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AHC Media

HIV/AIDS epidemic at 30 years: Promised land or wasteland?

Treatment as prevention possible answer

Thirty years after the world first became aware of a strange syndrome that caused young men to acquire rare diseases like Pneumocystis carinii pneumonia (PCP) and Kaposi's Sarcoma, nations across the globe continue to battle against the HIV/AIDS epidemic.

Scientists have discovered after years of research that a combination of potent antiretroviral therapy (ART) drugs can help HIV-infected patients lead relatively healthy lives. Most recently, they've learned that these same drugs are a potent public health weapon against transmission of this pernicious virus. Studies show that the drugs lower the virus to undetectable levels with very low risk of transmission. Also there are proven behavioral methods for reducing risk, including condom use, clean needle exchange programs, ARTs to prevent mother-to-child transmission, circumcision, etc. Other prevention methods seem always on the verge of game-changing breakthroughs, including antimicrobials for women and some sort of vaccine.

So with this much knowledge and progress, the question remains: why is HIV still an epidemic in the United States?

Investigators who have studied HIV disparities, timing of HIV diagnosis, the U.S. national prevention strategy, and the AIDS Drug Assistance Program (ADAP) each present a piece to a puzzle that suggests the technical and scientific solutions to the epidemic are within our reach, but the economic and political will are not. As AVAC — Global Advocacy for HIV Prevention — states on its website at www.avac.org, the HPTN 052 trial using ART as a prevention strategy shows conclusively that treatment is prevention.[1]

All that is needed is the political and economic will to make that happen.

"It's very difficult to implement a national strategy," says **Baligh Yehia**, MD, a post-doctoral fellow in the division of infectious diseases at the University of Pennsylvania in Philadelphia, PA. Yehia also is a student at the Woodrow Wilson School of Public Health and International Affairs at Princeton University in Princeton, NJ.

Yehia has studied the U.S. HIV prevention strategy from over the past

30 years and evaluated the latest goals proposed by the Centers for Disease Control and Prevention (CDC) of Atlanta, GA. *(See story evaluating the U.S. national HIV/AIDS strategy, p. 136.)*

"The biggest thing is unfortunately that in our economy right now there are no new funds devoted to this HIV prevention plan, and that's a major hurdle to accomplishing this strategy," Yehia says. "Folks are shuffling around different pots of money, and that's important and making us more focused, but there is no new money being contributed other than what was put in the Affordable Care Act."

The CDC's most recent five-year goals included the aim of reducing new HIV infections by 25%.

"It is hard to measure the impact of the strategy, given the delay in CDC estimates, which is a call for a better, more real-time measuring systems," Yehia says.

"The latest CDC estimates suggest 48,000 new infections a year, including huge increases among young men who have sex with men (MSM)," he says. "Young MSM of color is the populace most at risk of contracting HIV in this current time."

What has not changed is chronic underfunding. The Obama administration's National HIV/AIDS Strategy for the United States is the most comprehensive federal response to the domestic epidemic so far. The new prevention strategy's goals are to reduce the number of new HIV infections, improve access to care and health outcomes, and reduce HIV-related health disparities. Yet, it is critically underfunded with only $30 million dedicated funds to expand the strategy's prevention efforts.[2]

Yehia points out that electronic models suggest the total cost of implementing the Obama prevention plan would be about $15 billion, with more than two-thirds of the cost going toward treatment and medical care services.[2]

The U.S. national HIV/AIDS strategy and movement is heading in the direction of a population-based approach, says **Julia Dombrowski**, MD, MPH, acting instructor in the department of medicine at the University of Washington and deputy director for clinical services in the HIV/STD program at the Public Health Seattle King County in Seattle, WA. *(See related story, p. 137.)*

"The goal was to ensure people who are infected get diagnosed soon after getting the disease and are linked to medical care," Dombrowski says.

"Not only the individual benefits from doing all those things, but also the public health benefits since we know ART can reduce sexual transmission," she adds. "Treatment as prevention is an appealing concept, and we need to do more interventions on how to operationalize it."

Treatment and prevention are on a continuum in this epidemic, notes **David Hanna**, MS, a doctoral student in epidemiology at Johns Hopkins Bloomberg School of Public Health in Baltimore, MD. *(See story on state disparities, p. 138.)*

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"It's all related — if a person with HIV does not get treatment, we've known for years that his chances of disease progression and eventually death are significantly higher," Hanna says. "But recent studies have found improvements in shorter-term prevention-related outcomes, as well: someone getting on therapy may be able to reduce her viral load to undetectable levels and in turn the likelihood she'll transmit her infection to somebody else."

