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First medication in new class of ARTs poised to be available for salvage therapy

Tropism testing helps determine best patients for drug

HIV clinicians will have a powerful new weapon in the AIDS arsenal when the first CCR5 antagonist receives marketing approval from the Food and Drug Administration. Approval was expected to be given sometime in July or August.

Maraviroc, which is expected to be marketed by Pfizer under the trade name of Celsentri, targets the earliest stage yet in the HIV infection cycle.

"Maraviroc is the first in a class that works by stopping HIV from being able to attach to a human cell prior to infecting the cell," says **W. David Hardy**, MD, director of the Division of Infectious Diseases and the AIDS Program at Cedars-Sinai Medical Center in Los Angeles, CA. Hardy also is an associate professor of medicine in residence at the Geffen School of Medicine at the University of California — Los Angeles.

Research showed that patients treated with maraviroc alone had a viral load decrease of 1.7 logs at 10 days, Hardy says.

"That shows it has a high activity and potency in those patients with CCR5-tropic virus," he says. "That's at the same order as what we'd seen earlier with protease inhibitors and that we're now seeing with integrase inhibitors."

In another study, patients who were given either an optimized background antiretroviral (ART) regimen plus maraviroc once a day or twice a day had twice as good viral suppression and twice as good a rise in CD4 cell counts as patients who received the optimized background ART regimen plus placebo, Hardy says.

"The viral load dropped from 0.8 to 1.1 log greater than those on placebo," he adds. "Maraviroc showed high potency at 24 weeks of treatment."

The other good news is the safety profile for ART regimens that include maraviroc are identical to the safety profile of ART regimens

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plus placebo, Hardy says.

"That's very exciting because side effects have been a real problem for HIV patients," he says. "As we add more drugs we get more side effects, but in this case we saw that the side effects did not increase, and that includes the liver side effects."

Also, there was no increase in kidney toxicity, lipid adverse events, and bone marrow toxicity, Hardy says.

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Editorial Questions?
Call **Jennifer Corbett** at (404) 262-5431.

"The good news is that within 24 weeks of treatment, this drug was effective in terms of doubling its response rate, but without the additional side effects," he adds.

It's taken many years for HIV researchers to develop this type of drug, says Hardy, who has investigated HIV/AIDS since 1983.

"After 10 years or more of research, the detailed molecular biology of how HIV identifies, attaches to, and then inserts itself inside of a human cell has been discovered and clearly described," Hardy explains.

This background work has made it possible for investigators to discover a way to stop the virus from being attached to a cell and exploit this discovery, he says. **(See story on how entry inhibitors work, p. 88.)**

"CCR5 antagonists are a brand-new type of medication in the over-arching class of entry inhibitors," Hardy says. "There are a growing number of compounds called entry inhibitors, and maraviroc is the first one to come before the FDA as a CCR5 antagonist."

The first entry inhibitor to be marketed in the United States is enfuvirtide (Fuzeon), a fusion inhibitor, which blocks the fusion of the cell membrane and viral envelope.

Maraviroc also is the first HIV drug to inhibit a human target instead of a viral target, Hardy says.

"It is blocking on the human side the interaction between a viral protein and a human protein, which couple up for the virus to attach to a cell and get inside," Hardy explains. "Previously, all of our targets utilized as anti-HIV inhibitors have been viral targets."

Maraviroc is unique in other ways, as well. For example, it is used in conjunction with a diagnostic test called tropism testing to determine whether a specific patient's HIV infection would be susceptible to the drug.

When HIV first infects a cell, it can use either the CCR5 in its second attachment step, or it can use the CXCR4 molecule, or it can use both. HIV that uses solely the CCR5 molecule is called CCR5 tropic; HIV that uses both is called dual-tropic, and HIV that uses solely the CXCR4 is CXCR4 tropic, which is a small minority of infections, Hardy says.

Patients who have dual tropic or CXCR4 tropic virus wouldn't derive as much benefit from maraviroc, so clinicians will need to test patients prior to prescribing the drug. The test that's available for tropism testing is called Trofile, developed and marketed by Monogram Bioscience of South San Francisco, CA. Trofile was used by Pfizer

during clinical trials of maraviroc.

"We started working on this technology in 2000," says **Christos Petropoulos**, PhD, vice president of research and development and chief scientific officer of Monogram Biosciences.

"We anticipated this class of drug and used related technology to look at drug resistance to the fusion inhibitor [Fuzeon]," Petropoulos says. "The goal is to identify CXCR4 tropic viruses that are not going to respond to Celsentri, and our method is close to 95 percent sensitive."

With an enhanced technology, the company expects to increase the tropism test's sensitivity level to 95-99 percent, he adds.

