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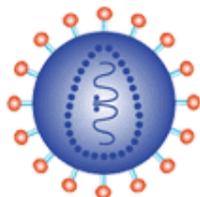
## 9th Conference on Retroviruses and Opportunistic Infections

Fecha de recepción: 31/12/2000

Fecha de aceptación: 31/12/2000

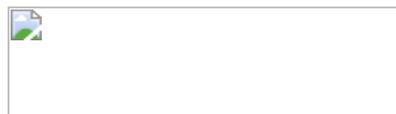
Washington State Convention & Trade Center Seattle, WA. El pasado mes de febrero se celebró la IX conferencia sobre retrovirus e infecciones oportunistas (CROI) en la ciudad de Seattle, Estados Unidos. Este evento es considerado uno de los de mayor relevancia en lo que se refiere a epidemiología, patogénesis y tratamiento del Virus de Inmunodeficiencia Humana (HIV), así como el desarrollo de nuevas drogas en el intento de controlarlo.

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9th Conference  
on Retroviruses and Opportunistic Infections

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### Mechanisms of NRTI Resistance and Implications for Therapy

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Wednesday, February 27, 2002, Seattle, Washington

In a plenary presentation noteworthy for a crystal-clear discussion of a very complex topic, John Mellors[1] of the University of Pittsburgh described the specific mechanisms of nucleoside reverse transcriptase inhibitor (NRTI) resistance, and explained the observed levels of resistance associated with the various patterns of mutations encountered in clinical practice.

The mutations associated with resistance to zidovudine were identified by Brendan Larder and colleagues[2] over a decade ago, well before any other antiretroviral drug was approved. These mutations -- 41L, 67N, 70R, 210W, 215Y/F, and 219E/Q --tend to accumulate during continued exposure to zidovudine in the absence of good viral suppression. Recently, it has been appreciated that these mutations can also be selected by stavudine, and that they have implications for resistance to all drugs in the NRTI class and to the recently FDA-approved nucleotide reverse transcriptase inhibitor, tenofovir.

Reverse transcription is the process whereby the single-stranded HIV RNA genome is converted to a double-stranded DNA version that can be integrated into the chromosome of the infected cell. The RNA genome serves as a template, and reverse transcriptase adds deoxynucleotide triphosphates (dNTPs) one at a time as the viral DNA chain elongates. During this process, 2 of the 3 phosphate groups are cleaved off; this double phosphate is called pyrophosphate. At the end of the chain, there is a hydroxy group (OH), which allows the next nucleoside monophosphate to be added onto the end of the chain. All of the NRTIs are "chain terminators" because they have a substitution other than OH at the end, and thus do not allow addition of the next building block.

The process of adding a new building block involves 3 steps:

1. Binding of the next nucleoside or nucleoside analogue (NRTI) triphosphate

2. Incorporation onto the end of the growing viral DNA chain and release of pyrophosphate
3. Translocation of the incorporated nucleoside to a different position to allow room for addition of the next nucleoside residue

For a long time, it was assumed that resistance mutations changed the shape of the binding pocket in such a way that the nucleoside analogues no longer were bound as well as the cellular nucleosides, rendering the drugs impotent. This view was recently changed by studies led by Meyer and colleagues[3,4] and confirmed by others, which showed that the nucleoside analogues are actually removed by mutant reverse transcriptase by a cleavage process called pyrophosphorylysis (PPi), the reverse of the step that led to their incorporation in the first place. Instead of pyrophosphate being released when the nucleoside analogue triphosphate is incorporated into the viral DNA chain, the presence of multiple resistance mutations in reverse transcriptase prevents translocation and allows removal of the nucleoside analogue. The extension process can then proceed by the addition of a cellular nucleoside building block.

This mechanism of resistance within reverse transcriptase containing the mutations selected by zidovudine has been shown to affect stavudine and abacavir as well as zidovudine. In view of the increasing levels of phenotypic resistance associated with increasing number of these mutations, [5] this mechanism also probably affects zalcitabine, didanosine, lamivudine, and tenofovir. Thus, these mutations are probably best referred to as nucleoside analogue mutations (NAMs), since they can affect the entire class.

The 184V mutation that can result in up to 1000-fold increases in resistance to lamivudine also appears to interact with NAMs to modulate resistance to all the other NRTIs.[5] In reverse transcriptase that contains no more than 2 or 3 NAMs, this mutation enhances translocation during reverse transcription, preventing PPi and excision of the nucleoside analogue residue. However, as the number of NAMs increases, 184V does not have enough effect to prevent PPi.

The structure of tenofovir results in some flexibility, which may make this substrate a moving target, making excision inefficient. This could explain why the activity of tenofovir is maintained in the presence of just a few NAMs. However, higher numbers of these mutations will still result in tenofovir resistance. Tenofovir resistance is also modulated by the 184V mutation through enhancement of translocation.

