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We often use category C drugs during pregnancy if we know that a drug is much more effective than a category B drug. However, specialists in other disciplines might recommend category B drugs, not because they are better but because of those specialists' unfamiliarity with the care of pregnant women and their fear of using category C drugs. We should be the ones to make that call, and should work with the HIV specialist in balancing efficacy and fetal safety.

The HIV specialists, on the other hand, are going to know all the ins and outs about drug combinations, about acceptable rates of viral load decrease, and about dosing schedules and other logistical details.

In general, the use of two nucleoside reverse transcriptase inhibitors along with a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor is recommended. It also is often useful to choose a regimen that spares one class of antiretroviral agents in case resistance develops. There are choices within each of the three drug categories, but there also are certain medications that should not be used in combination because of overlapping toxicities or diminished efficacy.

There are also certain potential perinatal risks. Nevirapine, for instance, can cause fulminant liver disease in women who have CD4 counts greater than 250 cells/mm^3. This drug should be used in pregnant women only if its benefit clearly outweighs the risk.

Treatment with efavirenz, for example, should be avoided during the first trimester because the drug has been associated with severe central nervous system anomalies. Overall, it's important to recognize and tell patients that we do not have long-term outcome data on the use during pregnancy of any of the available antiretroviral drugs.

The number of HAART regimens continues to increase, and there may be new reports of problems, so in addition to consulting with HIV specialists, obstetricians should also make use of the Public Health Service's Web site (www.aidsinfo.nih.gov/guidelines). The site provides thorough and regularly updated guidelines on the management of HIV in pregnant women, as well as fact sheets for patients. The perinatal guidelines—last updated in February—cover management broadly but also address the safety and toxicity of individual drugs.

Prevention of Resistance

Once therapy is underway, viral loads should be checked every month until the viral load is undetectable. At that point, monitoring should be done every 2-3 months. If the viral load is not dropping or does not become undetectable within 6 months, a decision about new therapy will have to be made.

Before therapy is stopped, however, your patient must undergo resistance testing—a practice that has become a standard component of HIV care, mainly for identifying therapies that should not be used in the new regimen.

If you stop therapy first and draw blood just a week later, the wild-type virus (the nonmutant strain) may have overgrown a minority mutant strain, and the resistant virus may not be detected. You must draw blood before discontinuing therapy.

Also remember that second regimens do not work as well as first regimens, so it is important to do everything possible to prevent nonadherence. Patients who are only intermittently adherent—who have intermediate drug levels—are more likely to develop resistance.

Be sure to explain at the start that it is critical for the patient to be committed to therapy and to take drugs in a timely fashion. And if a patient develops nausea and vomiting, have her stop her drug regimen until the symptoms subside.

Mode of Delivery

As a rule, women who have scheduled a cesarean delivery before the onset of labor and before rupture of membranes have a lower rate of perinatal HIV-1 transmission. However, for a patient whose viral load is very low, there really is no evidence that scheduled cesarean delivery can lower the risk of transmission.

In addition, there is some preliminary evidence to support the notion that even some patients whose viral load is not that low—plasma HIV-1 RNA levels higher than 1,000 copies/mL—may not benefit from cesarean delivery if they are being given HAART. Those data remain to be confirmed.

Considering all that is known and unknown, I would advise a cesarean section for women whose viral load is greater than 1,000 copies/mL. When a patient's viral load is low, however, I would tell her that there is no proven benefit to delivering surgically. ■

Indications for Plasma HIV RNA Testing

Clinical Indication	Information	Use
Syndrome consistent with acute HIV	Establishes diagnosis when HIV antibody test is negative or indeterminate	For diagnosis*
Initial evaluation of newly diagnosed HIV	Establishes baseline viral load set point	With CD4 T-cell count for decision to start or defer therapy
Every 3-4 months in patients not on therapy	Measures changes in viral load	With CD4 T-cell count for decision to start therapy
2-8 weeks after initiation of or change in antiretroviral therapy	Provides initial assessment of drug efficacy	In decision to continue or change therapy
3-4 months after start of therapy	Provides assessment of virologic effect of therapy	In decision to continue or change therapy
Every 3-4 months in patients on therapy	Measures durability of antiretroviral effect	In decision to continue or change therapy
Clinical event or significant decline in CD4 T cells	Confirms association with changing or stable viral load	In decision to initiate, continue, or change therapy