"We were working on this test, and Pfizer approached us in 2002 or 2003 and said, 'We heard you have this technology and what can we do to help?'" Petropoulos recalls. "So we collaborated with Pfizer scientifically."

The tropism test is as simple as viral load or genotype testing, Petropoulos says.

Providers take a blood sample and send it to Monogram Biosciences or to a large reference lab. The results are available on-line in about two weeks, he says.

Results from Pfizer's trials showed that patients who have CXCR4 tropic virus or dual tropic virus and were treated with maraviroc had no viral load reduction when compared to placebo, Petropoulos notes.

"Patients did seem to have increasing CD4 cell counts over the placebo arm, so there may be immunological benefit," he adds. "But a lot more work needs to be done before you can make that conclusion, and this was only 24 week data."

The research thus far suggests that providers will need to conduct a tropism test prior to prescribing maraviroc and perhaps during treatment when treatment failure occurs because there's evidence that HIV can switch tropism as patients become experienced in conventional ART, Petropoulos and Hardy say.

"If a patient is on the drug and has a failure, providers can look at it and see whether the drug tropism has switched," Hardy says.

"We don't know what causes a virus to switch from one type of tropic virus to another kind of tropic virus," Hardy adds.

By using the tropism assay, researchers know that among ART-naïve patients, from 85 to 90 percent will have a CCR5-only tropic virus and 10 to 15 percent will have dual-mixed tropic virus, while only about 1 percent will have CXCR4-only tropic virus, Hardy says.

These percentages change as patients become treatment experienced. The more ART regimens a patient has, the more likely it appears to be that his tropism has shifted, he says.

The percentage of treatment-experienced patients with pure CCR5 tropic virus drops down to 50 to 60 percent, with the percentage of dual-mixed tropic virus increasing to 40 to 45 percent, and the number with CXCR4-only tropic virus increasing to 2 to 3 percent, Hardy says.

"As a patient's CD4 t-cell count drops either with or without treatment, there also seems to be the same kind of shift," Hardy adds. "Patients develop some presence of CXCR4 tropic virus as the CD4 cell count gets lower and lower."

Pfizer's initial application for FDA approval is for treatment-experienced patients, but maraviroc could eventually be a good drug for treatment-naïve patients, as well, Hardy says.

More data about the drug's impact on treatment naïve patients are needed before this is possible, he says.

Another factor in maraviroc being offered first to treatment-experienced patients is that their options are much more limited, Hardy says.

"There are lots of different regimens available and very potent ones and well-tolerated ones, and it is a crowded area for treatment-naïve patients," Hardy explains.

Alternately, patients who have been treated on ARTs and are experiencing treatment failure have very limited treatment options, he adds.

"On a personal note, every single one of the patients I have placed on maraviroc has become [HIV] undetectable," he says. "It's the first time I've seen every single patient respond in this fashion, and it's been very rewarding to see that happen."

The study's been unblinded and Hardy knows which patients have received it once a day, twice a day, and which were on placebo, and all except the placebo patients have had an excellent response, he says.

"My perspective on this medication is that it will be a significant addition initially to our armamentarium for experienced patients who need a new medication," Hardy says. "The only qualifier is that they need to have HIV that is CCR5 tropic as defined by an assay, because we can't make that statement about patients who have dual-mixed virus or CXCR4 tropic virus."

An FDA panel of outside experts had recommended that the FDA approve maraviroc, but the FDA delayed its approval, which had been expected in June, 2007, and instead issued an approvable

letter and asked for additional information from Pfizer. The drug already is available in 30 countries through the expanded access program and, also, is pending approval by the European Union. ■

Herpes treatment can help co-infected HIV patients

Research suggests herpes infection increases risk of HIV infection

For about two decades research data have suggested that genital herpes is a risk factor in HIV acquisition. But now there is a growing consensus among investigators that genital herpes may account for a significant proportion of new HIV infection, an expert says.

"If you're HIV negative and have genital herpes -- even if you don't know you're infected with herpes — your risk of becoming HIV infected is increased by two-to-three fold," says **Connie L. Celum,** MD, MPH, a professor of medicine in the Department of Medicine, Division of Allergy and Infectious Diseases, at the University of Washington in Seattle, WA.

People who are co-infected with genital herpes and HIV can have an increase in their HIV levels during herpes reactivation, even when they don't recognize that their herpes is reactivated, Celum says.

"It increases one's viral load, and it increases the infectiousness of HIV in these individuals who have herpes," she explains.

These findings are significant because worldwide an estimated 80 to 85 percent of people who are HIV infected also are infected with herpes simplex virus type 2 (HSV-2), Celum notes.

