AIDS ALERT®

The most comprehensive source of HIV/AIDS information since 1986

NOTE: New CNE procedures. See. p. 84 for details.

July 2011: Vol. 26, No. 7
Pages 73-84

IN THIS ISSUE

Statement of Financial Disclosure: Editor **Melinda Young** and Executive Editor **Gary Evans** report no relationships with companies related to this field of study. Physician Reviewer **Morris Harper**, MD, reports consulting work with Agouron Pharmaceuticals, Gilead Sciences, Abbott Pharmaceuticals, GlaxoSmithKline, and Bristol-Myers Squibb. Nurse Planner **Kay Ball** is a consultant and stockholder with Steris Corp. and is on the speaker's bureau for the Association of Perioperative Registered Nurses.

AHC Media

HIV resurges where it started three decades ago: MSM

MSM networks, lax condom use driving increases

Thirty years into an epidemic that began with cryptic reports of a new disease among gay American men, there is this discouraging finding: AIDs Studies and reports worldwide point to a resurgent HIV epidemic among men who have sex with men (MSM).

HIV incidence among MSM has been increasing worldwide, and condom use has been low in many areas around the world.[1]

"There have been multiple reports from countries both resource-rich and limited, and the major contextual factors are related to these increased rates of HIV among MSM," says **Susan Little**, MD, professor of medicine at the University of California — San Diego (UCSD).

The challenge is there has been an incomplete amount of research conducted and available in resource-limited settings, she adds.

"There's still a significant amount of stigma and discrimination in resource-limited settings," Little says. "A lot of the information available is from more recent studies in resource-rich countries."

In countries with high HIV prevalence, such as those in sub-Saharan Africa, the distinct risk associated with being gay is not as high as in resource-rich countries, she notes.

"In low prevalence countries, HIV is not as diffused," she explains.

"It's more concentrated in subpopulations," she adds. "So if you are in one of those sub-populations like men who have sex with men, then your risk of contracting HIV is much higher than if you are a heterosexual man."

One challenge is controlling for confounders of transmission, Little says.

"For instance, we looked at concurrent partnerships," she says. "There are many factors associated with HIV transmission in an HIV population, and one practice is linked to sexual concurrency, having multiple sexual partners that overlap in time."

Studies show that black and Latino MSM have no increased risk when

you control for neighborhoods in which they live, so their increased risk for HIV infection could be most closely linked to their sexual network rather than their race or specific sexual practices, Little says.[1]

"Even if you engage in low-risk activities, if you engage in those activities within a sexual network with high HIV prevalence then you are much more likely to become infected than if you are engaging in high risk activities in a low network of HIV prevalence," she explains.

"One big strategy is to increase testing," Little says. "If people don't know their status they can escape medical attention and can unwittingly transmit HIV."

One of the key areas of future HIV research will be to find out what the predictors of infection are among sub-populations of sexual networks that have unique characteristics driving the epidemic forward, Little says.

"We need much more focused prevention strategies and multi-level prevention approaches that don't just target an individual," she says. "Because even if you target an individual and lower that person's risk behavior, it doesn't address the person's sexual network which could place the person at high risk for HIV infection."

There is a need for both individual-level and population-level prevention strategies.

"And, frankly, we're very limited in what those interventions might be," Little says. "The largest idea is using antiretroviral therapy as prevention, but that has huge resource issues tied up with it."

Still, some groups worldwide are proposing that governments scale up HIV screening and treatment, targeting populations at risk.

"One big strategy is to increase testing," Little says. "If people don't know their status they can escape medical attention and can unwittingly transmit HIV."

In the United States, an estimated 45% of people have ever been tested for HIV, and only 10% have been tested within the past year, Little says.

"We have a long way to go before we raise the level of awareness of how important testing is to limit transmission of disease within a population," she adds.

Although national public health guidelines have called for widespread HIV testing for five years now, routine HIV screening remains uncommon except among some communities of high risk, Little says.

Universal treatment is even more problematic. HIV providers remain uncertain about treating

AIDS Alert® (ISSN 0887-0292), including AIDS Guide for Health Care Workers®, AIDS Alert International®, and Common Sense About AIDS®, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to AIDS Alert®, P.O. Box 105109, Atlanta, GA 30348.

AHC Media is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity has been approved for 15 nursing contact hours using a 60-minute contact hour.

Provider approved by the California Board of Registered Nursing, Provider #14749, for 15 Contact Hours.

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 18 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This enduring material is intended for HIV/AIDS physicians and nurses. It is in effect for 36 months from the date of publication.

This continuing education program does not fulfill State of Florida requirements for AIDS education.

