Laurence Editorial

Update From Seattle: The 9th Annual Retrovirus Conference

Jeffrey Laurence, MD


Introduction

The opening ceremony for the 9th Annual Retrovirus Conference, held in Seattle on February 24 to 28, 2002, was different from any I can recall. First, the keynote speaker was not a scientist or public health official but a philanthropist, Bill Gates, chairman of Microsoft and president of the Bill and Melinda Gates Foundation. Second, Mr Gates was one of the few -- if not the only -- opening plenary speakers in the history of the conference to take questions from the audience. This exchange was more than a bit amusing but did make an interesting introduction to the state of HIV vaccine technology.

Computer Viruses, Digital Sentinels, Vaccines

After making a somewhat strained analogy between vaccines and the "digital sentinels" built into some computers -- permitting them to become infected, so that the types of electronic viruses and worms they might be exposed to could be sampled and appropriate defenses designed -- Gates focused on a key mission for funding by his foundation: testing of AIDS vaccine candidates. When questioned as to why he had taken this approach, given that an effective sterilizing vaccine was almost certainly decades away while new treatments and distribution of available drugs were needed by millions right now, he admonished the audience to be less pessimistic about current vaccine technology. "I've seen the CTL data," Gates quipped.

Cytotoxic T lymphocytes (CTLs), along with viral neutralizing antibodies, were certainly much discussed at the conference. But, despite this plug from arguably the world's richest man, advances were modest. Dr Richard Wyatt and colleagues, working at the new NIH AIDS Vaccine Research Center, set the stage in their scholarly analysis of what every vaccine ought to target but at this moment cannot: the CD4-binding epitopes of the HIV outer-envelope glycoprotein gp120. Wyatt presented data and arguments to demonstrate that if the immune system could be focused on a very
"small patch" of the V3 loop of gp120, the Phe43 region, binding of virus to its high-affinity receptor would be destroyed.

But this is not so simple. Large pieces of variable loop structures known as V1 and V2 surround that site, protecting it from immune attack. This steric hindrance, aided by sugar molecules attached to those loops, serves as a gate, permitting CD4 transient access, which is denied to the much larger active sites of a vaccine-induced antibody. The cavity an immune response must access is roughly 1 nm in diameter; immunoglobulins and killer T-cell receptors would be at least twice as wide. In addition, gp120 binds as a trimeric structure and is noncovalently linked to the virion. This means that knobs of gp120 are constantly being shed into the milieu, serving as decoys eliciting nonneutralizing anti-gp120 antibodies.

The magnitude of this problem was outlined mathematically when Wyatt presented a thermal analysis of the CD4-gp120 binding data. There is a huge release of heat (263 kcal/mol), and a large increase in entropy, on viral binding to CD4. The structure of CD4 remains stable, but gp120 changes conformation, locking itself firmly into a bound state. The immune system never gets to see this new critical structure. Given these 5 obstacles to a key vaccine target -- glycosylation, steric barriers, conformational flexibility, variable domains, and unstable subunit association ("shedding") -- what is to be done?

One thought was to force open the binding pocket of gp120/Phe43; such pocket-filling structures are being sought during gp120-CD4-HIV coreceptor crystallizations through a process known as "soaking," and some have been found. (Fortuitously, I had speculated some 12 years ago, based solely on analogy with rhinovirus neutralizations, that this approach might serve as a novel vaccine strategy for AIDS. [2])

Dr Emini [3] described a more practical approach to vaccination, based on currently available technology. He noted 3 goals of a vaccine program: to decrease the likelihood of persistent viral infection or initiate a clinically significant decrease in viral load if infection does occur; to elicit HIV-specific CD8[^+^] CTLs, which are broadly neutralizing; and to investigate the utility of a vaccine in a therapeutic strategy with antiretrovirals. His current design involves intramuscular injections of plasmid DNA derived from the Gag capsid of HIV-1 clade B, "codon-optimized" for best gene transcription. The DNA, in an alum or other adjuvant, would be given in conjunction with a replication-defective adenovirus type 5 vector.

Phase 1 clinical trials with HIV-negative and -positive volunteers are to be completed in February 2003. In terms of DNA vaccinations administered among 109 HIV-negative persons, the highest dose (5 mg) showed T-cell production of interferon-\(\gamma\) in response to HIV Gag peptide pools in 9 of 37 persons at week 12 and in 16 of 38 at week 30. In terms of the virus vector, preliminary data using titers of gag-Adeno from \(10^8\) to \(10^7\), administered at 0, 4, 8, and 26 weeks, presented little toxicity: no significant anti-DNA reactivity and only sporadic malaise and body aches. Neutralizing titers against adenovirus were seen that were above those found in the general population of North America (1:200), but at the highest dose of virus, they were not thought to be an obstacle to inducing immune response to Gag.
However, those responses, in terms of killing activity and generation of interferon-\textit{gamma} in response to Gag peptides, were, according to Emini, "moderate." To put this in context, the mean number of Gag peptides recognized by naturally infected persons was 2.8 (range, 1 to 8) but only 1.8 (range, 1 to 4) for vaccinees.

**New Agent: Coreceptor Blockade**

Additional data on an orally bioavailable antagonist of the principal HIV chemokine coreceptor, CCR5, first introduced at this conference last year, looked quite promising. SCH-C, a product of Schering-Plough, is a 558 molecular weight molecule that has a 90\% inhibitory concentration for most primary viral isolates of 100 nmol/L or less.\textsuperscript{[4]} It was administered to 62 healthy volunteers at doses of 25 to 600 mg, with the only side effect being a prolongation of the QT interval for upward of 50 milliseconds (still within the normal range).