In a study of 4,295 high-risk, HIV-negative men who have sex with men (MSM), Celum and co-investigators found that the overall HIV acquisition rate was 1.9 per 100 person-years. But among participants who had been recently infected with HSV-2, the HIV acquisition rate was 6.9 per 100 person-years.[1]

This data came from the EXPLORE behavioral intervention study conducted in six United States cities, including San Francisco, CA; Denver, CO; New York, NY; Chicago, IL; Boston, MA, and Seattle.

"We went back at the end of the study and determined HSV-2 data at entry to study and exit and found out who was already infected with herpes when they entered the study and who became infected during the study," Celum says.

"Close to 2 percent acquired herpes during the follow-up period," Celum says. "The risk factors for acquiring herpes were being African American, having unprotected anal sex, having an HIV-positive male sex partner, and having multiple partners, meaning six or more male partners in the prior month."

One out of five men had herpes at baseline, and the men who were infected with HSV had about a 50 percent higher risk of becoming HIV infected than those who were not HSV infected, Celum says.

"The highest risk was among the men who acquired herpes during the follow-up," she adds. "Their risk was more than double."

Researchers now are studying whether herpes treatment can reduce HIV transmission.

"Among HIV-infected persons with herpes, randomized to placebo or a herpes drug, you can lower HIV blood levels by little over a half log during herpes suppression, and there's a little less infection in the genital tract," Celum says.

"So people now are beginning to believe this is not a spurious observation in epidemiological studies," she adds. "You can demonstrate that by doing nothing else, you can get a viral load reduction by suppressing herpes."

In one recent study, investigators found that women infected with HIV who received HSV suppressive therapy with valacyclovir and who were ineligible for highly active antiretroviral therapy (HAART) had a significant decrease in the frequency of genital HIV-1 RNA and in the mean quantity of HIV. HSV treatment also resulted in a reduction in the mean plasma HIV-1 RNA.[2]

The study concludes that its results may be relevant to HIV-1 prevention and management.[2]

"Now we're waiting for a couple of big studies that are asking questions on a larger scale: Can you reduce risk of HIV acquisition among gay men in the Americas and among women in Africa [with HSV treatment]?" Celum says.

Also, researchers would like to answer a question that's very important in the AIDS field about whether viral load reductions in people treated with HSV therapy were durable and significant enough to have an impact on disease progression, Celum notes.

"What one would like to see is a delay to HAART," Celum says.

These are the questions that still need to be more definitively answered, she says:

* Can you suppress herpes and not have someone become HIV infected?

* Can you reduce the risk of transmitting HIV through HSV suppression?

* Can you benefit someone in terms of disease progression through HSV therapy?

Until recently, the HIV medical community has paid less attention to herpes/HIV co-infections than to other co-infections.

"People in general have been [apathetic] about dealing with chronic viral infections," Celum says. "Until you can tell there's an intervention that works, they're not that keen to find another virus, and then when you do you open counseling questions such as when did they get herpes and what does it mean?"

It takes time and resources for HIV clinicians to test and counsel for herpes, and until the recent studies were published, there hasn't seemed to be much reason for doing so, she notes.

"Unless you know it will have an impact on behavior or another transmission risk, they're not interested in doing it," Celum says.

Early in the AIDS epidemic, many providers identified people with HIV because they had persistent HSV-2 infection, but now co-infection largely is overlooked.[3]

"In the post-HAART era, most providers don't see patients come in with painful chronic herpes ulcers that last for weeks, so herpes is not staring them in the face as much as it did 15 years ago, and providers view it as a minor problem," she says. "It's not an opportunistic infection that kills people, and it's largely asymptomatic, so why bother?"

With the recent herpes/HIV studies already published and more on the way, this attitude could change, Celum says.

"We think these data we're waiting for so eagerly may impact public health issues," she says. "Can we use herpes suppression for HIV prevention, or can we use herpes suppression to delay the time until a patient begins HAART? People are watching with interest, but are waiting for those data before they can take this issue more seriously." ■

References:

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Here's how maraviroc and other entry inhibitors work

Expert offers nutshell explanation

Current entry inhibitors under study, including maraviroc, target one of the three stages of HIV's entry into cells.

In the first step, HIV's gp120, which is a glycoprotein, attaches itself to the CD4 protein (helper T-cells), which HIV particularly likes to destroy, explains **W. David Hardy**, MD, director of the Division of Infectious Diseases and the AIDS Program at Cedars-Sinai Medical Center in Los Angeles, CA. Hardy also is an associate professor of medicine in residence at the Geffen School of Medicine at the University of California -- Los Angeles.