Because of the importance of investigational research relating to HIV/AIDS treatment, AIDS Alert sometimes discusses therapies and treatment modalities that have not been approved by the U.S. Food and Drug Administration.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

SUBSCRIBER INFORMATION

Customer Service: (800) 688-2421. Fax: (800) 284-3291. Hours: 8:30 a.m.-6 p.m. M-Th, 8:30 a.m.-4:30 p.m. Friday EST. E-mail: customerservice@ahcmedia.com. Web site: www.ahcmedia.com.

Subscription rates: U.S.A., one year (12 issues), $499. Add $17.95 for shipping & handling. Approximately 15 nursing contact hours or 18 AMA PRA Category 1 Credits™, $549. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue date. Back issues, when available, are $83 each. (GST registration number R128870672.)

Editor: **Melinda Young**, (864) 241-4449.
Executive Editor: **Gary Evans**, (706) 310-1727, (gary.evans@ahcmedia.com).
Production Editor: **Kristen Ramsey**.

EDITORIAL QUESTIONS?
Call Gary Evans at (706) 310-1727.

everyone who is infected, Little notes.

"I support universal treatment, but I understand their concerns," she says.

"My strong support of treatment is drawn from my own interpretation and extension of current studies," she adds. "There are no studies that address individual risk and risk to a population if you start ART significantly above 500 CD4 cell counts."

There is no consensus in the medical community about the best use of ART for individuals who are newly infected and have both high viral loads and high CD4 cell counts. These people are at high risk of transmitting HIV, so it would appear they're an ideal group to target for early treatment, Little explains.

"Some people believe those treatments are well-tolerated and the benefits to the population is quite high, and so they recommend treatment," Little says. "But even if we treat everyone who knows their HIV status today, that leaves potentially a large number of people who don't know their status and who have high rates of HIV in their blood and can transmit at a higher frequency than those with lower levels of virus."

Breaking down networks

How does one reach these people with unknown infection? One answer is literally door-to-door. Investigators in San Diego, CA, have begun an HIV screening and prevention project targeting populations of people who are at a high but unperceived risk for HIV infection, Little explains.

Called the Lead the Way Campaign, the project is funded through a one-year study of whether a comprehensive HIV screening approach will lead to increased testing in the general population.

"We've identified populations in two zip codes and are rolling out an aggressive, comprehensive marketing approach to HIV testing in the general community," she says.

"We're trying to normalize HIV testing, and we're not asking about HIV risk," she says. "We say, 'Just as you receive a cholesterol test when you pass a certain age, you should receive an HIV test when you're an adult.'"

The idea is to reach concentrated sexual networks of people who are at high risk of HIV transmission even when they engage in relatively low risk sexual behavior.

"We don't know where those concentrated networks are until we have a vast majority of people tested," Little says.

"A CDC statistic shows that 21% of the people in this country who are infected are untested," she explains. "If we're marketing testing and prevention to people who think they are at risk then we still have not made a huge impact on that number."

The project's goal is to get people tested early and into care and treatment to improve their own health and the health of the targeted population, Little says.

"It's non-risk-based testing, and we're marketing testing to adults of all races, ages, and socioeconomic status with the hope that using more novel marketing techniques and role models will increase HIV testing," Little says.

"One of the things we're trying to make people in the general community aware of is we can't answer this question without your participation," Little says. "If they think it's a problem with distinct, well-characterized communities then we have a challenge controlling this epidemic."

The Lead the Way Campaign stresses that taking the HIV test is easy and fast.

"We hope the more people who take the test, the freer of stigma it becomes," Little says. "It should be part of a general health screening for every adult in the United States."

One of the zip code communities selected for the project has strong interest in HIV care, she adds.

"In this community, we believe the awareness and compassion and concern about controlling HIV as a disease is already quite high," Little says. "If we can demonstrate success in a population heavily engaged in HIV treatment and care, then our hope is we can take the tools and strategies we've learned to expand and generalize to other communities and metropolitan areas."

One of the biggest differences in the Lead the Way Campaign's marketing approach is that it will have trained health care professionals going door-to-door to do HIV testing.

"We're taking the lead from politicians who go door-to-door to engage community support for their cause," Little explains. "We'll ask people what are their beliefs and concerns about HIV testing and then offer them a test."

If people turn down the offer, that's fine, but the health care professional will ask them why not.

"We hope we can modify our approach to proposing or marketing testing within those communities, so we'll ask about their beliefs, motivators,

and barriers surrounding HIV testing," Little says. "We hope to evaluate 10,500 people in one year."

The study has a long start-up period in which community education and marketing paves the way for the door-to-door visits.

"Our hope is that by the time we start door-to-door testing most people will have heard about it so they won't be caught off guard," Little says. "This is an amazing study and quite a challenge; it's something new, and we really are relying on the support and engagement of the community to get out the message."

REFERENCE

1. Morris SR, Little SJ. MSM: resurgent epidemics. *Curr Opin HIV/AIDS* 2011; [Epub ahead of print]. ■

ART effective for HIV prevention in couples

'A very powerful and desirable strategy'

The search for an HIV vaccine will continue, but in the meantime, there is little doubt that an aggressive HIV screening and early treatment strategy could make a big impact on reducing HIV transmission. The latest study to show success with using antiretroviral therapy (ART) to prevent HIV transmission had such early and dramatic results that it was halted early.