Hanna's research has found striking differences in HIV case-fatality rates between regions of the country. For instance, Southeastern states have among the nation's highest HIV case-fatality rates in the nation. While there are eight states that have HIV case-fatality rates of 25.3 (or higher) per 1,000 HIV-infected person years, all but two of these states are in the Southeast. The exceptions are Wyoming and Oklahoma.[3]

On the other side of the equation, two Northeastern states with the highest conventional HIV death rates, which are calculated by HIV deaths per 100,000 general population person years, are New York and New Jersey, which have large HIV populations and lower HIV case-fatality rates. This difference between the two measures is especially striking in the case of New York which has the third highest conventional HIV death rate, but only the 30th (out of 37 states) HIV case-fatality rate. Wyoming is its counterpart with the second lowest conventional HIV death rate, but the 9th highest HIV case-fatality rate. These differences suggest there are disparities in how efficiently various state and regional populations access HIV care and treatment.[3]

"The data are consistent with other studies showing greater disparities in the South with respect to HIV, but our study uniquely focuses on differences in mortality that may have arisen from the availability, use, and quality of HIV care in these states," Hanna notes.

States manage their ADAPs differently, and the programs' formularies, waiting lists, and funding can vary widely, he adds.

"Budgets play a role in states' decisions on how to run the program," Hanna says. "We think it's worth looking into differences in how programs like ADAP are run, and we're hoping to understand these scenarios better in our ongoing work."

Hanna's study looked at the HIV case-fatality rates between 2001 and 2007. But a look at a recent ADAP waiting list report might predict that disparities have only increased in the four years since then. In the September, 2011, ADAP table, there are 11 states with waiting lists — a phenomenon that had disappeared briefly before the Great Recession. Of those 11 states, six are in the Southeast. And those six states account for 7,774 out of the nation's total of 9,066 HIV-infected people on ADAP waiting lists.

Since ADAPs are the source of antiretroviral drugs for a large proportion of uninsured HIV-infected people, their formularies and waiting lists can play pivotal roles in the epidemic. As one recent study found, ADAPs are an important medication resource for HIV-positive women.[4]

The ADAP study used data from 2008, looking at state ADAP formularies in New York, California, and Illinois — all of which are states with large ADAPs, says **Nancy Hessol**, MSPH, adjunct professor, University of California — San Francisco.

"We collected extensive amounts of data on women study participants every six months, used their blood pressure data and asked about HIV antiretroviral medications," Hessol says.

Investigators compared access to highly active antiretroviral therapy (HAART) among women who had access to ADAP with those who did not have access to ADAP.

"The most important thing we found was that women without ADAP were more than two times more likely to not be on HAART," Hessol says. "The women on ADAP were more likely to be on HAART."

In all cases, the women were clinically eligible for HAART, she adds.

"A lot of things have happened since 2008," Hessol says.

The small increases in federal appropriations for HIV testing and prevention, coupled with high drug costs and new treatment guidelines calling for earlier initiation of HAART, all could lead to greater demand for antiretroviral therapy as more people enter treatment and remain in treatment, she explains.

"It's unfortunate because there is a growing number of individuals on ADAP waiting lists," Hessol says. "When you disenroll somebody and kick them out of ADAP, you increase the chance that person will develop virologic resistance to the virus and medicine."

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HIV prevention goal still elusive

30 years and 1 million infected

Researchers who have closely studied the United States' national HIV/AIDS prevention strategy as it has developed over the past three decades have concluded that it has been underfunded, and it's very difficult to implement.[1]

"Many presidential administrations have tried to put together a plan," says **Baligh Yehia**, MD, a postdoctoral fellow in the division of infectious diseases at the University of Pennsylvania in Philadelphia, PA. Yehia also is a student at the Woodrow Wilson School of Public Health and International Affairs at Princeton University in Princeton, NJ.

"What people have learned over the years is that you cannot have too many goals," Yehia says. "When you look at recommendations from the Reagan commission and the Clinton plan, and now Obama's, you can see they are becoming more and more focused."

Specifically, the Obama HIV/AIDS strategy calls for reducing the annual number of new infections by 25% by 2015. This would reduce new infections from the current estimate of 56,300 to 42,225. The plan also has the goal of reducing the HIV transmission rate by 30% and increasing the percentage of people living with HIV who know their serostatus from 79% to 90%. The strategy calls for increasing the proportion of newly diagnosed patients linked to clinical care within three months from 65% to 85%, as well as increasing the proportion of HIV patients in continuous care.[1]

Like many public health prevention expenses, the estimated $15 billion in upfront spending on HIV prevention and care would have a greater return on investment, estimated to be about $18 billion.[1]

"There are many important challenges, and those challenges are formidable," Yehia says. "The most important one is to secure new federal funds for this strategy."