"They're very important cells and are termed the conductor of the immunological orchestra," he says. "HIV attaches initially to the CD4 molecule, and there are some entry inhibitors working to disrupt that first attachment step, but those medications are still in clinical development and are not any where near licensure."

The second step is when HIV's gp120 attaches to the second human target called the CCR5 molecule, and once those two attachments have occurred, it allows the virus to stick to the outside of the cell, Hardy says.

"Once it's attached, there's a change that occurs in the virus that allows the virus to harpoon the human cells and cause fusion," he adds. "When the envelope of the virus and cell membrane fuse together the contents [of HIV] are pushed inside the cell."

In short, the three steps are as follows:

* Attachment of gp120 to human CD4 cell;
* Attachment of gp120 to human CCR5 cell;
* Fusion where cell membrane and viral envelope are fused together and attached.

The use of maraviroc, a new antiretroviral that is first in the CCR5 antagonist class, has helped push HIV treatment to an early step in the interaction of HIV and human cells, Hardy notes.

"It's very scientifically satisfying because the earlier we think we can stop the virus from attaching to the cell, the better it is," he says. ■

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Adherence Strategies

Simple pill box organizers improve HIV adherence

Pill boxes work for marginally housed, homeless

San Francisco, CA, investigators found a significantly higher adherence among HIV-infected people who used pill boxes, and the same patients had increased viral suppression.

Researchers studied adherence among a cohort of marginally-housed and homeless people in San Francisco, says **Maya Petersen**, MS, PhD, a medical student at the University of California - San Francisco School of Medicine.

HIV patients were enrolled and followed for several years. Investigators tracked down the participants and conducted unannounced pill counts to measure their medication adherence, Petersen says.

"There are several advantages to unannounced pill counts over other measures," Petersen says. "If you have people come in to the clinic there is an incentive to empty pills ahead of time, and people who self-report often over-report how many pills they've taken."

Investigators collected data on the participants' demographics, viral loads, and CD4 cell counts, as well as their use of recreational drugs, she says.

"We tried to replicate using statistics what we would have seen in randomized, controlled trial," Petersen says. "We needed measurements of all the ways they used pills that might have been different."

Overall, investigators found that participants who used pill boxes were associated with 4 percent higher adherence, as well as increased viral suppression, she says.

"Four percent doesn't sound like a lot, but it is quite a bit in a retrospective study," Petersen says. "It's been associated with an 11 percent reduction in risk progression to clinical AIDS."

The average adherence rate in the entire cohort was 73 percent, Petersen says.

"Those using pill boxes had an 8.8 percent higher adherence," she says. "We didn't take that as the final estimate because it was also true that people who were using pill boxes were in fact different from those who were not using them."

For example, women were more likely to use pill boxes, and people who were homeless were less likely to use them, Petersen explains.

"So we said, 'Women or homeless people might have different underlying abilities to adhere, so we don't want to attribute adherence to them necessarily because of the use of pill boxes,'" she says.

After using various statistical techniques to control for the two groups, the adherence comparison still showed significantly higher adherence for those who used pill boxes, she adds.

On the plus side, pill boxes are very inexpensive, making this step toward improved adherence extremely cost effective, Petersen says.

"When people look in general at interventions to improve adherence, they are quite expensive and involved," she says. "So that's something we thought was exciting about this finding: it's not a piece of high technology, and it costs about $5 at the pharmacy."

Also, there are no apparent risks to people adopting this intervention, and many HIV patients already are using them, including about 60 percent of the cohort studied, Petersen says.

"We think this should be part of routine treatment, not just used when someone is at high risk," Petersen says. "It should be routinely provided by the provider or recommended by the provider." ■

FDA Notifications

FDA approves new formulation of Lexiva

On June 14, 2007, FDA approved a new formulation of fosamprenavir calcium (Lexiva).

Fosamprenavir calcium is now available as an oral suspension (50-mg/mL). The package insert was updated to include information on this new formulation and to provide dosing information

for pediatric patients and patients with hepatic impairment as follows:

A copy of the full prescribing information is attached.

DOSAGE AND ADMINISTRATION:

Pediatric Patients (2 to 18 years of age): The recommended dosage of fosamprenavir calcium in patients > 2 years of age should be calculated based on body weight (kg) and should not exceed the recommended adult dose. The data are insufficient to recommend: (1) once-daily dosing of fosamprenavir alone or in combination with ritonavir, and (2) any dosing of fosamprenavir in therapy-experienced patients 2 to 5 years of age.

Therapy-Naïve 2 to 5 Years of Age: Fosamprenavir Oral Suspension 30 mg/kg twice daily, not to exceed the adult dose of fosamprenavir, 400 mg twice daily.