Twelve HIV-positive patients infected for a mean of 5.3 years (range, 2 to 10 years) whose antiretrovirals were discontinued for at least 8 weeks and who had CD4 cell counts above 250/\mu L and median viral loads of 38,000 copies/\mu L (range, 8000 to 200,000 copies/\mu L) were then given 25 mg of SCH-C twice a day for 10 days. All patients had CCR5-using, non-syncytium-inducing viral types, as is typical for this stage of infection. Side effects were minimal, including a bad taste (2 of 12), headache (3 of 12), and vasovagal syncope (1 of 12). However, the effects on viral load were dramatic. After a 3-day lag, there was a steep decline in viral load, which was maximal by day 12, followed by a slow increase to baseline by day 28. Responses were variable, averaging 0.5 log in 10 responders. Four patients had a greater than 1 log decrease, however. The reasons for lack of response in 2 patients are unclear; mutations are difficult to define, given lack of data about the precise sites of gp120-CCR5 interactions. Yet, this study indicates that CCR5 is a valid new target for drug discovery.

**When to Start HAART**

Late last year, the culmination of this ongoing discussion seemed to indicate that given the side effects of all HAART regimens and the limited evidence of survival benefit for initiating therapy in asymptomatic persons even at relatively low CD4 cell counts, 200/\mu L might be the new magic number. In an editorial accompanying 2 large studies of surrogate markers and disease progression in relation to HAART, Dr Roger Pomerantz\textsuperscript{[5]} suggested further tailoring of therapy, with the 200 cell/\mu L cutoff appropriate for many patients and clearly inappropriate for those seen within 6 months of HIV seroconversion, when HAART, in securing a low viral setpoint, might be of long-lasting value. As for everyone else, further points of distinction might be needed, such as correction for rate of decline of CD4 cell count and patient age.

Much of this is being driven by some prominent cardiovascular, endocrine, and bone metabolism effects of HAART, particularly the protease inhibitors (PIs). In one recent autopsy comparison of the HIV-infected population over 2 decades,\textsuperscript{[6]} it was found that in those seen in years 1996 to 2000, when HAART came into use, the prevalences of many viral and fungal illnesses, \textit{Mycobacterium avium} complex infection, systemic lymphoma, and Kaposi sarcoma (KS) were lower than in groups
from 1979 to 1986 and 1987 to 1995. Changes in incidence of *Pneumocystis carinii* pneumonia and KS were statistically significant. There was, however, a statistically significant increase in cirrhosis and arteriosclerosis.

Nothing presented at the conference settled this issue. In the key group to consider -- those with CD4 cell counts between 200 and 350/µL -- viral levels alone are clearly insufficient to make a decision regarding therapy; such levels should trigger closer monitoring. What was of interest was the management of those patients already receiving therapy whose therapy seemed to be failing.

Dr Ann Collier addressed this issue in a plenary session. She noted the importance of distinguishing between viral and primary host factors for resistance. The latter include host genetics, poor absorption, impaired clearance, poor activation, and drug-drug interactions. Adherence -- related to social issues, toxicities, and complexity -- is another problem. Given all this, she said it was important to establish key goals for therapy. Generally, the goal is not simply to achieve the maximal obtainable level of suppression of viral RNA (vRNA) but also to improve or maintain immune function to a level that might prolong life or delay disease progression, as well as to achieve a good quality of life and acceptable toxicities.

Collier reviewed a recent study by Dr Steve Deeks of an observational cohort of 483 HIV-positive patients receiving a PI-containing regimen. Sixty-three percent had detectable viral loads, and 291 had CD4 cell counts at or greater than baseline at the time of virologic failure. Of these, about one third (29%) had a successful switch to a salvage regimen, 14% continued with their "failing" regimen, 42% maintained viral suppression for more than 16 weeks before their regimen failed, and 15% died. Of interest were the predictors of failure: vRNA greater than 4.59 log, minor change in vRNA while receiving an initial regimen; and higher baseline CD4 cell count. She concluded that if one had many therapeutic options, changing HAART regimens early made sense. If not, one might better preserve immune function by maintaining a regimen despite rising vRNA load.

In advanced HIV disease (CD4 cell counts below 50/µL), there were independent predictors of poor outcome. These included prior clinical AIDS diagnosis, low hemoglobin level, fewer antiretrovirals taken over the past 3 months, and absence of *Pneumocystis* prophylaxis. In terms of what to do in this situation, Collier was not an advocate of "mega-HAART," because of its complexity, toxicity, and cost. These are 6- to 9-drug regimens that in some trials have achieved complete viral load suppression at 6 to 12 months but often without a rise in CD4 cell count and at a great increase in toxicity. She instead suggested focusing on pharmacokinetic enhancement of existing drug actions, such as with ritonavir-boosted regimens, and investigation of new agents. There are new agents in all classes: nucleoside reverse transcriptase inhibitors such as amdoxovir and D4FC; nonnucleoside reverse transcriptase inhibitors capravine, DPC083, and TMC125; PIs atazanavir, tipranavir, and TM114; and the new entry inhibitors such as T-20. More about these next month.

**References**


---

**Dr Laurence** is professor of medicine and director of the Laboratory for AIDS Virus Research, New York Presbyterian Hospital-Weill Medical College of Cornell University, New York; senior scientific consultant for programs, American Foundation for AIDS Research (amfAR); and editor in chief of *The AIDS Reader*. 

---