoscopy. Hopefully this study will also lead pulmonary physicians to lower their thresholds for performing bronchoscopies in this population.

The other important clinical implication is that physicians caring for HIV-infected patients should strongly encourage smoking cessation. HIV infection and its treatment are associated with an increased cardiovascular risk, and this study demonstrates that the development of lung cancer in this population carries a particularly poor prognosis. Smoking cessation can decrease both the incidence of vascular disease and lung cancer to ultimately improve the long-term clinical outcomes in these patients.

Does Enfuvirtide Interact With Other Antiretrovirals?

A review of:

Unexpected drug-drug interaction between tipranavir/ritonavir and enfuvirtide. Daniel Gonzalez de Requena, Andrea Calcagno, Stefano Bonora, Laura Ladetto, Antonio D'Avolio, Mauro Sciandra, Marco Siccardi, Olivia Bargiacchi, Alessandro Sinicco, Giovanni Di Perri. AIDS. October 3, 2006;20(15):1977-1979.

Sometimes you notice an article that, although intriguing, you can't tell whether it's going to end up having any significance. This research letter that was published in *AIDS* is one such article. This study might unveil something that is extremely important, or it may be just a fluke. As is usual with such ambiguous studies, the main conclusion of this paper is that further studies are needed.

In summary, these Italian investigators looked at the concentrations of tipranavir (TPV, Aptivus) and ritonavir (RTV, Norvir) in HIV-infected patients, half of whom were also receiving enfuvirtide (T-20, Fuzeon). To their surprise -- and to mine

-- they found that the levels of tipranavir + ritonavir were higher among the patients who were concomitantly receiving enfuvirtide. These elevations were significant, at approximately 50% above the values observed in patients not on enfuvirtide, which could have at least two clinical implications for tipranavir + ritonavir administration in combination with enfuvirtide: (1) increased antiretroviral activity and (2) increased toxicity.

STUDY SNAPSHOT

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| Design: | Observational analysis of tipranavir and ritonavir plasma concentrations determined using high-pressure liquid chromatography. |
| Population: | Fifty-five HIV-infected individuals receiving tipranavir + ritonavir + two NRTIs ± enfuvirtide (n = 27 with enfuvirtide; n = 28 without enfuvirtide). |
| Main Results: | Individuals receiving enfuvirtide, in comparison with those who were not, demonstrated higher mean trough tipranavir concentrations (41,069 ± 20,174 ng/mL vs. 27,261 ± 17,516 ng/mL; <i>P</i> = .011) and ritonavir concentrations (371 ± 333 ng/mL vs. 188 ± 139 ng/mL; <i>P</i> = .017). Pharmacokinetic modeling suggested that the primary factors driving tipranavir + ritonavir increases included higher volumes of distribution and longer half-lives. |
| Significance: | Increased tipranavir + ritonavir exposure during co-administration with enfuvirtide could affect the virologic potency and/or the toxicity of the antiretroviral regimen. |

The Bottom Line

Many studies have shown that the addition of enfuvirtide to optimized background regimens increases the probability of a virologic response in patients with multi-drug resistance. It has always been thought that this was due to the potent antiretroviral activity of enfuvirtide. This study suggests that *increased concentrations* of some antiretrovirals in the presence of enfuvirtide might also play a role in virologic suppression. Moreover, treatment with tipranavir + ritonavir has been associated with increases in liver enzyme levels and sometimes hepatotoxicity. Since tipranavir + ritonavir is almost always used in conjunction with enfuvirtide, these problems may be caused by increased protease inhibitor exposure resulting from drug-drug interactions between tipranavir + ritonavir and enfuvirtide.

No major clinical implications should be drawn from this study until the results are confirmed. The main, and very significant, limitation of this report is that the analysis was not a formal pharmacokinetic study; the investigators used samples that were collected for other reasons, and then the pharmacokinetics were retrospectively modeled. The authors also had difficulty finding a biologically plausible mechanism to explain the drug-drug interaction.

Other studies looking at enfuvirtide have not found significant interactions with other antiretrovirals. My feeling after reading this article is that I want to hear more about potential drug-drug interactions with enfuvirtide. However, at this point, I am not going to change my practice as a consequence of these preliminary findings.