Therapy-Naïve > 6 Years of Age: Either fosamprenavir Oral Suspension 30mg/kg twice daily not to exceed the adult dose of fosamprenavir 1,400 mg twice daily or fosamprenavir Oral Suspension 18 mg/kg plus ritonavir 3 mg/kg twice daily not to exceed the adult dose of fosamprenavir 700 mg plus ritonavir 100 mg twice daily.

Therapy-Experienced > 6 Years of Age: Fosamprenavir Oral Suspension 18 mg/kg plus ritonavir 3 mg/kg administered twice daily not to exceed the adult dose of fosamprenavir 700 mg plus ritonavir 100 mg twice daily.

When administered without ritonavir, the adult regimen of fosamprenavir tablets, 1,400 mg twice daily, may be used for pediatric patients weighing at least 47 kg.

When administered in combination with ritonavir, fosamprenavir Tablets may be used of pediatric patients weighing at least 39 kg; ritonavir capsules may be used for pediatric patients weighing at least 33 kg.

Patients with Hepatic Impairment: Mild Hepatic Impairment (Child-Pugh score ranging from 5 to 6): Fosamprenavir should be used with caution at a reduced dosage of 700 mg twice daily without ritonavir (therapy-naïve) or 700 mg twice daily plus ritonavir 100 mg once daily (therapy-naïve or PI-experienced).

Moderate Hepatic Impairment (Child-Pugh score ranging from 7 to 9):

Fosamprenavir should be used with caution at a reduced dosage of 700 mg twice daily (therapy-naïve) without ritonavir, or 450 mg twice daily plus ritonavir 100 mg once daily (therapy-naïve or PI-experienced).

Severe Hepatic Impairment (Child-Pugh score ranging from 10 to 12):

Fosamprenavir should be used with caution at a reduced dosage of 350 mg twice daily without ritonavir (therapy-naïve). There are no data on the use of fosamprenavir in combination with ritonavir in patients with severe hepatic impairment. ■

Structural basis for coreceptor selectivity by the HIV type 1 V3 loop

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP

Dr. Winslow serves as a consultant to Siemens Diagnostics and is on the Speakers Bureaus of Boehringer-Ingelheim and GSK. This article originally appeared in the July 2007 issue of Infectious Disease Alert. *It was peer reviewed by Connie Price, MD and edited by Stan Deresinski, MD.* Infectious Disease Alert's *Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Peer reviewer Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.*

Source: Cardozo T, et al. Structural basis for coreceptor selectivity by the HIV type 1 V3 loop. *AIDS Res Hum Retroviruses* 2007; 23:415-426.

Synopsis: *217 clinical isolates of HIV-1 had tropism determined using various biological techniques and included virus actually isolated by the authors and viruses reported in the literature where sequence of the V3 loop was known. Sequencing of the V3 loop resulted in the development of a reliable prediction rule where X4 tropic virus was predicted by the presence of a positively charged amino acid at position 11, 24, or 25. Otherwise the virus was R5 tropic.*

Over the last 15 years increased understanding of the complicated process of HIV attachment and entry into host cells has developed. After initial binding of the virus' external envelope glycoprotein gp120 to CD4, the trimeric gp120 structure undergoes conformational change resulting in exposure of the third variable domain of gp120 (V3 loop) which then interacts with one of two coreceptors, CCR5 or CXCR4. This coreceptor binding is then followed

by fusion of the viral transmembrane glycoprotein gp41 to the host cell. The natural ligands of CCR5 are the chemokines MIP-1 alpha, MIP-1 beta, and RANTES whereas the natural ligand for CXCR4 is SDF-1.

The need for determining coreceptor tropism of HIV isolated from patients has taken on some importance in the last year due to the availability and impending FDA clearance of maraviroc, a small molecule CCR5 antagonist. The widely used cell-based biological assay developed by Monogram (formerly ViroLogic) is expensive, difficult to perform, has a turnaround time of several weeks, and is probably not capable of detecting mixed tropic virus when the proportion of X4-tropic viruses present in a mixture are less than 10-20% of the population. Development of a sequenced based assay (if demonstrated to reliably predict coreceptor usage) would clearly result in more reliable, rapid, more sensitive determination of virus coreceptor usage. In addition, a sequence based assay would clearly be a fraction of the cost of the Monogram bioassay.

This paper nicely demonstrates and uses computer modeling to illustrate the structural basis for the tight correlation between the presence of any positively charged amino acid at positions 11, 24, and 25 (e.g. arginine, lysine) and X4 virus as well as the absence of a positively charged amino acid with the presence of generally one negatively charged amino acid (e.g. aspartate, glycine) and R5. As expected, computer modeling of the natural ligands of CXCR4 (SDF-1) and CCR5 (MIP-1 beta) and the corresponding viral V3 loops show remarkable structural similarity.