For HIV patients and public health, the stakes are high given current trends.

"We know a lot of people today are linked to care after they have AIDS," Yehia says.

An estimated 45% of patients develop AIDS within three years of receiving their HIV diagnosis, a dire statistic that points to failures in HIV screening and linkage to care and treatment.[1]

By the time HIV-infected patients are tested and placed in care, many are very sick, requiring more intensive and expensive health care. And they likely have transmitted the virus to other people. Alternatively, if they had been identified far earlier in their infection, their health could have been preserved, and the public health would have benefited from a dramatically reduced risk of HIV transmission to others.

"This is something we need to start thinking about," Yehia notes. "When we find someone infected with HIV and put them on antiretroviral therapy, this helps control the disease and prevents spreading infection to other people."

One of the low-hanging fruit in using treatment as a public health prevention strategy would be the 9,000-plus Americans on the AIDS Drug Assistance Program (ADAP) waiting lists in 11 states. These patients already have been identified as HIV positive and in need of antiretroviral therapy (ART). Yet, their medical care is jeopardized by inadequate federal and state funding, he says.

"We need funding," Yehia says. "There are certain states that don't have enough funds to pay for people who know they have HIV, and that's not including the 25% to 28% of people who don't know they're infected."

These statistics and the waiting lists are a sign that access to HIV treatment is in jeopardy and disparities are increasing.

"Obviously, as a nation we have to weigh our national priorities, and HIV is definitely important, as are education and other things," Yehia says. "But we have to use our money wisely, and if there is an area that would be beneficial, it would be to make sure everyone has access to HIV medicine because that has a big impact on patients and the community."

If the latest HIV/AIDS prevention strategy does not reach its goals of decreasing new infections, eliminating disparities, and increasing access to care, then it will not be the first prevention strategy to fail. As the evaluation of the nation's succession of

HIV/AIDS strategies shows, previous administrations also failed to reach many of their goals.[1]

Under the Bush administration, the Centers for Disease Control and Prevention (CDC) revised HIV testing recommendations to increase HIV screening in all health care settings, but it has encountered pragmatic and social barriers to full implementation.[1]

The lack of adequate public health funding coupled with systemic socioeconomic issues make it extremely difficult for the national HIV/AIDS plan to succeed.

"It's very hard to decrease disparities in HIV care if you solely focus on race/ethnicity and gender," Yehia says.

Improved health literacy rates, needle exchanges, economic disparities, lifestyle and housing issues, and other social challenges also need to be addressed, he adds.

"In the national strategy, they focus on Latinos, blacks, and men who have sex with men, and those are groups that we can measure," Yehia explains.

"But to reduce disparities in those groups you have to look beyond that: are the folks getting incarcerated more? How do you break that cycle in the community where folks are not always in jail? How do you provide some wealth for a family where the mother has to exchange sex for food or money?" he adds. "It goes deeper than just race."

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Rethinking metrics used for goals

Ensure early diagnosis

One obstacle to the success of the U.S. national HIV/AIDS strategy involves the accuracy of metrics used for monitoring HIV care, including late diagnoses and linkage to sustained care, a new study notes.[1]

"We have not worked on the metrics to use in progress of the strategy's goals," says **Julia Dombrowski**, MD, MPH, acting instructor in the department of medicine at the University of Washington and deputy director for clinical services in the HIV/STD program at the Public Health Seattle King County in Seattle, WA.

"That was our paper's purpose, to evaluate metrics that other public health networks can use to evaluate the goals," she adds.

Dombrowski and co-investigators found that 32% of persons living with HIV/AIDS in King County (WA) in 2009, had been diagnosed with AIDS within one year of their HIV diagnosis.[1]

"Within that group, a significant proportion — almost a third — said they had their last negative test within two years," Dombrowski says. "That brings up the question of whether having AIDS in one year is the best method for measuring late diagnosis."

Investigators found no trends in a five-year period that would suggest there is a more virulent form of HIV in this population, she notes.

"Another explanation is that some people progress to AIDS more quickly, and it could be that some people reported their last negative test incorrectly," she adds.

Researchers also looked closely at linkage to care. They found that a focus on linking a newly-diagnosed HIV patient to his or her first appointment might be less informative than measuring linking patients to sustained medical care, Dombrowski says.