The take-home message is that NAMs are bad for this class of antiretrovirals, and the accumulation of high numbers of these mutations should be assiduously avoided. The drugs that are most likely to select for these mutations should probably be avoided in initial regimens, and viral load and resistance monitoring should be used together to ensure that therapy is changed before high numbers of NAMs evolve. The appearance of the 184V mutation may improve sensitivity to many of the drugs in this class, but it will not "reverse" high-level resistance. Nonetheless, inclusion of lamivudine in salvage regimens may improve the effectiveness of the NRTI components of therapy, and it is certainly a well-tolerated drug -- an important issue for most patients receiving salvage therapy.

These recent findings also identify a new target for antiretroviral therapy: inhibition of PPi. This has been shown with foscarnet, and development of a more effective and better-tolerated derivative of foscarnet is currently underway in Dr. Mellors' laboratory.

## References

1. **Mellors J.** New insights into mechanisms of HIV-1 resistance to reverse transcriptase inhibitors. Program and abstracts of Program and abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Abstract L6.
2. **Larder BA, Kemp SD.** Multiple mutations in HIV-1 reverse transcriptase confer high-level resistance to zidovudine (AZT). *Science*. 1989;246:1155-1158.
3. **Meyer PR, Matsuura SE, Schinazi RF, So AG, Scott WA.** Differential removal of thymidine nucleotide analogues from blocked DNA chains by human immunodeficiency virus reverse transcriptase in the presence of physiological concentrations of 2'-deoxynucleoside triphosphates. *Antimicrob Agents Chemother*. 2000;44:3465-3472.
4. **Meyer PR, Matsuura SE, Mian AM, So AG, Scott WA.** A mechanism of AZT resistance: an increase in nucleotide-dependent primer unblocking by mutant HIV-1 reverse transcriptase. *Molecular Cell*. 1999;4:35-43.
5. **Whitcomb JM, Paxinos EE, Huang W, et al.** The presence of nucleoside analogue mutations (NAMs) is highly correlated with reduced susceptibility to all NRTIs. Program and abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Abstract 569.

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## NRTI Cross-Resistance May Be More Common Than We Thought

Peter Ruane, MD Disclosures

Tuesday, February 26, 2002, Seattle, Washington

New dimensions were added to our understanding of nucleoside reverse transcriptase inhibitor (NRTI) resistance and cross-resistance by a poster by Whitcomb and colleagues[1] from ViroLogic.

From a database of 4174 samples with matched genotype and phenotype measurements, they excluded all isolates containing recognized multidrug resistance mutations (ie, Q151M and T69 insertions). The remaining samples were phenotypically categorized as either (1) wild-type (susceptible to all NRTIs); (2) > 20-fold zidovudine-resistant but with little or no cross-resistance to other NRTIs; or (3) zidovudine-resistant and cross-resistant to other NRTIs. Genotypic correlates were then sought, evaluating the fold change in NRTI susceptibility as a function of the number of nucleoside analogue mutations (NAMS: M41L, D67N, K70R, L 210W, T215Y/F and K219Q/E) and the presence of M184V or other RT substitutions. Pairwise comparisons were made as continuous variables with all the appropriate statistics.

An increasing number of NAMS was associated with decreased susceptibilities to all NRTIs, although to differing degrees for each drug. Unexpectedly, mutations that resulted in 100-fold reduced susceptibility to zidovudine were also associated with 6.5-fold resistance to lamivudine. The presence of mutations at positions 41 and 210 in particular was linked to an increased likelihood of cross-resistance, including to tenofovir. Higher levels of cross-resistance were also associated with additional substitutions not currently recognized as NAMS, especially at positions 39, 40, 43, 44, 68, 69, 74, 118, 208, and 228.

The M184V mutation is well known to enhance susceptibility to zidovudine. Today's data showed that it also improved susceptibility to stavudine, adefovir, and tenofovir, and reduced susceptibility to lamivudine, abacavir, didanosine, and zalcitabine.

These data provide additional evidence that resistance to NRTIs and protease inhibitors is similar, in that the presence of multiple mutations confers substantial cross-resistance in a linear fashion. The reported association between additional non-NAM mutations and cross-resistance should lead us to look for these more carefully, and to assume that in heavily pretreated patients greater resistance may be present than may be recognized from the typical genotype reports from reference labs. It is also high time for these labs to provide us with full genotypic reports with all the sequencing information they have, so we can make more complete interpretations both now and in the future. To my knowledge, at present only one (also FDA-approved) assay provides this routinely.

### Reference

1. Whitcomb JM, Paxinos EE, Huang W, et al. The presence of nucleoside analogue mutations (NAMS) is highly correlated with reduced susceptibility to all NRTIs. Program and abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Abstract 569.

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### Update on Adherence: Interventions and Outcomes

Richard A. Elion, MD Disclosures

Tuesday, February 26, 2002, Seattle, Washington

Rates of adherence to antiretroviral therapy have been correlated with virologic success,[1] so there is considerable interest in clinical strategies that might promote improved adherence. Posters presented today reported the results from trials of a variety of techniques, including phone calls, counseling interventions, and directly observed therapy (DOT).