These results have potentially important implications for not only guiding therapy with coreceptor antagonists, but for design of future small molecule inhibitors and immunogens targeting the V3 loop. ■

Screening for abacavir hypersensitivity

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

This article originally appeared in the July 2007 issue of Infectious Disease Alert. *It was peer reviewed by Connie Price, MD and edited by Stan Deresinski, MD.*

Infectious Disease Alert's *Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Peer reviewer Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.*

Source: Chui CK, et al. Simple screening approach to reduce B*5701-associated abacavir hypersensitivity on the basis of sequence variation in HIV reverse transcriptase. *Clin Infect Dis* 2007; 44:1503-1508.

Synopsis: *A major drawback to the routine use of abacavir in the treatment of HIV-1 infection is the occurrence of a hypersensitivity reaction in as many of 8% of recipients of this nucleoside analog reverse transcriptase inhibitor. Individuals carrying the HLA class I allele B*5701 have a >100-fold increased risk of such hypersensitivity reactions. T Direct screening for the presence of HLA-B*5701 is an alternative but expensive. The authors describe an alternative, relatively inexpensive screening method.*

The immune response to HIV exerts a selective pressure, just as do antiretroviral drugs. Cytotoxic T lymphocytes (CTL) that recognize HLA class I-restricted viral epitopes expressed on the surface of infected cells exert a pressure on these epitopes. Mutation in these viral epitopes may allow escape of HIV-1 from the CTL immune response. Just as viral mutations allowing escape from the action of antiretroviral drugs often follow a predictable path, similar predictable sequences of HLA-restricted epitope mutations may also occur so that this aspect of viral evolution may potentially be predictable on the basis of the HLA profile of the infected host.

As a consequence of the above, Chui and colleagues have examined the hypothesis that identification of a signature CTL-driven immune escape that resides within the viral reverse transcriptase (RT) may represent a simple means, available by routine HIV-1 genotypic assays used to screen for antiretroviral associated resistance mutations, capable of abacavir hypersensitivity risk screening. They set out to demonstrate that detection of a HLA-B*5701 amino acid change at HIV-1 RT codon 245, which is known to lie within the epitopes restricted to this HLA allele, predicts the presence of HLA-B*5701 and, therefore, an increased risk of hypersensitivity to abacavir.

The relationship between codon 245 variation, the presence of HLA-B*5701, and premature abacavir discontinuation was investigated in 392 HIV infected adults receiving their initial antiretroviral therapy. The sensitivity of codon 245 mutations in predicting the presence of HLA-B*5701 was 96% and its specificity was 75%, while the positive and

negative predictive values were 20% and 99.6%, respectively. This association remained strong even after the patients had received antiretroviral therapy. The presence of codon 245 substitutions was significantly associated with premature discontinuation of abacavir therapy.

Thus, the inclusion of RT codon 245 in genotypic assays meant to assess antiretroviral resistance could provide an effective means, without significant added cost, of screening for risk of hypersensitivity to abacavir in North America and Europe where clade B virus are prevalent and HLA-B*5701 is present in up to 10% of whites. ■

Progress report: researchers make strides in global battle against HIV

Scientific advances may aid in stemming spread of disease

By Rebecca Bowers

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Good news on the research front: Results from a major study indicate that treating genital herpes may help keep the AIDS virus under control in women with both infections and may reduce the spread of HIV as well.[1] In the laboratory, scientists have successfully mapped a spot on the surface of HIV that may be vulnerable to an assault by antibodies, which could lead to development of an effective vaccine.[2]

Progress needs to continue at a rapid pace. In 2005, an estimated 4.1 million people worldwide were newly infected with HIV, mostly through heterosexual intercourse.[3] At the end of 2003, an estimated 1,039,000 to 1,185,000 people in the United States were living with HIV/AIDS, with 24%-27% undiagnosed and unaware of their HIV infection.[4]

Why are scientists focusing on the virus that causes genital herpes (herpes simplex virus-2, HSV-2) in relation to HIV? HSV-2 infection almost doubles the risk of HIV acquisition; results from a meta-analysis indicate.5 Data from Rakai, Uganda, in HIV-discordant couples suggest that, on a per-contact basis, HSV-2 increases the risk of HIV acquisition fivefold.[6]

The problem is compounded when looking at the prevalence of the disease:

- Approximately one out of five sexually active adults in the United States is HSV-2-seropositive.
- In studies in Latin America and Peru, 60% of HIV-uninfected men who have sex with men are HSV-2-seropositive.
- The rate rises even higher among HIV-infected women in parts of sub-Saharan Africa, South Africa, and Zimbabwe, where the HSV-2 prevalence is 70%.[7]

To conduct the trial among women coinfected with HIV and HSV-2, scientists from the Centre Muraz in Burkina Faso, the University of Montpellier (France), and the London (UK) School of Hygiene & Tropical Medicine enrolled 140 Burkina Faso women who were infected with the herpes and AIDS viruses. The women received valacyclovir or placebo pills for three months. Study findings indicate that having the herpes virus increased the replication of HIV and also revealed that the quantity of HIV in the blood and in the vagina was reduced by continuous anti-herpes treatment over three months.[1]

What is the next step?