The study found that linkage to sustained care had a significant association with virologic suppression, but linkage to initial care, was not.[1]

"We as a public health community and medical community need to focus on getting people into sustained medical care," she adds.

Measuring a proportion of people in sustained care is limited by obstacles to follow-up.

For instance, patients can move out of state or die without their death being reported, Dombrowski says.

"None of us has a good handle on the status of people with no recent labs," she adds. "They could be out of care, moved away, or they might have died."

One best practice for improving linkage to care is to provide a one-on-one program in which patients meet with doctors to discuss HIV engagement in care and prognosis, she says.

"We'll make sure people are linked to sustained care and make sure that happens over the first year of care," Dombrowski says.

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Study looks at state disparities in HIV

Data comes from 37 states

HIV/AIDS mortality data highlight disparities between states, suggesting differences in HIV treatment and care, a new study shows.[1]

Investigators compared HIV/AIDS data from 37 states that have collected confidential HIV reporting data for most of the past decade. They found geographic disparities in HIV mortality.

"We combined data from two national sources," says **David Hanna**, MS, a doctoral student in epidemiology at Johns Hopkins Bloomberg School of Public Health in Baltimore, MD.

"The first source was the national HIV/AIDS reporting system maintained by the Centers for Disease Control and Prevention (CDC) in Atlanta," he says. "The other data source is the national vital statistics system maintained by the National Center for Health Statistics, which contains data for all reported deaths in the country."

With data from 2001 to 2007, researchers calculated mortality rates due to HIV and AIDS, finding out what the HIV death rate was in the state's general population, calculated as HIV death rate per 100,000 population person-years. Then they looked more specifically at the mortality rate among only HIV-positive populations, describing this as the HIV case-fatality rate per 1,000 HIV-infected person-years.

"We collaborated with the CDC to generate this information," Hanna says.

When investigators charted the conventional HIV death rate and compared it with the HIV case-fatality rate among HIV-infected populations, they found that the Southeast was dominant in both measures. States like Mississippi, North Carolina, Tennessee, Louisiana, Georgia, South Carolina, and Florida were ranked in the top 10 on both lists. For instance, Florida has the highest HIV death rate with 12.5 HIV deaths per 100,000 population, and it has the 10th highest HIV case-fatality rate with 24.2 HIV deaths per 1,000 HIV-infected person-years.[1]

Louisiana ranks second in both measures with 11.2 HIV deaths per 100,000 person-years and 32.5 HIV deaths per 1,000 HIV-infected person-years.[1]

New York and New Jersey rank third and fifth in the conventional HIV death rate, but their rankings fall to 30th and 15th when it comes to HIV deaths per 1,000 HIV-infected person-years.[1]

"We know that New York has a relatively high number of residents infected with HIV, and consequently a high number of deaths due to the sheer size of its HIV population," Hanna explains.

"However, when we calculated the HIV case-fatality rate to take into account the number of deaths occurring among HIV-infected people only, we found that at 14.7 per 1,000, New York's rate is quite low," he adds. "This suggests that the risk of death for those with HIV is lower in New York state than in many other states."

It might also suggest that New York does a good job at identifying new HIV infections and getting people into care, although the epidemiological findings can only suggest this as a possibility.

"Then, let's look at South Carolina, which has a conventional death rate ranking of sixth out of 37 states — with 8.6 deaths per 100,000 person-years," Hanna says.

"Similarly, the state's case-fatality rate ranks at seventh out of 37 states, with 25.2 deaths per 1,000 person-years" he says. "So with respect to South Carolina, HIV mortality appears relatively high regardless of the metric used."

As national public health policymakers address the HIV epidemic and disparities, they should keep in mind geographic disparities, Hanna suggests.

"Ultimately, we're trying to identify factors that policymakers can understand to help them formulate strategies to improve the health of people with HIV," he adds.

"Race and transmission risk are important, but we want to show there are other factors that should be taken into consideration, like geography," Hanna says. "States provide different environments with respect to health insurance, prescription drug coverage, and other economic factors, and these cannot be ignored."

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AMA: Amend HIV transplant law

1,000 people a year could be saved

The American Medical Association recently voted to support amending a federal law that bars clinical research of HIV-infected organ donation, as a potentially lifesaving measure for people living with HIV infection.

Advances in the medical management of HIV infection coupled with improvements in transplant outcomes could make organ transplantation a viable clinical option for many HIV-infected patients. Despite these scientific advances, the Federal National Organ Transplant Act of 1984 precludes donations of HIV-infected organs, thereby prohibiting investigational studies on a source of organs for HIV-infected patients.

