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Expert Interpretation of HIV-1 Genotyping: It's Almost Anyone's Guess

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Barcelona, Spain; Thursday, July 11, 2002 -- Andrew Zolopa and colleagues[1] today reported the findings of the GUESS study, which evaluated the interpretation of HIV-1 genotypic resistance tests performed on clinical specimens. The study tested the ability of an international panel of experts to predict the results of a phenotypic resistance assay performed on the same sample that was genotyped. Agreement between the experts with regard to predicting antiretroviral drug activity and making specific treatment recommendations also were evaluated.

A total of 50 randomly selected genotypes with matching phenotypes were selected for analysis from the VIRCO database. All viral isolates had to be resistant to at lease 1 drug (ie, > 4-fold increase in IC_{50} compared with wild-type HIV-1). The 12 experts were asked to predict each isolate's susceptibility to 16 antiretroviral agents by assigning it to a category of fold-change (FC) in IC_{50}, namely < 2.5, 2.5 to < 4, 4 to < 7, 7 to < 10, 10 to < 20, and > 20. They were also asked to rate the expected degree of activity of each drug on a 6-point scale, and to state whether it would be recommended for use.

The experts' accuracy in predicting susceptibility to each antiretroviral varied by class. For nucleoside reverse transcriptase inhibitors (NRTIs), accuracy of predicting phenotype from genotype varied from 25% for abacavir susceptibility to 74% for lamivudine susceptibility. For protease inhibitors (PIs), it varied from 26% for nelfinavir to 40% for lopinavir/ritonavir. However, experts were able to correctly predict nonnucleoside reverse transcriptase inhibitor (NNRTI) susceptibility about two thirds of the time for all 3 NNRTI agents. Of note, the median difference between predicted FC and assayed FC category was found to be 0 (meaning there was no difference) for all drugs except zidovudine, stavudine, didanosine, zalcitabine, and abacavir; the median difference was +1 category for all 5 of these agents. Correlation of agreement (rho) among the experts for predicting phenotypes in each class ranged from 0.23 for tenofovir to 0.84 for lamivudine; from 0.89 for efavirenz to 0.93 for nevirapine; and from 0.68 for amprenavir to 0.79 each for indinavir and ritonavir.

Predictions for drug activity mirrored the same ranges as for predicting phenotype. Consensus among the experts on treatment recommendations for each antiretroviral agent ranged from 62% for didanosine to 90% for lamivudine, with a median of 79%.

In summary, although the experts were able to predict the phenotype fairly well, they frequently overestimated the FC (ie, they underestimated the susceptibility) of zidovudine, stavudine, didanosine, zalcitabine, and abacavir. Of note, while there was generally a high level of agreement regarding drug activity and treatment recommendations, there was significant variability for individual antiretroviral agents.

There are several important conclusions to draw from this study. First, it demonstrates that even among the experts, the "science" of genotypic interpretation remains variable and imprecise. Even for the NRTIs, the oldest and most heavily studied class of agents, there remains significant difficulty in reaching consensus for genotypic interpretation. Second, genotypic interpretation is easier and more consistent for agents such as the NNRTIs, where at least 2 mutations convey class-wide, high-level resistance. Third, interpretation of genotypic resistance to the PIs continues to evolve, as the list of available agents and the number of mutations increases, and their specific effects grow more complex to interpret. The use of boosted PIs may make genotyping less important by increasing the ratio of drug level to IC_{50}, allowing the drugs to retain activity against virus with some degree of loss of susceptibility. Overall, this study appears to reinforce the notion that resistance testing will get much more complex, rather than less so, as we learn more.

Reference

1. Zolopa AR, Lazzeroni LC, Rinehart A, Kuritzkes, D. The GUESS study. An international evaluation of the accuracy, precision and consistency of expert interpretation of HIV-1 genotype interpretation. Program and abstracts of the XIV International AIDS Conference; July 7-12, 2002; Barcelona, Spain. Abstract ThOrB1385.