The Time for HPV Prevention Has Come

A review of:

Prevalence of HPV infection among men: a systematic review of the literature. Eileen F. Dunne, Carrie M. Nielson, Katherine M. Stone, Lauri E. Markowitz, Anna R. Giuliano. The Journal of Infectious Diseases. October 15, 2006;194(8):1044-1057.

Infection with human papillomavirus (HPV) is an important health issue. We all know that HPV infection is of considerable concern in women, because of its association with cervical cancer. Women acquire HPV infection from men, yet surprisingly little is known about the epidemiology of this viral infection and its natural history in men.

Fortunately, infection with the virus is now preventable. The U.S. Food and Drug Administration recently approved a new vaccine for the prevention of HPV infections among women. This vaccine, manufactured by Merck & Co., Inc., is very effective at preventing new infection with serogroups 16 and 18, which are the oncogenic

viruses that produce most cases of cervical cancer in women. The vaccine is also effective at preventing infection with serogroups 6 and 11, which are responsible for genital warts. The vaccine has not yet been approved for use in males, although it is currently being evaluated in men who have sex with men.

STUDY SNAPSHOT

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| Design: | A systematic review of 40 articles on HPV DNA detection and HPV risk factors in men published between Jan. 1, 1990 and Feb. 1, 2006. Of the 40 articles, 27 examined multiple anatomical sites/specimens for HPV detection, 10 evaluated single sites/specimens and three evaluated risk factors or optimal sites/specimens. |
| Main Results: | The prevalence of HPV in men ranged from 1.3% to 72.9% in studies evaluating multiple anatomical sites/specimens; 15 (56%) of these studies reported an HPV prevalence \geq 20%. HPV prevalence varied based on sampling methods, processing methods and the sites/specimens assessed. In nine studies that evaluated HPV seroprevalence in both men and women, eight showed that HPV seroprevalence was lower in men than in women. |
| Significance: | The prevalence of HPV infection is high in sexually active men. Future natural history studies and studies that model the potential impact of prophylactic HPV vaccination may benefit from this analysis. |

This study from the U.S. Centers for Disease Control and Prevention (CDC) is a systematic review

of the literature that was designed to evaluate the frequency of HPV infection in heterosexual men.

The CDC investigators reviewed all papers published over more than a decade on HPV infections in men. The results of this study are not earth shattering: The prevalence of HPV infection among heterosexual males in the United States is greater than 20%, similar to the prevalence of genital herpes. In addition, increased sexual activity is associated with an increased risk of infection with HPV.

The investigators also found that consistent condom use was associated with a decreased rate of infection -- a factor that has been questioned in the past, even on the CDC Web site. Circumcision, which lately is becoming popular as a potential tool to prevent HIV transmission, was also protective against HPV infection. The prevalence of HPV types 16 and 18 was lower among men than among women for reasons that are not completely clear.

The Bottom Line

I am not a big fan of literature reviews, but the issue of HPV is currently in the news and it is impossible to ignore it.

The information provided by this study can help evaluate the potential impact that a vaccine could have in the general population. There has been considerable controversy about the use of the HPV vaccine, even among women. In order for the vaccine to be successful, it has to be administered before women become infected with the virus. In other words, the vaccine has to be given to girls between 11 and 13 years of age before they become sexually active. In a very twisted argument, some ultraconservative activist groups claim that this type of vaccination encourages increased sexual activity, because it removes the fear of acquiring HPV and hence gives young girls a false sense of security. It is very difficult for me to comprehend the rationale behind this type of argument, so I will not even try to go there.

Studies like this one show the profound impact that HPV infection can have on our society, and hopefully this information will promote a rational evaluation of the utility of an HPV vaccine in males. Clinicians should remember that this vaccine is extraordinarily effective in women and thus far has demonstrated 100% effectiveness in preventing cervical cancer. This is the first real cancer vaccine -- one of the Holy Grails for medicine in the 21st century.

Reference

1. Panel on Clinical Practices for Treatment of HIV Infection. [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#). U.S. Dept of Health and Human Services; October 10, 2006.

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