Research is needed to fully evaluate the clinical risks and benefits of organ transplantation between HIV-infected individuals," said AMA Board Member Ardis D. Hoven, M.D. "The new policy adopted extends the AMA's support for a change in federal law that will permit the necessary scientific investigation."

It is estimated that there are approximately 500-600 potential HIV-infected kidney and liver donors per year in the United States. Organs from these donors have the potential to save the lives of approximately 1,000 HIV-infected patients each year.

The new policy supporting research on organ transplantation between HIV-infected individuals was adopted today at the AMA's semi-annual policy making meeting in New Orleans. ■

What's new in HIV treatment?

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

Synopsis: Most of the changes in the guideline deal with the choice of antiretroviral therapy in the previously treatment-naïve patient.

Source: Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. October 14, 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf. Accessed Nov. 8, 2011.

A revision to the Jan. 10, 2011, Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents was published on Oct. 14, 2011. This update focuses on the choice of an initial regimen for antiretroviral treatment-naïve HIV patients: "What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient." The changes recommednded by the Panel are summarized here.

Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)-Based Regimens

• **Rilpivirine** (RPV) was added as an alternative NNRTI option for initial therapy in treatment-naïve patients.

Background: On the basis of clinical trial results and safety data, the Panel recommends that efavirenz (EFV), RPV, or nevirapine (NVP) may be used as part of an initial regimen. In most instances, EFV is preferred, based on its potency and tolerability. RPV may be used as an alternative NNRTI option in treatment-naïve patients, whereas NVP may be used as an acceptable NNRTI option (C) in women with pretreatment CD4+ counts ≤ 250 cells/mm3 or in men with pretreatment CD4+ counts ≤ 400 cells/mm3.

Although RPV demonstrated overall non-inferiority to EFV, among participants with higher pre-treatment HIV RNA (> 100,000 copies/mL), virologic failure occurred more frequently in those randomized to receive RPV. Subjects with virologic failure on RPV were also more likely to have genotypic resistance to other NNRTIs (EFV, ETR, and NVP) and to have resistance to their prescribed NRTIs. For those reasons, the guideline indicates that RPV should be used with caution in patients with pre-treatement HIV RNA > 100,000 copies/mL.

The drug interaction tables were also updated to include information regarding RPV. Table 14 indicates that the following should not be coadministered with this NNRTI: rifamycins, proton pump inhibitors, St. John's wort, other NNRTIs, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin. Table 15b indicates that antacids may be administered at least 2 hours before or 4 hours after RPV, and H2 antagonists may be given at least 12 hours before or 4 hours after. The use of proton pump inhibitors is totally contraindicated, as are carbamazepine, phenobarbital, phenytoin, rifampin, and rifabutin. Because of a likely interaction with clarithromycin, azithromycin is recommended as an alternative in patients receiving RPV. More than a single dose of dexamethasone is contraindicated in patients on the NNRTI.

Dosing of RPV was also addressed. Appendix B,

Table 2 recommends a daily 25 mg dose (alone or as part of Complera®, which also contains emtricitabline and tenofovir). It was noted that RPV is a CYP3A4 substrate with serum half-life of 50 hours and that the adverse events most commonly associated with its use are rash, depression, insomnia, and headache. In addition, Appendix B, Table 7 indicates that no dosage adjustment is indicated in patients with renal insufficiency, including those undergoing chronic peritoneal dialysis or hemodialysis. Finally, no dosage recommendation is indicated for patients with Childs Class A or B hepatic impairment, while no recommendation is made for those in Childs Class C.

• **All nevirapine-based regimens** were reclassified as acceptable options for treatment-naïve patients (females with pretreatment CD4+ count < 250 cells/mm3 or males with pretreatment CD4+ count < 400 cells/mm3). Previously, "nevirapine + zidovudine/lamivudine" was classified as an alternative regimen and "nevirapine + abacavir/lamivudine" and "nevirapine + tenofovir/emtricitabine" were recommended as regimens that may be acceptable but should be used with caution.

Background: Patients who experience CD4+ count increases to levels above the thresholds indicated above in response to NVP-containing therapy can safely continue therapy without an increased risk of adverse hepatic events. At the initiation of NVP, a 14-day lead-in period at a dosage of 200 mg once daily should be instituted before increasing to the maintenance dosage of 400 mg per day (as an extended-release 400 mg tablet once daily or 200 mg immediate-release tablet twice daily). Some experts recommend monitoring serum transaminases at baseline, at 2 weeks, then 2 weeks after dose escalation, and then monthly for the first 18 weeks. Clinical and laboratory parameters should be assessed at each visit.

