# Thorough Anal Exam Crucial For Detecting Cancer in HIV

BY ROBERT FINN
*San Francisco Bureau*

SAN FRANCISCO — A look at the epidemiology of anal cancer shows the need for thorough anal exams, particularly in patients of either sex with HIV disease, Joel M. Palefsky, M.D., said at a meeting on HIV management sponsored by the University of California, San Francisco.

Before the HIV epidemic, reported rates of anal cancer among men who have sex with men (MSM) were as high as 35/100,000, about the same as the cervical cancer rate in women before universal screening. Data now suggest that MSM with HIV disease have anal cancer rates as high as 100/100,000, or about 10 times the rate of cervical cancer in screened women, which has declined to about 8/100,000, said Dr. Palefsky of the university.

Visual inspection of the anal opening is not enough, although it should not be dispensed with. It can, for example, show the plaques of Bowen's disease. Two centimeters inside the anal canal is a transformation zone where the rectal columnar epithelium meets the anal squamous epithelium. This is where most disease occurs.

After visual inspection, the next step is an anal Pap smear, which must be done without lubricant. Moisten a Dacron (not cotton) swab with tap water or saline and insert it past the anal-rectal junction as far as it will go. As it's pulled out, it will capture a good sample of cells from the transformation zone, which can then be examined cytologically and tested for human papilloma virus (HPV). Virtually everyone with HIV disease—women as well as men—will have an HPV infection, some with as many as 10 virus types.

The next step is a digital rectal exam, which is a good cancer-screening tool, Dr. Palefsky said. Put a lubed finger into the anal canal and feel for masses.

The next step is anoscopy with a standard plastic anoscope. Cancerous and precancerous lesions in the anus appear similar to what one would see in the cervix.

Dr. Palefsky cautioned against dismissing standard-seeming warts, especially in individuals with HIV disease. These patients often have high-grade disease mixed in with the warts. "We recommend sampling, through biopsy, lesions of different appearance when patients have multiple lesions." ■

# Weigh the Options Before Choosing One HIV Drug-Resistance Test Over Another

BY ROBERT FINN
*San Francisco Bureau*

SAN FRANCISCO — All official guidelines on HIV treatment either recommend drug-resistance testing or suggest considering such testing depending on the individual patient, Brad Hare, M.D., said at a meeting on HIV management sponsored by the University of California, San Francisco.

But deciding whether to use genotypic or phenotypic assays can be difficult, said Dr. Hare, a physician in the positive health program at the university.

Genotypic drug-resistance assays identify the presence of specific mutations in the HIV genome. Drug resistance is then inferred through an algorithm or a database analysis that matches these mutations to patterns of drug resistance.

Phenotypic assays use viral isolates or recombinant virus derived directly from the patient's plasma. The analysis derives from a culture-based system, and the concentration of a specific drug needed to inhibit viral replication can be quantified. In general, genotypic testing holds the edge early in a patient's disease, before the virus develops complex patterns of resistance. Phenotypic testing tends to be better late in a patient's infection, when the patient may see more regimen failure due to virus with complex mutations. (See box.)

Both tests may be required in complicated patients. ■

## Comparing HIV Drug-Resistance Tests

### Genotypic Assay

| Advantages | Disadvantages |
|---|---|
| ▶ Results are available in days. | ▶ Is an indirect measure of resistance. |
| ▶ Is less technically complex than phenotypic assay. | ▶ Requires a viral load ≥1,000 copies/mL. |
| ▶ Has proven value in predicting short-term virologic outcome. | ▶ May not detect viral species with <20% prevalence. |
| ▶ Mutations may precede phenotypic resistance. | ▶ Requires interpretation. |
| ▶ Can detect mixtures of resistant and wild-type virus. | ▶ Cannot assess interactions between mutations. |
| ▶ Is less expensive than phenotypic assay. | ▶ Correlates of resistance are less clear for some (especially new) drugs. |
| | ▶ Cannot test new drugs immediately. |