These findings open new avenues for the prevention of HIV transmission and for the management of patients coinfected by the two viruses, says Philippe Mayaud, a scientist at the London School of Hygiene & Tropical Medicine and co-author of the current paper.

What are the next steps in HSV-HIV research? On the HIV transmission front, scientists will need to demonstrate that the effect seen on infectiousness or transmissibility of the virus actually translates into decreased transmission, says Mayaud. Several trials are ongoing, and results should be available within the next 18 months, he reports. Modeling studies will need to explore the population level impact of these therapies to assess their public health benefit, he notes.

When it comes to HIV disease progression, research should focus on the potential usefulness of using anti-HSV treatment during HIV disease, says Mayaud. For those infected with HSV-2, long-lasting therapies should be developed that do not depend on long-term intake of tablets, Mayaud believes. Safe and effective vaccines that would at least control the replication of HSV— if not prevent it altogether — would go a long way to prevent the transmission of HSV and HIV, he states.

"Such vaccines are currently not available," Mayaud says. "This should be an important priority area of research."

Progress on the HIV vaccine front has been challenged by the nature of the shape-shifting virus. Scientists led by a team at the National Institute of Allergy and Infectious Diseases (NIAID) now say they have been able to identify a key portion of an HIV surface protein as it looks when bound to an infection-fighting antibody.[2] The protein component is stable and appears vulnerable to attack from a specific antibody, known as b12, that can broadly neutralize HIV, researchers report.[2]

The HIV virus mutates rapidly and continuously, which stymies attempts by the immune system to identify and destroy it. To further compound the problem, the virus is covered by sugary molecules, which prevent antibodies from slipping in and blocking the proteins the virus uses to latch onto a cell and infect it.

NIAID researchers have been able to decipher how the b12 antibody is able to bind to an unchanging surface on the tip of the HIV virus. They used an X-ray snapshot of the antibody as it locked into the target site on the virus, then used chemical blocks to provide a 3-D map of the target site.[2] The resulting "map" may give researchers valuable clues in designing an effective vaccine. By understanding the structure of the virus, researchers may be able to improve on nature by designing an antibody that binds better than b12 and is easier for humans to produce.

Tongqing Zhou, PhD, a staff scientist in the NIAID's Vaccine Research Center's Structural Biology Section and lead author of the current research, says, "The detailed atomic level information from the HIV gp120:b12 structure tells us how a 'good' antibody works by attacking this weak link in the HIV armor, and it will guide us in the rational design of a future vaccine."

The next step in science is to use the information in designing and creating vaccines that will stimulate the immune system to generate large amounts of antibodies that would replicate or surpass b12's virus-killing power, says Zhou. However, the creation of such vaccines and the animal/human test processes may take a long time, and there will be many technical bumps ahead, he notes. ■

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Prediction and Diagnosis of HIV Dementia

ABSTRACT & COMMENTARY

By Michael T. Lin, MD

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Dr. Lin reports no financial relationships relevant to this field of study.

This article originally appeared in the June 2007 issue of Neurology Alert. *It was peer reviewed by M. Flint Beal, MD, and edited by Matthew Fink, MD. Drs. Beal and Fink report no financial relationships relevant to this field of study.*

Synopsis: *Several CSF biomarkers, sphingomyelin, sphingomyelinase, ceramide, 4-hydroxynonenal, and vitamin E, are associated with the development of HIV dementia in patients being treated with highly active antiretroviral therapy (HAART).*

Source: Bandaru VV, et al. Associative and predictive biomarkers of dementia in HIV-1-infected patients. *Neurology.* 2007,68:1481-1487.

Highly active anti-retroviral therapy (HAART) has changed the nature of HIV dementia: the degree of cognitive impairment is milder, the course may improve as well as worsen, and traditional biomarkers such as CSF viral load or levels of monocyte chemotactic protein 1 (MCP-1) are less likely to be associated with dementia. The objective of this study was to identify new CSF biomarkers that are associated with or predictive of HIV dementia in the setting of HAART.