This new research also emphasizes the importance of adjusting public health policies to support long-term ART adherence.

"This is the largest prevention benefit ever reported in the HIV prevention field," says **Myron Cohen**, MD, director of the Institute for Global Health and Infectious Diseases at the University of North Carolina at Chapel Hill. Cohen is an investigator on the study and also is a professor of medicine, microbiology and public health at UNC.

The National Institutes of Health (NIH) announced in May, 2011, that an HIV Prevention Trials Network study, titled HPTN 052, found the risk of transmitting the virus to uninfected sexual partners could be reduced by 96% if the HIV-positive partner adhered to an effective antiretroviral therapy (ART) regimen.

"The HPTN study will fuel the argument that treatment might be one of the most effective and scalable prevention interventions for individuals and populations, but [the lack of] resources will be the argument thrown at that strategy," says **Susan Little**, MD, professor of medicine at the University of California — San Diego (UCSD).

"It might be cost-effective, but it's not inexpensive," she adds.

HPTN 052 took place at 13 sites in nine countries, enrolling 1,700 sero-discordant couples, including 900 couples in sub-Saharan Africa. It began in May, 2007, and continued through April, 2011, Cohen says. The study enrolled people living with HIV with a CD4 cell count between 350 and 550. The couples enrolled had to be in a stable relationship and have sex on a regular basis. Those enrolled were not eligible for treatment according to the latest international guidelines of the time.

The results were tremendously satisfying, demonstrating a quick and rapid reduction in sexual transmission of HIV among those receiving ART, Cohen says.

"It was assumed we wouldn't see a difference in infection rates until 2015," Cohen says. "But the data safety monitoring board that oversees the study met on April 28, 2011, and they recommended that the results be made public."

There was one case of HIV transmission in the ART arm and 27 cases of HIV transmission in the delayed treatment arm, he says.

Each couple enrolled in the study received counseling and condoms, and their rates of transmission were low historically.

"Even with very low rates of transmissions, ART offers greater than 96% prevention from transmission," Cohen says. "So we decided to essentially stop randomization and offer treatment to people in the delayed arm."

The immediate issue is how to counsel discordant couples about HIV prevention, Cohen says.

"We still have to talk about safe sex and condoms," he adds. "And there were 11 unlinked transmission events, showing that ART is not going to help someone who is having sex with someone else who might be infected."

The new normal

The study's findings underscore the importance of adjusting treatment and prevention policies and reimbursement to reflect the reality of HIV-infected patients living long and productive lives, says **James M. Sosman**, MD, FACP, medical direc-

tor of the HIV care program, division of general medicine and infectious diseases, and associate professor of medicine at the University of Wisconsin School of Medicine and Public Health in Madison, WI.

Research has come full circle, showing improved health benefits, reduced risk of serious morbidity and mortality, fewer common side effects, and now, significantly lower HIV transmission, when ART is initiated early.[1]

All of this suggests that policy changes involving economics need to center on the reality that people are going to be starting ART earlier and taking it for much longer, Sosman says.

"Now we have data that really show that treatment is prevention," he says. "And that means we need HIV patients to maintain impeccable adherence to reduce the risk of new infections."

Newly-infected individuals have high viral loads and are more likely to transmit HIV, Little says.

"Those with new infections have much higher levels of virus in their blood than people at any other stage of infection," she adds. "And people with new infection are often unaware of their diagnosis because they've been infected for a short period of time."

These facts and the new data emphasize the importance of early detection and links to medical care. While this is something the Centers for Disease Control and Prevention (CDC) has been promoting for five years, it hasn't translated into routine HIV testing in medical settings, Sosman says.

It takes time to bring a change in policy and practice regarding HIV screening in hospitals and clinics, he adds.

"It's a long, incremental process going from guidelines to policy to implementation," he says.

Unlike many other chronic illnesses, HIV adherence must be extremely high for patients to maintain good health, Sosman notes.

"When adherence is not up to snuff then it will compromise treatment options over the long term," he explains. "While that can be true of other chronic conditions, it's very true and can happen very quickly in HIV."

One of the benefits of the HPTN 052 intervention and study was that it promoted ART adherence to couples, as opposed to focusing on the individual who is HIV-positive, Cohen notes.

"They have a collective goal of protecting the health of the HIV-positive partner," he explains. "It's very powerful and a very desirable strategy for this disease."

HIV adherence is challenging and will take a community's efforts.

"We want to empower the health system to allow folks to take their medications over decades," he adds.

"Although we have once-a-day regimens now, we have to look at things that would interfere with someone taking them over 20 years," he says. "It might not be nausea or diarrhea; it might be mental health issues, insurance issues, access to care, and all of these issues that can interfere with long-term adherence."