### Phenotypic Assay

| Advantages | Disadvantages |
|---|---|
| ▶ Is a direct measure of resistance. | ▶ It takes weeks to get results. |
| ▶ Results are similar to assays of bacterial resistance. | ▶ Results may oversimplify the situation. |
| ▶ Results are easily understood. | ▶ Resistance thresholds are not defined for all drugs or standardized for different assays. |
| ▶ Can be used for any drug. | ▶ Does not take into account the activity of drugs in combination. |
| ▶ Requires no knowledge of genotypic correlates of resistance. | ▶ Requires a viral load ≥500-1,000 copies/mL. |
| ▶ Assesses effects of interactions between mutations. | ▶ May not detect minor species. |
| ▶ Able to test new drugs immediately. | ▶ Is more expensive than genotypic assay. |

Source: Dr. Hare

# *In HIV Therapy Adherence, Almost Isn't Good Enough*

BY MICHELE G. SULLIVAN
*Mid-Atlantic Bureau*

Being almost compliant with antiretroviral therapy was associated with a sharp increase in the risk that HIV-infected patients would develop resistance to one or more of the drugs, P. Richard Harrigan, Ph.D., reported at an American Medical Association press briefing.

In a prospective cohort study of 1,191 HIV-infected patients, those who picked up 80%-90% of their prescription refills, and those who occasionally had low serum drug levels even if they picked up 95% of their medication, had more than a fourfold increase in the risk of developing drug-resistant mutations, said Dr. Harrigan, director of the British Columbia Center for Excellence in HIV Research Labs, Vancouver, B.C.

Inconsistent drug levels allow viral loads to increase and also put pressure on the virus to adapt. Patients who consistently take all their medication suppress viral reproduction so well that mutations are unlikely, and those with poor adherence don't have enough drugs in their system to stimulate mutations.

"Physicians should get this message to patients: Be fully, completely adherent as much as humanly possible," he said.

In the study of patients in British Columbia, the median age was 37 years, the median CD4 cell count was 280 cells/ L, and the median viral load was 120,000 copies/mL. All patients began antiretroviral therapy during 1996-1999; 26 drug combinations were used. Viral load, drug levels, and resistance genotyping were assessed at baseline, after 1 month of therapy, and then quarterly (J. Infect. Dis. 2005:191;339-47).

After an average follow-up of 2.5 years, 25% of the cohort developed resistance to one or more drugs. Among these, 68.5% were resistant to lamivudine (3TC), 40% to nonnucleoside reverse transcriptase inhibitors, 33% to nucleoside reverse transcriptase inhibitors, and 23% to protease inhibitors.

The highest risk of resistance mutations occurred in those who picked up 80%-90% of their prescription refills. This group was 4.15 times more likely to develop resistance mutations than were those who picked up 0%-20% of their refills.

An 80%-90% refill rate is "pretty reasonable for some diseases, but not for this. It's not like in horseshoes, where close is good enough. Here, close is a bad thing," Dr. Harrigan said.

Patients with one or two abnormally low drug concentrations in their first two post-therapy plasma samples were 1.45 times more likely to develop mutations than were those with normal drug levels.

But some patients who picked up more than 95% of their medication still weren't taking it consistently, and they, too, were at a high risk of developing resistance mutations. Among this group, those who had two abnormally low drug plasma levels were 4.57 times more likely to develop mutations than were those with normal drug plasma levels.

As long-term survival increases, drug resistance is becoming more of a problem, Dr. Harrigan said. In recent studies, up to 50% of the U.S. population being treated for HIV infection had some degree of resistance.

The 25% resistance rate among the study patients reflects conditions that many American HIV patients don't experience: free access to antiretroviral drugs, provided by Canada's nationalized health system. Still, even with free access to medication, only 30% of the study group was fully adherent, picking up 100% of medication refills and having therapeutic plasma drug levels at every test.

The risk of nonadherence increases as patients move beyond initially prescribed regimens, which usually are the most manageable, said Kathleen Squires, M.D., of the University of Southern California, Los Angeles.

"We're taking patients with adherence problems to begin with, and then putting them on a more complex regimen that can cause even more adherence problems," she said.

"Nonadherence has punishing effects," said John Bartlett, M.D., founding director of the Johns Hopkins HIV Care Program. "We've got to figure out better ways to make patients understand they must take their medication as prescribed." ■