Protease Inhibitor (PI)-based Regimens

• **"Ritonavir (RTV)-boosted darunavir (DRV) + abacavir/lamivudine"** was reclassified as an alternative regimen (BIII). This regimen had previously been recommended as one that may be acceptable, although more definitive data were needed (CIII).

Background: The Panel uses the following criteria to distinguish between preferred vs. alternative PIs in ART-naïve patients: 1) demonstrated superior or non-inferior virologic efficacy when compared with at least one other PI-based regimen, with at least published 48-week data; 2) RTV-boosted PI with no more than 100 mg of RTV per day; 3) once-daily dosing; 4) low pill count; and 5) good tolerability. Using these criteria, the Panel recommends atazanavir (ATV)/r (once daily) and DRV/r (once daily) as preferred PIs.

The ARTEMIS study compared DRV/r (800/100 mg once daily) with LPV/r (once or twice daily), both in combination with tenofovir (TDF)/emtricitabine (FTC), in a randomized, open-label, non-inferiority trial. At 96 weeks, virologic response to DRV/r was superior to response to LPV/r. Based on these data, the Panel recommends DRV/r + TDF/FTC as a preferred PI-based regimen (AI). No randomized controlled trial exists to evaluate the efficacy of DRV/r with the other two-NRTI combinations. A small retrospective study suggested that DRV/r + ABC/3TC may be effective in treatment-naïve patients for up to 48 weeks. Based on this preliminary information, the Panel recommends this combination as an alternative PI-based regimen (BIII).

• Regimens with **unboosted fosamprenavir** were removed as PI options for treatment-naïve patients because they have inferior potency compared with other PI-based regimens and because of the potential for selection of mutations that confer resistance to darunavir in patients who experience virologic failure while on these regimens.

Raltegravir-based Regimens

• **"Raltegravir + abacavir/lamivudine (RAL)"** was reclassified as an alternative regimen (BIII). This regimen was previously classified as a regimen that may be acceptable, but more definitive data are needed (CIII).

Background: Comparisons of RAL-based regimens with other regimens in ART-naïve subjects have not yet been reported, and experience with RAL is less than with EFV or boosted PIs for initial therapy. In addition, RAL must be administered twice daily, a potential disadvantage when compared with some other regimens. RAL, like EFV, has a lower genetic barrier to resistance than RTV-boosted PIs, and resistance mutations were observed at approximately the same frequency in the comparative trial.

Dual-nucleoside Reverse Transcriptase Inhibitor (NRTI) Options

• **"Zidovudine + lamivudine"** was reclassified from an alternative dual-NRTI option to an accept-

able option because the combination has greater toxicities compared with tenofovir/emtricitabine and abacavir/lamivudine and requires twice daily dosing. However, zidovudine + lamivudine remains as the preferred dual-NRTI for pregnant women receiving antiretroviral therapy for prevention of perinatal transmission of HIV.

• **"Didanosine + lamivudine"** was removed as a dual-NRTI option for initial therapy because the combination has the least clinical trial experience and greater toxicity compared with other available dual-NRTI options.

• Discussion on the **association between abacavir use and the risk of a cardiovascular event** was updated.

Background: The D:A:D observational study found that recent (within 6 months) or current use of abacavir, but not TDF, was associated with an increased risk of myocardial infarction, particularly in participants with pre-existing cardiac risk factors. Since this study, however, multiple studies have explored this association and come to varying conclusions. To date, no consensus has been reached either on the association of abacavir use with myocardial infarction risk or a possible mechanism for the association. ■

Abstract & Commentary

HIV-1 Protein linked to insulin resistance

By **Dean L. Winslow**, MD, FACP, FIDSA

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Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostics.

Synopsis: The HIV-1 regulatory protein, Nef, was shown in cell cultures of adipocytes to cause reduced glucose uptake, inhibition of glucose transporter protein 4 (GLUT 4), decreased phosphorylation of signal transducing proteins, and alteration in cortical actin organization.

Source: Cheney L, et al. Nef inhibits glucose uptake in adipocytes and contributes to insulin resistance in human immunodeficiency virus type I infection. *J Infect Dis* 2011;203:1824-1831.