Which First-line Regimen? Boosted PI vs Efavirenz vs Triple-NRTI

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Barcelona, Spain; Tuesday, July 9, 2002 -- With 15 antiretroviral agents now in common use, there is a myriad of potential 3- and 4-drug combinations available. Most commonly, treatment is given as 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus 1 or 2 protease inhibitors (PIs), a nonnucleoside reverse transcriptase inhibitor (NNRTI), or a third NRTI. The choice of which drug class to use is difficult, let alone the choice of which specific drug, and at present there are few comparative data on their relative merits.

The CLASS trial, also known as ESS40001, has engaged with this problem, comparing a PI-based vs an NNRTI-based vs a triple-NRTI regimen in treatment-naive patients. John A. Bartlett, MD,[1] of Duke University, Durham, North Carolina, presented initial 48-week data from this planned 96-week trial. Patients were randomly assigned to receive abacavir and lamivudine as the NRTI backbone, plus either ritonavir-boosted amprenavir (PI), efavirenz (NNRTI), or stavudine (triple-NRTI). Second-line regimens for patients experiencing toxicity or failure are preplanned in the protocol: PI patients switch to efavirenz/zidovudine/didanosine; NNRTI patients switch to amprenavir/ritonavir/zidovudine/didanosine; and triple-NRTI patients to amprenavir/ritonavir/efavirenz. Each patient starting a second-line regimen is also randomly assigned to continue abacavir or to discontinue it. The trial end point is the percentage of patients with plasma HIV-1 RNA < 400 copies/mL at 96 weeks.

A total of 297 patients were enrolled, with similar baseline demographic distribution between the 3 groups. Of interest, the patients enrolled were 70% black or Hispanic. Baseline viral load was relatively high, with a median of 4.9 $\log_{10}$ copies/mL; 44% of patients had viral load > 100,000 copies/mL. The median CD4+ cell count at baseline was approximately 300 cells/mm^3, and 35% of subjects had < 200 cells/mm^3.

In-class drug substitution was allowed, and occurred in 12-15 patients per group. This was mostly switches in NRTIs, although 4 patients switched from efavirenz to nevirapine.

By week 48, 6 NNRTI patients had been switched to the second-line regimen: 5 for adverse events (AEs) and 1 for virologic failure. In the PI group there had been 5 AEs and 5 virologic failures; and in the triple-NRTI group there had been 4 AEs and 8 virologic failures.

In an intent-to-treat (ITT) analysis, plasma HIV-1 RNA < 400 copies/mL was achieved in 83% of the NNRTI group, 75% of the PI group, and 80% of the triple-NRTI group. The equivalent proportions in an on-treatment analysis were 98%, 91%, and 90%, respectively. None of these differences was statistically significant.

When analyzed using a viral load assay with a limit of detection of 50 copies/mL, the proportions achieving undetectable viremia were 76% for NNRTI, 59% for PI, and 62% for triple-NRTI by ITT analysis (P = .047 in favor of the NNRTI arm). In the on-treatment analysis, the proportions were 89%, 72%, and 71%, respectively.

Among subjects with baseline viral load > 100,000 copies/mL, the proportions achieving viral load < 50 copies/mL by ITT analysis were 77% in the NNRTI arm, 53% in the PI arm, and 55% in the triple-NRTI arm. This was statistically significant.

Increases in CD4+ cell count ranged from 173 to 196 cells/mm^3, with no significant difference between the arms. There were no significant differences in AEs.

Thus, in this patient population with a high baseline viral load, all 3 arms provided effective treatment, with a slight edge to the efavirenz-based regimen. These preliminary data provide reassurance that any of these 3 treatment regimens can provide similarly good outcomes, so that we can tailor treatment decisions to individual preferences. The final 96-week results of this trial will eventually provide even more robust data to help us decide between these approaches. "Back-up" regimens always need to be considered when making treatment choices, and by having preplanned second regimens, this trial may eventually provide information on the "salvageability" of these different treatment approaches.

Reference

1. Bartlett JA, Johnson J, Herrera G, et al. Abacavir/lamivudine (ABC/3TC) in combination with efavirenz (NNRTI), amprenavir/ritonavir (PI) or stavudine (NRTI): ESS40001 (CLASS) preliminary 48 week results. Program and abstracts of the XIV International AIDS Conference; July 7-12, 2002; Barcelona, Spain. Abstract TuOrB1189.