This is a different set of adherence issues than HIV clinicians experienced 10 years ago, he notes.

"We don't have patients take as many pills as many times a day with as many short-term side effects as we did 10 years ago," Sosman says. "But adherence issues still are potent."

REFERENCE

1. Sosman JM. Optimizing HIV care: policy implications. *Am J Man Care*. 2010;16(11):S339-S344. ■

Q&A interview:

Ugandan ART study foreshadowed HPTN 052

[Editor's note: The recent HPTN 052 study that showed such dramatic success from antiretroviral therapy (ART) being given early to help prevent HIV transmission among HIV discordant couples followed on the footsteps of early research that suggested such a trend. One such study was conducted in Uganda between 2003 and 2007. It followed ART-naïve, HIV-infected adults in an AIDS program that provided many standard prevention interventions, including annual counseling and testing for cohabiting partners, risk reduction plans, condom distribution, and prevention support. The HIV-infected partners were started on ART. The study found that despite a reported increase in sexual activity that was 41% at 36 months, consistent condom use was high with discordant partners, and estimated HIV transmission risk was reduced 91%.[1] AIDS Alert *asked two investigators with the Ugandan study*

to discuss their research findings, particularly in light of the recent announcement that HPTN 052 was halted early so all study participants could be offered early ART. ***Rebecca Bunnell****, ScD, MED, associate director for public health practice at the National Center for Chronic Disease Prevention and Health Promotion of the Centers for Disease Control and Prevention (CDC) in Atlanta, GA, and* ***Jonathan Mermin****, MD, MPH, director of the division of HIV/AIDS prevention at the CDC, answered a few questions about their study and its implications in this email question-and-answer (Q&A) exchange.]*

AIDS Alert: What was the chief finding of your study on Ugandans with HIV and antiretroviral therapy?

Bunnell & Mermin: Providing antiretroviral therapy and sexual behavior education through a home-based care program was associated with a 91% reduction in estimated HIV transmission risk even though the median HIV viral load at baseline was high, at 122,500 copies/ml. The reduced risk occurred even in a challenging rural African setting where the average per capita daily income was less than $1, there was no access to electricity or running water, and three-quarters of people had not had education beyond primary school.

AIDS Alert: What are the implications of these findings, especially in light of the recent good news that ART significantly reduces the risk of HIV transmission?

Bunnell & Mermin: These results are consistent with the recent findings of a randomized trial among people with relatively high CD4 cell counts, a measure of immune function. In our study, people with HIV had advanced disease, with CD4 cell counts below 250 cells/uL and high viral loads, suggesting a high chance of transmission. Together, the two studies support efforts to increase access to antiretroviral therapy and sexual behavior education to all people with HIV, and highlight the synergistic effects of prevention and care.

AIDS Alert: The CDC has focused on HIV screening and referral to care for some time now. Do you think the findings, such as those in your study and the HPTN -052 study, will lead to public health policy and guidance changes? Why or why not?

Bunnell & Mermin: In the United States and internationally with Ministries of Health, CDC has highlighted the importance of HIV screening and linkage to care—both for the life-prolonging effects of antiretroviral therapy and care and for the prevention benefits, yet in most countries in Africa less than 25% of people with HIV know they have the virus. In the United States, the Department of Health and Human Services therapy guidelines already support offering antiretroviral therapy to people with CD4 cell counts below 500 cells/uL and are permissive for all people with HIV regardless of CD4 cell count with consideration of particular circumstances, such as being in an HIV-discordant couple. The findings of these new studies and previous research support a flexible approach, and may have implications for many countries that are currently balancing a tremendous need for HIV-related care, restricted health sector budgets, and a realization that providing antiretroviral therapy to more people with HIV, even with higher CD4 cell counts than currently indicated by some Ministries of Health and the World Health Organization, will help people live longer, healthier lives and reduce the number of new HIV infections. The difficult choice presented here is a classic public health conundrum: potential benefits to individuals and society are clear, but resources are limited. Will we make an explicit choice, and if so, what scientific, ethical, and economic factors will be incorporated into our decision-making?

REFERENCE

1. Morris SR, Little SJ. MSM: resurgent epidemics. *Curr Opin HIV/AIDS*. 2011. [Epub ahead of print] ■

HPV vaccine may prevent anal cancer

By **Stan Deresinski**, MD, FACP, FIDSA
Associate chief of infectious diseases, Santa Clara Valley (CA) Medical Center.