3T3L1 pre-adipocytes in cell culture were treated overnight with myristoylated or non-myristoylated recombinant Nef. Glucose uptake was measured with and without insulin stimulation. Adipocytes transfected with a Myc-GLUT4-green fluorescent protein (GFP) were studied after treatment with Nef with or without insulin stimulation. Actin polymerization was studied using rhodamine-stained cells. Immunoblot analysis of phosphorylation of signal transduction proteins Akt and AS160 was performed.

Nef was shown to inhibit insulin-stimulated glucose uptake in a dose-dependent manner. Nef also inhibited GLUT4 fusion with the plasma membrane in insulin-stimulated adipocytes. Finally, Nef was shown to alter the proximal signal transduction pathway of insulin and to disrupt F-Actin at the cortical actin ring.

Commentary

While a number of antiretroviral agents have been implicated in contributing to both insulin resistance and lipid abnormalities, HIV also directly causes metabolic disturbances. Nef, a 27 kDa nonstructural protein essential for replication and evasion of host responses, is one of several regulatory proteins encoded by HIV-1 and modulates a number of cellular processes by protein-protein interactions. Nef has been shown to down-regulate CD4 and MHC1 molecules, alter signal transduction pathways, interact with the actin cytoskeleton, and affect actin polymerization. These processes are important for insulin action and glucose homeostasis. Nef is secreted into the extracellular compartment and can be measured in plasma. Insulin resistance is found in ARV-naïve patients, and HIV viral load is a predictor of metabolic syndrome.[1]

This in vitro study presents a nice demonstration of what is most likely a clinically relevant mechanism contributing to the problem of insulin resistance with resultant Type 2 diabetes and dyslipidemia so commonly seen in HIV-infected patients.

REFERENCES

1. Squillace N, et al. Detectable HIV viral load is associated with metabolic syndrome. *J Acquir Immune Defic Syndr* 2009;52:459-464. ■

Darunavir package updated

Updates to the darunavir (Prezista®) package insert, specifically sections: 6 Adverse Reactions, 12.4 Microbiology, 14 Clinical Studies and were approved on Oct. 19, 2011, to include results from the 192-week safety, resistance and efficacy data from study TMC114-C211, "A randomized, controlled, open-label Phase 3 trial comparing darunavir/ritonavir 800/100 mg once daily versus lopinavir/ritonavir 800/200 mg per day (given as a twice daily or as a once daily regimen) in antiretroviral treatment-naïve HIV-1-infected adult subjects."

In addition section 5.3 Severe Skin Reactions now includes the following text about darunavir/ritonavir + raltegravir containing regimens. Rash occurred more commonly in treatment-experienced subjects receiving regimens containing darunavir/ritonavir + raltegravir compared to subjects receiving darunavir/ritonavir without raltegravir or raltegravir without darunavir/ritonavir. However, rash that was considered drug related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

The complete revised label will be posted soon at Drugs@FDA. ■

Pegasys antiviral approved

On Sept. 29, 2011, the Food and Drug Administration approved a135 mcg/0.5ml and 180 mcg/0.5 ml disposable autoinjector (DAI) to administer peginterferon alfa-2a (Pegasys®), an antiviral indicated for treatment of Chronic Hepatitis C (CHC) by subcutaneous injection.

Pegasys continues to be available in a vial or prefilled syringe, and now also in a 135 mcg/0.5ml and 180 mcg/0.5 ml PEGASYS disposable autoinjector. The package insert and the Medication Guide have been updated to provide new information and instructions for use related to the disposable autoinjector.

Because the autoinjectors are designed to deliver the full content, autoinjectors should only be used for patients who need the full dose (180 or 135 mcg). If the required dose is not available in an autoinjector, prefilled syringes, or vials should be used to administer the required dose. The autoinjector is for subcutaneous administration only.

The updated label and Medication Guide can be found on the FDA web site at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103964s5204lbl.pdf

Pegasys is a product of Hoffmann-La Roche, of Nutley, NJ. ■

ART guidelines updated

On Oct. 14, 2011, updated Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents were made available through the AIDSinfo web site.

Guidelines for treating HIV-infected adults and adolescents, including utilization of resistance testing, initiation of treatment, preferred first-line regimens, adverse events to antiretroviral medications, managing treatment-experienced patients, and considerations for special populations.

This revision to the guidelines is focused on What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient. Additions and key changes to the section are outlined below. More detailed discussion of the rationale for changes to the What to Start recommendations can be found in the updated section. Tables in the guidelines corresponding to the What to Start section have also been updated to reflect changes.

• **Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-Based Regimens**

Rilpivirine added as an alternative NNRTI option for initial therapy in treatment-naive patients.

