HAART Simplification

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The past year has brought 4 new antiretroviral therapies, 3 of which contribute to the simplification of antiretroviral therapy. It is now possible to construct potent once-daily combinations, or twice daily therapies of relatively low pill burden. Emtricitabine (FTC, emtriva) is a potent, single-pill, once-daily nucleoside reverse transcriptase inhibitor, with a longer half-life than its related drug, lamivudine (3TC, epivir). This drug also has acitivity against hepatitis B DNA virus, but not against lamivudine-resistant hepatitis B. Emtricitabine is well-tolerated, and can occasionally cause palm hyperpigmentation in 2-3% of patients.

Atazanavir (reyataz) is a new, potent, once-daily protease inhibitor that is two capsules daily. In its unboosted form, it compared favorably to nelfinavir (viracept) and efavirenz (stocrin, sustiva) in clinical trials, and when boosted with 100 mg of ritonavir (norvir), performed well in protease inhibitor-experienced patients compared to lopinavir/ritonavir (kaletra) at 48 weeks.[1] Atazanavir is generally well-tolerated, though it can have mild GI side effects, with the most common biochemical effect being indirect hyperbilirubinema, leading to clinical jaundice in 3-6% of patients. This is infrequently associated with a chemical hepatitis, and is similar to the asymptomatic hyperbilirubinema seen with indinavir (crixivan). In addition, atazanavir has a lipid-friendly profile, and does not increase cholesterol or triglycerides. The beneficial lipid effects can still be seen even when boosted with 100 mg of ritonavir. This drug is the first once-daily protease inhibitor and will be a nice option for patients needing a simple, potent regimen.

Near the end of 2003 the prodrug of amprenavir (agenerase) know as fosamprenavir (lexiva) became available. A single 700 mg tablet replaces 4 large amprenavir capsules, greatly simplifying the use of this agent. Fosamprenavir is two tablets twice daily, or it may be used once daily if boosted with 200 mg of ritonavir in antiretroviral naïve patients. For antiretroviral experienced patients, fosamprenavir 700 mg twice daily should be boosted with ritonavir 100 mg twice daily. The once daily dosing should not be used for experienced patients.

The other big story of 2003 has been the inferiority of triple nucleoside regimens, including trizivir, when compare to non-nucleoside or protease-based regimens. In ACTG 5095, the triple nucleoside trizivir (zidovudine, lamivudine, & abacavir) was inferior to the 2 efavirenz-based arms, with only 74% in the trizivir arm compared to 89% in the pooled efavirenz arms at week 48 reaching undetectability at the 200 copies/ml level.[2] Similar inferiority of other triple nucleoside regimens was found in subsequent trials, leading to the recommendation by numerous expert panels that only efavirenz and lopinavir/ritonavir but included in the "strongly recommended" category of the antiretroviral therapy guidelines.[3] There is also good potency data with nevirapine (viramune), but its higher incidence of hepatotoxicity kept it out of the "strongly recommended" category of the US Public Health Service Antiretoviral Therapy Guidelines for Adolescents and Adults. New information pertaining to nevirapine released in February, 2004 addresses its potential for hepatotoxicity, especially in women with CD4+ cell counts over 250

cells/cmm. Other risk factors for hepatitis from nevirapine include baseline elevated AST (SGOT) or ALT (SGPT), hepatitis B and/or C coinfection, higher CD4+ cell counts at initiation of nevirapine, and female gender.

In summary, we have come a long way since 1987 when zidovudine was first available to be taken every 4 hours, and are current armamentarium offers broader options for designing, simple, potent cocktails for our patients to be successful and healthy. The talk will review some of the data for the newer therapies outlined above and currently recommended combinations most likely to result in full viral suppression.

1. DeJesus E *et al*. Efficacy and safety of atazanavir with ritonavir or saquinavir vs lopinavir/ritonavir in patients who have experienced virologic failure on multiple HAART regimens: 48-week results from BMS A424-045. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections, Feb 8-11, San Francisco, CA 2004. Abstract 547.
2. Gulick RM *et al.* ACTG 5095: a comparative study of 3 protease inhibitor-sparing antiretroviral regimens for the initial treatment of HIV infection. In: Program and abstracts of the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment; July 13-16, 2003; Paris, France. Abstract 41.
3. U.S Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. November, 10, 2003.