GARDASIL™ (Human Papillomavirus Quadrivalent [Types 6, 11, 16, 18) Vaccine, Recombinant) previously received FDA approval for prevention of cervical, vulvar, and vaginal cancer and associated precancerous lesions and for prevention of genital warts in males and females 9-26 years of age. More recently, it failed to receive approval for these indications

in women 27-45 years of age because of lack of demonstrated efficacy.[1] Now, at the end of 2010, FDA approved the use of this viral-like particle vaccine for the prevention of anal cancer and associated precancerous lesions due to human papillomavirus (HPV) types 6, 11, 16, and 18 in people (all genders) ages 9-26 years.[2,3]

It is estimated that approximately 5,300 individuals receive a diagnosis of anal cancer each year in the United States. While the total number affected is relatively low, effective treatment of this potentially life-threatening malignancy is difficult. Most anal malignancies are squamous cell cancers in which infection with oncogenic types of human papilloma virus (HPV), especially types 16 and 18, play an etiologic role.

While a majority of anal carcinomas occur in women, men who have sex with men (MSM) have the highest incidence and, as a result, comprised the study population in a randomized placebo-controlled trial in which they were a subset. The full trial, which enrolled a total of 4,055 males, 16-26 years of age, demonstrated the efficacy of the vaccine in the prevention of anogenital warts and precancerous lesions. Among these were 299 MSM who received placebo and 299 who received GARDASIL™ who were followed for a median duration of 2.3 years. Cases of anal intraepithelial neoplasia grades 1/2/3 and anal cancer made up the composite efficacy endpoint used to assess prevention of HPV-related anal cancer.

GARDASIL™ had a 77.5% efficacy in prevention of the composite endpoint caused by HPV types included in the vaccine in a per-protocol analysis of subjects who were naïve (by PCR and antibody) to these viruses at baseline. This finding led the FDA to approve the use of this vaccine for the prophylaxis of anal cancer and precancerous lesions. Because anal cancer is the same disease in both males and females, the approval was extended to females in the same age group.

This information strengthens the indication for vaccination of young females and indicates the desirability of targeting young MSM for vaccination as well. Among HIV-infected MSM, the Multicenter Aids Cohort Study (MACS) reported an overall incidence rate of anal cancer of 69 per 100,000 person-years.[4] Furthermore the incidence of anal cancer in this group has been increasing in the United States despite the introduction of effective antitetroviral therapy from 19.0 per 100,000 person-years in 1992-1995 to 48.3 in 1996-1999 (shorlty after the introduction of potent combination antiretroviral therapy) to 78.2 per 100,000 person-years in 2000-2003.[5] Condom use may reduce HPV transmission.

Another important element in the prevention of anal cancer could be implementation of screening. There is, however, a lack of general acceptance of routine screening analogous to that used for prevention of cervical cancer. The most recent USPHS guideline states that, until the issue is settled by definitive evidence, "some experts recommend an annual digital rectal examination as an important procedure to detect masses on palpation that may be anal cancer (BIII). There are no national recommendations for routine screening for anal cancer. However, some specialists currently recommend anal cytologic screening for HIV-seropositive men and women (CIII). If anal cytology is performed and indicates ASC-US or ASC-H, LSIL, or HSIL (BIII), then it should be followed by high-resolution anoscopy (HRA). Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer (BIII)."

REFERENCES

1. Clinical Review of Biologics License Application Supplement STN# 125126/773 — mid-adult women indication for GARDASIL. Available at: www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM251763.pdf.
2. Clinical Review of Biologics License Application Supplement STN# 125126/1297.0 — male indication for GARDASIL. Available at: www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM190977.pdf.
3. GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] Suspension for intramuscular injection. Available at: www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf.
4. Heard I. Human papillomavirus, cancer and vaccination. *Curr Opin HIV AIDS* 2011 Apr 23; Epub ahead of print.
5. Kaplan JE, Benson C, Holmes KH, et al; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009;58(RR-4):1-207. ■

Abstract & Commentary

cART start boosts AIDS-free survival

By **Stan Deresinski**, MD, FACP, FIDSA

Associate chief of infectious diseases, Santa Clara Valley (CA) Medical Center.

Synopsis: Early initiation of antiretroviral therapy is associated with increased AIDS-free survival.

Source: The HIV-CAUSAL Collaboration. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: An observational study. Ann Intern Med 2011;154:509-515.

In a prospective observational study, investigators of the HIV-CAUSAL Collaboration evaluated data from participating HIV clinics in Europe as well as in the U.S. Veterans Administration system to determine the optimal CD4+ T cell count at which combination antiretroviral therapy (cART) should be initiated. The analyzed population consisted of 8,392 patients among 20,971 with baseline CD4+ T cell counts ≥ 500/mm^3 whose counts decreased into the range of 200-499/mm^3. cART was initiated based on the judgment of treating physicians.

Complex analysis led to an estimate that, compared to initiating cART when the CD4+ T cell count first decreased below 500/mm^3, delaying its initiation until the CD4+ T cell count decreased below 350/mm^3 would result in a 38% increase in the incidence of AIDS-defining illness or death. The prevention of one new instance of this endpoint would require the treatment of 48 patients at the higher CD4 count. As one would expect at these relatively high cell counts, no reduction in death itself was identified.