The study involved 48 patients from the North Eastern AIDS Dementia cohort, assessed cognitively at 0, 6, and 12 months. CSF was drawn at the 6 month time point, and analyzed for biochemical

markers. Biochemical markers correlating with cognitive change over the preceding 6 months (between 0 and 6 months) were said to be biomarkers associated with cognitive change; biochemical markers correlating with cognitive change over the subsequent 6 months (between 6 and 12 months) were said to be biomarkers predictive of cognitive change. Based on previous work showing accumulation of sphingomyelin, ceramide, sterol, and lipid peroxidation products in brains of HIV dementia patients, these were the primary biomarkers the authors investigated.

Considering first the cognitive changes occurring before the CSF draw (between the 0 and 6 month time points), the authors divided the cohort into 3 groups: those who were not demented at both time points ("nondemented"), those who were initially demented and remained stably so ("inactive dementia"), and those who were initially not demented but became demented ("active dementia"). Those with inactive dementia over the preceding 6 months had 3-5 fold elevations of CSF sphingomyelin compared to nondemented or active dementia subjects. Those with active dementia over the preceding 6 months had increased CSF ceramide levels and sphingomyelinase activity, increased levels of lipid peroxidation products (4-hydroxynonenal), and decreased levels of the lipid antioxidant vitamin E.

Considering, next, the cognitive changes occurring after the CSF draw (between the 6- and 12-month time points), the authors divided the cohort into 3 groups, based on whether scores improved, remained stable, or worsened. The group that subsequently worsened had increased CSF levels of triglyceride C52 and vitamin E. Sphingomyelin, ceramide, and hydroxynonenal levels were not predictive of subsequent worsening.

Commentary

These are interesting findings, consistent with the known biology of HIV. In tissue culture, the HIV-1 coat protein gp120 and the trans acting protein Tat can increase sphingomyelin levels in 6 hours, followed by activation of neutral sphingomyelinase (Haughey et al. 2004; Jana et al.

CE/CME *questions*

23.Maraviroc, marketed by Pfizer, is expected to be approved soon as the first drug in which new class of antiretrovirals?

A. CXCR4 antagonists
B. Transcriptase inhibitors
C. CCR5 antagonists
D. Fusion inhibitors

24. New research shows that which of the following is true about the connection between HIV infection and infection with herpes simplex virus 2 (HSV-2)?

A. HIV-negative people who are at risk for HIV infection and acquire HSV-2 infection are at greater risk of becoming infected than those who remain HSV-2 negative.
B. Patients with both HIV and HSV-2 infection will have a significant reduction in HIV viral load if they are treated for HSV-2.
C. HIV-negative people who have genital herpes, whether or not they are aware that they're infected, have an increased risk of two-to-three fold of becoming HIV infected.
D. All of the above

25. HIV negative individuals who have genital herpes — even if they don't know they are infected with herpes — increase their risk of becoming HIV infected by two-to-three fold.

A. True
B. False

Answers: 23.(c) 24.(d) 25.(a)

COMING IN FUTURE MONTHS

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- Study shows link between substance abuse and HIV medication adherence
- Here's the latest news from the International AIDS Conference

2004). In response to inflammatory mediators, sphingomyelinase cleaves sphingomyelin to produce ceramide, which induces apoptosis and increases oxidant stress. Additionally, cleavage of sphingomyelin by sphingomyelinase disrupts the association between cholesterol and sphingomyelin. The cholesterol released can then accumulate in lipid droplets containing cholesterol esters and triglycerides. This sequence could explain the increases in sphingomyelin in stably demented subjects; the increased sphingomyelinase, ceramide, and lipid peroxidation seen in actively demented subjects; and the increased triglyceride C52 seen in subjects who subsequently worsened. The authors interpret the elevated vitamin E levels initially seen in subjects who subsequently worsened as a secondary compensatory response to ongoing pathology. When the pathology overwhelms defensive systems, decreased vitamin E levels would then be found in actively dementing subjects.

Several potential follow-up studies should be considered. Although the design of this study cleverly minimized the number of CSF draws, true biomarkers should be shown to vary over time in parallel with the process being followed. The results of this study should thus be confirmed with serial determinations of biomarkers in parallel with cognitive assessments. Additionally, with at least one key biomarker of active pathogenesis, ceramide, the magnitude of difference between groups, although statistically significant, was small, and it is not clear that such a biomarker could usefully discriminate between groups. The sensitivity, specificity, and ability to discriminate between groups should be characterized. Finally, the pathogenetic sequence identified could lead to new potential therapy of HIV dementia, targeting the HIV-induced perturbations of sphingomyelin/ceramide metabolism. ■

Background:

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