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HIV AND THE PATH OF LEAST RESISTANCE

HIV IS A quick change artist. Viral populations soon become genetically divergent in the infected host, and this variation is the key to its persistence in the human host. The consequences of this genetic plasticity include a remarkable capacity to develop drug resistance and to avoid immune surveillance. Lacking DNA proofreading mechanisms, RNA replication tends to be a sloppy process, with each progeny differing (on average) from its parent by one nucleotide. With an estimated 10 billion HIV-1 virions produced daily in an infected person and an average of 1 mutation per 9200-nucleotide genome, a strain of virus with every possible single drug-resistance mutation is generated every day. Double mutants are less likely and the probability of three or more resistance mutations is extremely low. Mutations can be neutral, deleterious, or advantageous, depending in part on environmental context (e.g., host immune responses or drug treatment). Like the rat and the cockroach, HIV is an *r*-strategist in the game of evolution, emphasizing quantity over quality.

When antiretroviral therapy (ART) is ineffective, and viral replication is not suppressed, resistant mutants are selected, resulting in treatment failure. Resistance is generally a two-step process. The first step is the selection of the mutation that confers reduced viral drug susceptibility. In most cases, this primary mutation also reduces viral fitness. In the next step, secondary (compensatory) mutations follow, increasing the variant's replication rate, leading to an increased viral load and ART failure. For some drugs (lamivudine, nevirapine), a single mutation can confer high-level resistance; drug-resistant variants can develop within weeks. With other drugs (zidovudine, stavudine, most protease inhibitors), high-level resistance requires several resistance mutations to accumulate, so highly resistant variants emerge more slowly.

Antibacterial sensitivity testing has been used in clinical practice for over 50 years. HIV resistance testing is much more complicated for a number of technical and biologic reasons.[1] The first resistant strains, detected using tube dilution assays, had high-level HIV-1 resistance to zidovudine, correlating with clinical progression and death. These *phenotypic* assays measure the 50% or 90% inhibitory concentration (IC50 or IC90) of a drug in vitro. A 4-fold increase is considered significant. Just as with antibacterial sensitivity testing, however, a "sensitive" designation does not assure clinical success. The clinical relevance of IC50 or IC90 values in multidrug regimens has not been defined. Paradoxically, virus suppression of drug-resistant virus is possible if high plasma or tissue concentrations of drug are achieved. Finally, phenotypic assays may fail to detect background mutant viruses, which may not affect the immediate IC50 value, but may be a harbinger of future problems. New technology has resulted in rapid phenotypic assays based on recombinant DNA technology, reducing the turnaround time from 6-8 weeks to 3 weeks. This ability to test many drugs and isolates via an automated approach may provide more rapid monitoring of sequential patient isolates for susceptibility changes from baseline during treatment with combination therapy.

Because of the time, expense and danger of working with live virus, polymerase chain reaction (PCR) methods were developed to detect mutations in the HIV genome. Mutations were then correlated with drug resistance and treatment failure. New *genotypic* assays have improved dramatically in the last 12 months; some are now very efficient and highly automated. Plasma samples with viral load of >1000 copies/ml are usually required and only those variants constituting >20% of the virus present are detected. Only known mutations that are associated with viral resistance are identified and viral resistance unrelated to a dominant primary mutation might be missed.

Can testing help identify the "path of least resistance" for ART? In a recent survey of HIV clinicians attending a major research conference, 66% had used resistance testing to guide therapy with at least some of their patients.[2] For those who did not use it, cost was the main objection. Knowing the antiviral drug susceptibility has potential use in at least two situations: initiating ART in a naive patient, and changing therapy in a patient who is failing the current ART regimen.

Decisions concerning therapy initiation revolve around plasma HIV RNA level, CD4+ cell count, and clinical status. Until recently, transmission of drug-resistant virus has not been a major concern. Transmission of zidovudine-resistant HIV was first described in 1992, and recent studies of primary HIV infection show resistance codons appearing in the isolates.[3] Widespread use of antiretroviral drugs will certainly lead to increased transmission of drug-resistant variants in the future. Oregon-specific data about primary resistance are not currentlyavailable. For high-risk occupational, and possibly non-occupational, HIV exposures, treatment with post-exposure prophylaxis should be started as soon as possible, and should be based on the antiretroviral treatment history of the source patient. Don't wait for resistance testing of the source.