Commentary

Previous non-randomized cohort analyses have yielded conflicting results in examining similar data sets, leading to a degree of confusion. At the same time, the efficacy, simplicity, and toxicity of antiretroviral therapy have continually evolved over time. As described in an accompanying editorial,[1] HIV clinicians attempting to follow national guidelines have experienced a roller coaster ride in their decisions regarding the time at which to initiate cART. The U.S. Department of Health and Human Services recommended its initiation at any CD4+ T cell count < 500/mm^3 in 1998, subsequently changed the threshold to 200-350/ mm^3, and, in 2011, changed course once again. At that time, they recommended that cART be routinely initiated at CD4+ T cell count < 500/mm^3 and that its initiation be considered at higher counts.

The investigators and others recommend that the issue be settled via randomized clinical trials. I disagree. I personally believe the issue is settled, and the results could be anticipated from a priori considerations. The ease of use, efficacy, and lack of toxicity of current cART regimens, together with considerations of the public health benefit of reducing the "community HIV load," as well as a vague notion that it cannot be good for an individual to be exposed to unrestricted viral replication, suggest to me that therapy should be offered to all infected individuals. While resource considerations are necessary, they should have little or no role in an economically advanced society. Forget huge expensive clinical trials to deal further with this issue — move on and spend the money and effort more wisely.

REFERENCE

1. Baker JV, Henry K. If we can't get what we want, can we get what we need? Optimizing use of antiretroviral therapy in the current era. *Ann Intern Med* 2011;154:563-565. ■

Abstract & Commentary

Treatment of HHV-8 disease with Antivirals

By **Dean L. Winslow**, MD, FACP, FIDSA
Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor, Stanford University School of Medicine. Dr. Winslow is a speaker for Cubist pharmaceuticals and GSK, and is a consultant for Siemens Diagnostics.

Synopsis: A pilot study of 14 HIV-infected patients with KHSV-associated multicentric

Castleman's disease (MCD) was conducted. A regimen of valganciclovir (VGCV) plus high-dose zidovudine (AZT) appeared to produce clinical response. A second study treated 5 HIV-negative patients with classic Kaposi sarcoma (KS) with conventional doses of valganciclovir and there was no evidence of response.

Sources: Uldrick TS, Polizzotto MN, Aleman K, et al. High-dose zidovudine plus valganciclovir for Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: A pilot study of virus-activated cytotoxic therapy. Blood 2011 April 12; Epub ahead of print; Krown SE, Dittmer DP, Cesarman E, et al. Pilot study of oral valganciclovir therapy in patients with classic Kaposi sarcoma. *J Infect Dis* 2011;203:1082-1086.

Uldrick et al performed a pilot study in which 14 HIV-infected patients with symptomatic MCD received high-dose AZT (600 mg PO Q6 hours) and VGC (900 mg PO Q12 hours). Eighty-six percent of patients attained major clinical responses (defined as resolution of symptoms and at least partial resolution of lymphandenopathy). Fifty percent attained major biochemical responses (normalization of hemoglobin, platelet count, albumin, sodium, and CRP). Median progression-free survival was 6 months and overall survival was 86% at 12 months. In patients who responded, levels of IL-6, IL-10, and KHSV viral load also were reduced. Hematologic toxicities were common.

Krown et al performed a pilot study in which 5 HIV-negative patients with classic KS were treated with VGCV for up to six cycles (each cycle 4 weeks). KS progressed in 4 patients after 1-4 cycles and remained stable in 1 patient after 6 cycles. KS biopsies showed minimal lytic KS antigen and gene expression at baseline and post-treatment.

Commentary

KSHV (HHV-8), like Epstein-Barr Virus (EBV), is a gamma herpesvirus. Both viruses generally have a lytic replication cycle in the oropharynx. In the case of EBV, a latent replication cycle where episomal DNA is associated with B-cell proliferation occurs. Examples of EBV disease include oral hairy leukoplakia (lytic infection predominates) and diseases where almost exclusively latent EBV replication is present (infectious mononucleosis, post-transplant lymphoproliferative disorder, and many cases of B-cell non-Hodgkin lymphoma). In the case of KHSV, three major clinical syndromes have been described: MCD, primary effusion lymphoma (PEL), and KS. Of these KHSV-associated syndromes, only MCD has been shown to possess significant lytic cycle KHSV.