Collier and her colleagues[2] investigated the impact of serial scripted telephone calls to patients about their medications. Treatment-naive patients enrolled in a large antiretroviral-therapy study were randomly assigned to receive either the clinic's usual standard of therapy support (n = 140) or intensified support including 16 telephone calls during 96 weeks (n = 142). Evaluation of the intervention was hampered by the high levels of self-reported adherence in the study: Approximately 64% of patients in each arm reported taking > 95% of their medications, and > 61% reported 100% adherence. As a result, there was no difference between the arms in adherence or virologic outcome, which may reflect either the high levels of adherence achieved in this context of a supervised clinical trial or a lack of effect of the telephone intervention.

Pradier and associates[3] randomly assigned 244 patients to receive either 3 counseling sessions in addition to normal care, and found that there were improvements in adherence in the

intervention group at month 6: 75% were 100% adherent at month 6, compared with 61% of controls ( $P = .04$ ). This was accompanied by decreases in HIV-1 RNA in the intervention group, although the proportion of patients with viral load  $< 40$  copies/mL remained similar in both arms.

Jordan and coworkers[4] described predictors of adherence and efficacy in the CNA3014 trial comparing coformulated zidovudine/lamivudine (Combivir) plus either abacavir or indinavir. This trial had previously reported improved efficacy for the simpler triple-NRTI (nucleoside reverse transcriptase inhibitor) regimen. These authors now demonstrate significant differences in adherence between the 2 arms, with 72% of subjects in the abacavir arm reporting  $> 95\%$  adherence, compared with 45% in the indinavir arm ( $P < .001$ ). Each 5% increase in adherence was associated with a 1.7-fold increase in the likelihood of achieving HIV-1 RNA  $< 400$  copies/mL. There was a suggestion that the abacavir-based regimen was slightly more effective among subjects with lower levels of adherence, but this was a small sample, and the "forgiveness quotient" of the regimen could not be adequately determined.

Conway and colleagues[5] reported on the use of DOT for once- and twice-daily regimens among a cohort of injection-drug users (IDUs). The twice-daily regimens were only partial DOT: Only the morning dose was observed, and the patient was queried regarding the evening dose the following morning. The overall success rates for viral suppression were modest, with only 44% achieving a viral load  $< 50$  copies/mL, but it was encouraging to note that concomitant cocaine use did not significantly affect the virologic success rate: 60% of active cocaine users achieved HIV-1 RNA  $< 400$  copies/mL compared with 65% of the overall study population of IDUs. The take-home message was that use of DOT seemed helpful in achieving a typical rate of virologic success despite ongoing recreational drug use. In a related report, Lucas and associates[6] showed that the transition from abstinence to substance use was associated with worse virologic outcomes; conversely, switching from substance use to abstinence was associated with improvements in virologic control and adherence.

The relationship between imperfect levels of adherence and the incidence of new resistance mutations was evaluated by Bangsberg and coworkers.[7] The relatively good news is that individuals with the worst adherence usually discontinued therapy sooner than more adherent patients, resulting in less resistance. A total of 78% of people who took  $< 50\%$  of their initial 3-month pill count discontinued therapy within 6 months, compared with 33% of those taking 50% to 79% of their pills ( $P < .01$ ).

The troubling corollary is that the more adherent patients were more likely to develop mutations. Thus, the population most at risk of developing resistance is those patients who take many -- but not enough -- of their pills.

## References

1. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133:21-30.
2. Collier A, Ribaud H, Feinberg J, Mukherjee L, Fischl M, Chesney M, for the ACTG Protocol 746 Team. Randomized study of telephone calls to improve adherence to antiretroviral therapy. Program and abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Abstract 540.
3. Pradier C, Bentz L, Spire B, et al. Counseling interventions can improve adherence to highly active antiretroviral therapy: results of a French prospective controlled study. Program and abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Abstract 541.
4. Jordan J, Cahn P, Vibhagool A, and the CNA3014 Study team. Predictors of adherence and efficacy in HIV-1-infected patients treated with abacavir/Combivir (ABC/COM) or indinavir/Combi vir (IDV/COM): final 48-week data from CNA3014. Program and abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Abstract 543.
5. Conway B, Prasad J, Reynolds R, et al. Nevirapine (NVP) and protease inhibitor (PI)-based regimens in a directly observed therapy (DOT) program for intravenous drug users (IDUs). Program and abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Abstract 545.
6. Lucas G, Gebo K, Chaisson R, Moore R. Longitudinal assessment of the effects of drug and alcohol abuse on HIV treatment. Program and abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Abstract 547.
7. Bangsberg DR, Charlebois ED, Grant R, et al. Low levels of adherence do not increase risk of HIV drug resistance mutations. Program and abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Abstract 546.

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