All nevirapine-based regimens reclassified as acceptable options for treatment-naive patients (females with pretreatment CD4 count <250 cells/mm3 or males with pretreatment CD4 count <400 cells/mm3). Previously, "nevirapine + zidovudine/lamivudine" was classified as an alternative regimen and "nevirapine + abacavir/lamivudine" and "nevirapine + tenofovir/emtricitabine" were recommended as regimens that may be acceptable but should be used with caution.

• **Protease Inhibitor (PI)-Based Regimens**

"Ritonavir-boosted darunavir + abacavir/lamivudine" reclassified as an alternative regimen (BIII); previously the regimen was recommended as a regimen that may be acceptable but more definitive data

are needed (CIII).

Regimens with unboosted fosamprenavir removed as PI options for treatment-naive patients. The Panel removed the regimens because they have inferior potency compared with other PI-based regimens and because of the potential for selection of mutations that confer resistance to darunavir in patients who experience virologic failure while on these regimens.

• **Raltegravir-Based Regimens**

"Raltegravir + abacavir/lamivudine" reclassified as an alternative regimen (BIII); previously, the regimen was classified as a regimen that may be acceptable but more definitive data are needed (CIII).

Dual-Nucleoside Reverse Transcriptase Inhibitor (NRTI) Options

"Zidovudine + lamivudine" reclassified from an alternative dual-NRTI option to an acceptable option because the combination has greater toxicities compared with tenofovir/emtricitabine and abacavir/lamivudine and requires twice daily dosing. However, zidovudine + lamivudine remains as the preferred dual-NRTI for pregnant women receiving antiretroviral therapy (ART) for prevention of perinatal transmission of HIV.

"Didanosine + lamivudine" removed as a dual-NRTI option for initial therapy because the combination has the least clinical trial experience and greater toxicity compared with other available dual-NRTI options.

Discussion on the association between abacavir use and the risk of a cardiovascular event updated.

In addition to the changes highlighted above, the following tables are updated with information relevant to rilpivirine:

• Tables 14, 15b, and 16b – Drug interaction tables

• Appendix B, Table 2 – Drug characteristic table

• Appendix B, Table 7 – Dosing recommendation for patients with renal or hepatic insufficiency ■

Raltegravir package insert updated

The FDA approved updates to the raltegravir (Isentress®) package insert on Nov. 2, 2011, to include a new subsection in the Warnings and Precautions section and update the postmarketing experience section. Specifically, the following subsection was added to section 5 Warnings and Precautions:

5.1 Severe Skin and Hypersensitivity Reactions

"Severe, potentially life-threatening, and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue ISENTRESS and other suspect agents immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping ISENTRESS treatment or other suspect agents after the onset of severe rash may result in a life-threatening reaction."

In Section 6 Adverse Reactions, subsection 6.2 Postmarketing Experience, cerebellar ataxia and drug rash with eosinophilia and systemic symptoms was added.

The Patient Counseling Information section and the patient labeling was also revised to incorporate the following paragraph, which was added at the beginning of the Patient Counseling Information section:

"Patients should be informed that severe and potentially life-threatening rash has been reported.

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.

Patients should be advised to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking ISENTRESS and other suspect agents, and seek medical attention if they develop a rash associated with any of the following symptoms as it may be a sign of a more serious reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis or severe hypersensitivity: fever, generally ill feeling, extreme tiredness, muscle or joint aches, blisters, oral lesions, eye inflammation, facial swelling, swelling of the eyes, lips, mouth, breathing difficulty, and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes, dark or tea colored urine, pale colored stools/bowel movements, nausea, vomiting, loss of appetite, or pain, aching or sensitivity on the right side below the ribs). Patients should understand that if severe rash occurs, they will be closely monitored, laboratory tests will be ordered and appropriate therapy will be initiated." ■

CNE/CME QUESTIONS

1. Which region of the country has the highest HIV case-fatality rates among HIV-infected populations, according to a new study on HIV death rates?
   A. Northeast
   B. Midwest
   C. Southeast
   D. Western

2. President Obama's National HIV/AIDS Strategy for the United States is a comprehensive federal response to the domestic epidemic. What are its actual funding versus what type of funding is needed to fully implement it, according to an electronic model?
   A. $56 million actual funding versus $1 billion necessary funding
   B. $220 million actual funding versus $500 million necessary funding
   C. $20 million actual funding versus $30 million necessary funding
   D. $30 million actual funding versus $15 billion necessary funding

3. True or False: A new study has found that linkage to sustained HIV care had a significant association with virologic suppression, but linkage to initial HIV care did not.
   A. True
   B. False