Ganciclovir (and its prodrug, valganciclovir), as well as other acyclic nucleoside analogues, has been shown to be active against the lytic replication cycle of both EBV and KHSV, but not against latent (episomal) cycle. This basic understanding of gamma herpesvirus biology seems to be lacking in many ID specialists who insist on treating diseases such as PTLD and KS with ganciclovir or VGCV despite the significant hematologic toxicities of these agents and lack of clinical evidence of efficacy. It should be noted that Uldrick and colleagues did not use AZT and VGCV for their antiviral effects but rather designed this regimen as antineoplastic/cytotoxic agents based on the observation that in MCD two KHSV lytic genes, ORF36 and ORF21, phosphorylate GCV and AZT, respectively, to cytotoxic metabolites. The positive results of their pilot study appear to validate this rationale and suggest the desirability of larger randomized comparative trials of treatment for MCD, recognizing that MCD is a very rare disease.

Similarly, Krown's small pilot study of VGCV treatment in classic KS support our understanding of KHSV biology. GCV and VGCV have no place in the treatment of KS (or PEL), but may have a role in treatment of MCD related to their targeted activation as cytotoxic agents, not as antivirals. ■

FDA NOTIFICATIONS

New draft guidance on financial disclosure

The Food and Drug Administration (FDA) has issued new draft guidance, "Financial Disclosure by Clinical Investigators, Guidance for Clinical Investigators, Industry, and FDA Staff." The document is now available from FDA's web site at the following link: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM256525.pdf

This guidance is intended to assist clinical investigators, industry, and FDA staff in interpreting and complying with the regulations governing

financial disclosure by clinical investigators, 21 CFR part 54.

Comments to the draft guidance are due by July 25, 2011. ■

Rilpivirine approved for HIV treatment

On Friday, May 20, 2011, the Food and Drug Administration (FDA) approved rilpivirine (Edurant®) 25 mg tablets, a new non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV. Rilpivirine is an antiviral drug that helps to block reverse transcriptase, an enzyme necessary for HIV replication. The recommended dose of rilpivirine is one 25 mg tablet once daily taken orally with a meal.

INDICATIONS AND USAGE:

Rilpivirine, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV 1) infection in antiretroviral treatment naïve adult patients (patients who have never taken HIV therapies, and are starting HIV therapy for the first time).

The following points should be considered when initiating therapy with rilpivirine: More rilpivirine treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy.

The observed virologic failure rate in rilpivirine treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz.

More subjects treated with rilpivirine developed lamivudine/emtricitabine associated resistance compared to efavirenz.

RESULTS OF CLINICAL TRIALS AND CLINICAL VIROLOGY SUMMARY:

The approval of rilpivirine is based on Week 48 safety and efficacy analyses from 2 randomized, double blind, active controlled, Phase 3 trials in treatment naïve subjects and Week 96 safety and efficacy analyses from a Phase 2b trial in treatment-naïve subjects.

The Phase 3 trials (TMC278-C209: ECHO and TMC278-C215: THRIVE) compared rilpivirine to efavirenz in antiretroviral-naïve HIV-1 infected subjects with HIV-1 RNA ≥ 5000 copies/mL and no NNRTI resistance. Both trials were identical in design, with the exception of the background regimen (BR). In TMC278 C209, the BR was fixed to the nucleoside (tide) reverse transcriptase inhibitors (N(t)RTIs), tenofovir disoproxil fumarate plus emtricitabine. In TMC278 C215, the BR consisted of 2 investigator-selected N(t)RTIs: tenofovir disoproxil fumarate plus emtricitabine or zidovudine plus lamivudine or abacavir plus lamivudine. In both trials, randomization was stratified by screening viral load. In TMC278 C215, randomization was also stratified by N(t) RTI BR.

The Week 48 efficacy outcome for the pooled data from TMC278-C209 and TIMC278-C215 are as follows.

Overall, the proportion of subjects with HIV RNA < 50 copies/mL was 83% for rilpivirine-based regimen compared to 80% for efavirenz based regimen. The predicted difference (95% CI) of response rates is 2.0 (-2.1; 6.1). The overall virologic failure rate was 13% for the rilpivirine compared to 9% for the efavirenz. The proportion of patients who discontinued study due to an adverse event or death was 2% for rilpivirine and 7% for efavirenz.

Response rate was also calculated by baseline plasma viral load. For subjects with baseline plasma viral load ≤ 100,000 copies/mL, >100,000 to ≤ 500,000 copies/mL and > 500,000 copies/mL, the proportion of subjects with HIV RNA < 50 copies/mL was 89%, 78% and 65% for rilpivirine compared to 83%, 78% and 73% for efavirenz respectively.

The virologic failure rate by baseline plasma viral load is as follows. For subjects with baseline plasma viral load ≤ 100,000 copies/mL, the proportion of subjects with virologic failure was 5% for both rilpivirine and efavirenz. For subjects with baseline plasma viral load >100,000 to ≤ 500,000 copies/mL and > 500,000 copies/mL, the proportion of subjects with virologic failure was 20% and 29% for rilpivirine compared to 11% and 17% for efavirenz, respectively.