In the patient on ART, increasing viral load is the main reason for considering a change in drugs. Viral resistance and treatment failure are closely linked, but resistance is not the only cause of HIV treatment failure. A clinical evaluation of previous ART and other causes of virologic failure (poor adherence, variable plasma drug levels, drug potency, and sanctuary sites) should be undertaken.

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Resistance mutations in some populations of HIV-positive persons may be as high as 60-70% and in these situations resistance testing may compliment the clinical analysis. There are few clinical studies that can guide the use of resistance testing in clinical decision making. Oregon's R&E Group contributed to the GART Study, demonstrating that HIV resistance information along with expert consultation improved ART selections and virologic outcome when changing therapy in a patient failing treatment.[4] Other researchers recently presented data showing that drug changes based on phenotypic testing produced sustained improved outcomes.[5]

HIV resistance testing may not be ready for "prime time" use due to relatively high cost, unclear interpretation of the results and scant data from prospective clinical trials. In the near future, however, we can predict that improved technology will reduce both cost and turn-around time and studies will clarify its clinical utility. Some current recommendations are possible. When initiating ART in a previously untreated (naive) person, order genotypic resistance testing only if there is evidence for recent infection (within past 2 years). In persons failing current ART, first rule out non-compliance as a cause for treatment failure. After adherence is assured, consider genotypic testing if only one or two primary mutations are likely to be present. Since genotypic testing usually demonstrates many primary and secondary mutations in persons with extensive ART, phenotypic testing may give better data on which to choose an effective "rescue" regimen. Finally, it is best to obtain a specialist consultation when interpreting HIV resistance test results.[4]

Dr. Michael McVeigh (503/248-5020) and Dr. Mark Loveless (503/731-4029) with the Northwest AIDS Education and Training Centers (AETC) are available to assist.

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Flu Hunting Season Opens

BEGINNING NOVEMBER 1, the Oregon State Public Health Lab will begin accepting specimens for "rule out influenza" testing. Throat wash kits will be available from the OSPHL (e-mail *osphl.ohd@state.or.us* or call 503/229-5882) or from you local health department. Lab slips should be marked "rule out influenza" so that we don't waste time looking for West Nile. There is no bag limit, but specimens must be collected within 3 days of clinical onset from patients who present with compatible illness, viz., temperature •38.3½C, cough, myalgia, and two or more of the following: headache, sore throat, rhinorrhea, malaise, chills, prostration). Specimens should be kept cool (but not frozen). If they will be >24 hours in transit, use a cold pack.

Pesticide Information to Help Health Care Providers

DID YOU KNOW that licensed health care providers have the right to access certain pesticide application records that may assist with differential diagnosis or treatment of patients?

The Oregon Health Division is collaborating with the Oregon Department of Agriculture (ODA) to inform health care providers of the laws providing access to the names of products to which a patient may have been exposed. You may already have received the brochure, *Pesticide Exposure*, from ODA. This pamphlet outlines what records are covered under two federal laws and explains what pesticide label information is most useful. It also includes a list of local and national resources for further assistance.

The Oregon Health Division has also begun distribution of the latest version of EPA's *Recognition and Management of Pesticide Poisonings*. This 236-page tome offers extensive information about diagnostic studies and treatment protocols for a broad range of pesticide products and includes an index of signs and symptoms with the pesticide products that may produce them. You just can't beat it.

Copies of this 1999 publication have been sent to emergency departments, local health departments and community clinics throughout Oregon. If you're not on the short list, do not despair: download it at *http://ace.orst.edu/info/nptn/rmpp.htm*. If you prefer the old-fashioned approach, call us (503/731-4025) or e-mail us (*tammy.cochell@state.or.us*) and we'll ship it to you at taxpayer expense.