*Diagnosis of HIV infection by HIV RNA testing should be confirmed by standard methods (ELISA and Western blot testing) 2-4 months after the initial indeterminate or negative test.

Notes: Acute illness (such as bacterial pneumonia, tuberculosis, herpes simplex virus, or *Pneumocystis jiroveci* pneumonia) and vaccinations can cause an increase in plasma HIV RNA for 2-4 weeks; viral load testing should not be performed during this time. Plasma HIV RNA results should usually be verified with a repeat determination before starting or making changes in therapy.

Source: Department of Health and Human Services

Drug Resistance Factors Into HIV Treatment Failures

BY HEIDI SPLETE
Senior Writer

BETHESDA, MD. — Drug resistance poses a problem in treating HIV patients, in part because of the virus's high mutation rate, Roy M. Gulick, M.D., said at an annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

Factors affecting HIV drug resistance include the virus itself, the antiretroviral drugs used, and the characteristics of the individual patient. Drug resistance is one of the main reasons why HIV treatments fail, said Dr. Gulick, director of the Cornell HIV Clinical Trials Unit at Weill Medical College of Cornell University, New York.

The goal of antiretroviral therapy (ART) is to suppress the viral load to as low a level as possible for as long as possible, he noted. Due to the high rate of mutation in the HIV virus, viral diversity is extensive. Failure to suppress viral load levels in the presence of antiretroviral drugs leads to the development of a resistant strain, Dr. Gulick explained.

Patient-related factors that can contribute to the development of resistance include the stage of disease, use of other medications, medication adherence, and side effects.

"We used to follow resistance clinically. If someone was taking their drugs, and their viral load went down, but then rose again, if we were sure that they were taking the medication, we assumed that they had developed resistance," he said. Today, genotypic tests provide viral sequencing of a patient's viral strain, and phenotypic tests can grow the patient's virus in vitro and assess resistance in the presence of the available antiretroviral drugs.

Are resistance tests clinically valuable? Dr. Gulick cited three studies, including one published in the Lancet, in which several hundred patients who had failed drug therapies were randomized to either genotypic or phenotypic drug resistance testing or standard care (Lancet 1999;353:2195-9).

Overall, the patients who fared better in terms of viral load reduction on their new regimens were those who had the resistance tests. "Simply put, resistance tests help clinicians choose active drugs for the next regimen," Dr. Gulick said. Guidelines from the Department of Health and Human Services recommend resistance tests in the clinical setting in cases of virologic failure, suboptimal virologic suppression, and acute HIV infection.

These tests could be considered in cases of HIV infection before starting ART, but they are generally not recommended for patients more than 4 weeks after ART drug use ends, or when viral load levels are less than 1,000 copies per million.

However, studies of the effectiveness of resistance testing are limited by several factors, including problems with the clinical cutoffs—when the drugs lose activity over time—and questions as to whether the studies had enrolled patients who had failed multiple treatments.

Other studies show conflicting results on the use of resistance tests, especially for highly resistant patients. "The best resistance tests can't help a patient if they have no drug options to go to," Dr. Gulick said.

Asked whether he recommends genotypic or phenotypic testing for patients who are just starting antiretroviral therapy or who already have resistance, Dr. Gulick commented that although sufficient clinical evidence is lacking, most experts recommend a genotype test for patients who are treatment naive or have failed their first regimen, when it is relatively easy to figure out what the mutations mean. But in patients who have been through multiple regimens, phenotype is easier to interpret. ■