In the pooled resistance analysis from the Phase 3 Studies C209 and C215, the emergence of resistance among subjects was greater in the rilpivirine arm compared to the efavirenz arm. In the combined studies, 41% (38/92) of the virologic failures in the rilpivirine arms had genotypic and phenotypic resistance to rilpivirine compared to 25% (15/60) of the virologic failures in the efavirenz arms who had genotypic and phenotypic resistance to efavirenz. Moreover, resistance to a

background drug (emtricitabine, lamivudine, tenofovir, abacavir or zidovudine) emerged in 48% (44/92) of the virologic failures in the rilpivirine arms compared to 15% (9/60) in the efavirenz arms.

Emerging NNRTI substitutions in the rilpivirine virologic failures included V90I, K101E/P/T, E138K/G, V179I/L, Y181I/C, V189I, H221Y, F227C/L and M230L, which were associated with a rilpivirine phenotypic fold change range of 2.6 - 621. The E138K substitution emerged most frequently on rilpivirine treatment commonly in combination with the M184I substitution. The emtricitabine and lamivudine resistance-associated substitutions M184I or V and the tenofovir resistance-associated substitutions K65R or N emerged more frequently in rilpivirine virologic failures compared to efavirenz virologic failures.

Cross-resistance to efavirenz, etravirine and/or nevirapine is likely after virologic failure and development of rilpivirine resistance. In the pooled analyses of the Phase 3 clinical trials, 38 rilpivirine virologic failure subjects had evidence of rilpivirine resistance. Of these subjects, 89% (n = 34) were resistant to etravirine and efavirenz, and 63% (n = 24) were resistant to nevirapine. In the efavirenz arm, none of the 15 efavirenz-resistant virologic failures were resistant to etravirine at failure. Subjects experiencing virologic failure on rilpivirine developed more NNRTI resistance-associated substitutions conferring more cross-resistance to the NNRTI class and had a higher likelihood of cross-resistance to all NNRTIs in the class than subjects who failed on efavirenz.

CONTRAINDICATIONS:

Rilpivirine is contraindicated with the following drugs, as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction or gastric pH increase, which may result in loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs:

The anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin the antimycobacterials rifabutin, rifampin, rifapentine proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, the glucocorticoid systemic dexamethasone (more than a single dose), St John's wort.

WARNINGS AND PRECAUTIONS:

The Warnings and Precautions for rilpivirine include fat redistribution, immune reconstitution syndrome and the following:

Drug Interactions: Caution should be given to prescribing rilpivirine with drugs that may reduce the exposure of rilpivirine.

In healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram. Rilpivirine should be used with caution when co-administered with a drug with a known risk of Torsade de Pointes.

COMING IN FUTURE MONTHS

- Is an HIV clinician shortage on horizon for 2020?
- Proven strategies for improving long-term adherence
- The HIV infected provider – no longer an issue?
- Prevention focus trends explained

CNE/CME QUESTIONS

1. The National Institutes of Health (NIH) announced in May, 2011, that an HIV Prevention Trials Network study, titled HPTN 052, found the risk of transmitting the virus to uninfected sexual partners could be reduced by what percentage if the HIV-positive partner adhered to an effective antiretroviral therapy (ART) regimen.
   A. 96%
   B. 89%
   C. 81%
   D. 75%

2. Research involving men who have sex with men and resurgent HIV epidemics has led researchers to conclude that multi-level prevention approaches are needed because targeting individuals' risk behaviors doesn't address another risk factor that may be even more relevant. What is it?
   A. The person's race or culture
   B. The person's age
   C. The person's sexual network
   D. All of the above

3. The Lead the Way Campaign in San Diego is an HIV testing and prevention project that seeks to increase HIV awareness, reduce HIV stigma, and increase testing through what type of marketing strategy?
   A. Door-to-door testing for HIV
   B. Flash mob HIV prevention dances and gatherings
   C. Billboards, TV spots, and satellite radio interviews
   D. All of the above

Depressive Disorder: The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with TRADENAME. During the Phase 3 trials (N = 1368), the incidence of depressive disorders (regardless of causality, severity) reported among rilpivirine (n = 686) or efavirenz (n = 682) was 8% and 6%, respectively. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for both rilpivirine and efavirenz. The incidence of discontinuation due to depressive disorders among rilpivirine or efavirenz was 1% in each arm. Suicide attempt was reported in 2 subjects in the rilpivirine arm while suicide ideation was reported in 1 subject in the rilpivirine arm and in 3 subjects in the efavirenz arm. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to rilpivirine, and if so, to determine whether the risks of continued therapy outweigh the benefits. ■

CNE/CME OBJECTIVES & INSTRUCTIONS

The CNE/CME objectives for AIDS Alert, are to help physicians and nurses be able to:

- Identify the particular clinical, legal, or scientific issues related to AIDS patient care;
- Describe how those issues affect nurses, physicians, hospitals, and clinics;
- Cite practical solutions to the problems associated with those issues.

To earn credit for this activity, please follow these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.*
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.