Compelling Evidence of HIV-1 Superinfection: Health Implications for HIV-Infected Persons

W. David Hardy, MD   Disclosures

Barcelona, Spain; Thursday, July 11, 2002 -- Striking virologic evidence that HIV-infected individuals can become reinfected with a second strain of HIV-1 was reported by Jost and colleagues[1] from the University of Geneva, Switzerland. This phenomenon, known as superinfection, has been commonly demonstrated in vitro, as well as with SIV in subhuman primates. Although there have been previous reports of possible HIV-1 superinfection in humans,[2,3] there has not been conclusive evidence of this phenomenon.

In the case reported today, a 38-year-old man noted to have an acute retroviral syndrome (ARS) following multiple unprotected sexual contacts with male partners was enrolled in a treatment trial (QUEST; zidovudine, lamivudine, abacavir, and amprenavir) and monitored for 25 months. The study also included 6 months of concomitant vaccination with ALVAC vCP 1452 at the end of the study, followed by treatment interruption. The patient's viremia was noted to decline from > 1 million copies/mL to < 200 copies/mL while receiving highly active antiretroviral therapy (HAART). One month after discontinuation of HAART and the therapeutic vaccine, his viremia rebounded to 80,000 copies/mL, then declined to 20,000 copies/mL, and finally rebounded again 2 weeks later to 200,000 copies/mL. Viremia then fluctuated between 200,000 and 400,00 copies/mL for 5 months before HAART was resumed.

Curious about the patient's second and persistent viremic rebound, the investigators undertook intensive gene sequencing of the viral isolates, analyzing the protease (Pr), reverse transcriptase (RT), gag, and C2V3 portion of the envelope genes. This analysis demonstrated that the patient was initially infected with a subtype AE HIV-1 strain during the ARS. However, a subtype B HIV-1 isolate was found at the time of the second rebound of viremia.

To rule out the possibility that the patient was infected with the 2 subtypes from the outset, as opposed to acquiring the subtype-B strain subsequently, the investigators set up a polymerase chain reaction (PCR) assay using subtype-specific primers for AE and B viral isolates, designed according to the patient's viral sequences. The subtype-specific PCR confirmed (1) the absence of subtype-B virus both in plasma and in the form of proviral DNA before the second viremia, and (2) the appearance of subtype-B virus during the second rebound and thereafter as the major viral isolates in both DNA and plasma. In addition, the C2V3 envelope sequences of the subtype-B virus was found to be closely related to subtypes found in Brazil. Of note, the patient had had several unprotected sexual contacts during a vacation in Brazil 3 weeks before the second viral rebound. Viral cultures of the subtype-B primary isolate demonstrated that it had a much higher replicative capacity than the AE subtype.

Thus, these investigators have used sophisticated molecular virology techniques coupled with epidemiologic data to demonstrate conclusively the occurrence of HIV-1 superinfection in this patient. Whereas previous reports strongly hinted at this phenomenon, proof from molecular virology was lacking. The fact that the 2 HIV-1 subtypes acquired by this patient were different subtypes (AE and then B) increases the certainty that superinfection occurred in this patient. Although this report holds significant virologic and epidemiologic interest, its most compelling message is that HIV-1-infected persons must avoid risk behaviors if they wish to avoid reinfection with potentially more virulent or possibly multidrug-resistant virus. HIV-treating physicians and treatment advocates should take heed of this well-documented scientific report to inform their patients and clients of this phenomenon, and encourage them to observe safe sex guidelines.

References

1. Jost S, Bernard MC, Kasise L, Yerly S, et al. HIV-1 super-infection: AE subtype supplanted by B subtype. Program and abstracts of the XIV International AIDS Conference; July 7-12, 2002; Barcelona, Spain. Abstract ThOrA1381.

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3. Daar ES, Frost SDW, Wong JK, et al. Mixed infection with multidrug resistant (MDR) and wild type HIV strains in primary HIV infection (PHI): Early viral rebound suggests loss of immune control. Program and abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Abstract 96.