

AVRC Updates

UCSD | Antiviral Research Center

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Winter 2010

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The AVRC has Moved!

Dear Friend:

To accommodate our growing research programs and expand our community outreach, the AVRC has moved to larger quarters in the Theodore Gildred Facility, across the street from the UCSD Medical Center on Dickinson. The newly renovated and comfortable building is just a few blocks from the old location, and it also houses the HIV Neurobehavioral Research Center (HNRC).

We are excited about this new location and welcome you to stop by and take a look.

With over twenty years leading the field in HIV research, the AVRC is renewing its commitment to improving the management of HIV disease by developing new antiretroviral agents and determining the best approaches to initiating HIV treatment, treating drug

resistant HIV, and treating and preventing co-infections like Hepatitis C and tuberculosis. With our added engagement in new research related to primary HIV infection, and greater collaborations with HIV prevention networks, the AVRC remains on the cutting edge of the overall research and clinical management of HIV disease.

We continue to be humbled and grateful to the research volunteers, financial donors, referring healthcare providers, and other San Diego collaborators in the community effort to fight HIV infection.

Sincerely,

Constance A. Benson M.D.

Constance Benson, M.D.
UCSD AVRC Clinic Director



Defining New Antiretroviral Treatment Strategies: Is Once a Day Everything?

Richard Haubrich, M.D.

As the number of possible regimen choices increase for the treatment of naïve HIV-infected people, clinicians have to weigh the relative benefits and disadvantages of several possible combinations. The current DHHS guidelines lists five preferred agents that can be combined with fixed dose tenofovir (TDF) and emtricitabine (FTC), efavirenz and four boosted protease inhibitor combinations. Given the availability of a fixed dose combination of EFV/TDF/FTC, this regimen is an attractive option. Is the convenience and simplicity of the one-pill once-daily regimen with efavirenz plus TDF/FTC the most important factor in determining long-term success of therapy? Although it is clearly desirable to have the simplest dosing regimen, other considerations may be equally or even more important if the therapy is initiated early in the disease course, before HIV symptoms appear, and needs to be maintained for the life of the individual. A meta-analysis of recent adherence research suggests that a complex regimen (> 10 pills/day or complicated dosing) was important in predicting poor adherence while dosing once versus twice daily was only a weak predictor (1). Thus, other factors should be considered when selecting among options for naïve individuals.

For certain patients a regimen other than efavirenz may work better. These include subjects who are intolerant to efavirenz (rash or severe central nervous system side effects), those with elevated lipid values or other high and not modifiable cardiovascular risk factors, those with transmitted NNRTI drug resistance (usually 8-10% of newly identified subjects), those with existing depression or psychiatric disease, and women of child-bearing potential. For these people, a once-daily protease inhibitor option that has lower lipid effects (such as darunavir or atazanavir) may have advantages. Newer drugs, such as raltegravir may also have advantages. The need to dose raltegravir twice daily can be balanced against the improved safety and tolerability and the possibility that there may be lower longer-term effects on the cardiovascular system. In the STARTMRK study, excellent virologic responses were seen with both efavirenz and raltegravir given with TDF/FTC at week 48, but CNS side effects and lipids were significantly less in the raltegravir treated subjects (2). How these differences in tolerability and lipid effects translate into long-term success of therapy need to be evaluated.

ACTG 5257 was designed to answer some of these questions. The study was designed to evaluate alternative

treatments for those who can't or don't want to follow an efavirenz-based regimen. The primary objectives of the study are to compare the virologic efficacy and tolerability of combination regimens that include FTC/TDF plus raltegravir (twice daily) to atazanavir or darunavir, given with low-dose ritonavir boosting, for the treatment of ARV-naïve subjects. We hope to enroll 1800 naïve subjects across the U.S.; all will be randomized to receive open-label treatment with one of the three regimens. To be eligible, subjects should be non-pregnant adults (at least 18) with no prior ARV and

HIV RNA above 1000 copies/mL. Transmitted drug resistance mutations to the NNRTI are allowed, but not mutations to the protease or NRTI classes.

In addition to the usual viral load and safety/tolerability evaluations, a large subgroup (330 subjects) will undergo intensive cardiovascular evaluations. These will include non-invasive measures of early blood vessel disease-flow mediated vasodilation (FMD) and carotid artery intima-media thickness (CIMT). Both of these tests have been shown to predict the development of cardiovascular disease in HIV negative and infected subjects. Since HIV alone increases the risk of

cardiovascular disease, as do the usual cardiovascular risk factors (lipid elevations, hypertension, age, hyperglycemia, cigarette smoking), untangling the contribution of HIV, traditional risk factors and effects of ARV treatment is complex. By enrolling and following 330 subjects initiating ARV in this study, and measuring the pre-treatment and on treatment effects of HIV and therapy on FMD and CIMT, we will be able to better understand how HIV, and its therapy, interact to effect blood vessels and ultimately define the risks of cardiovascular disease. The study will also explore pathogenic mechanisms by which HIV and HIV therapies may exacerbate or mitigate vascular disease.

Notes

¹ MJ Atkinson, JJ Petrozzino. "An evidence-based review of treatment-resistance determinants of patient's adherence non-adherence to HIV medications." *AIDS Patient Care and STDs* 23(11): 903-914, 2009.

² JL Lennox, et al. "Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment naïve patients with HIV infection: a multi-centre, double-blind randomized controlled trial. *Lancet* 374 (9692): 796-806, 2009.

Initial Regimens
Research study open for accrual
A5257
Raltegravir + Truvada
vs.
Darunavir/Ritonavir + Truvada
vs.
Atazanavir/Ritonavir + Truvada
All drugs provided except ritonavir.

Multi-Class ARV Exposure and Treatment Failure in the Past 8 Years: How are We Doing?

Results from the CFAR Network of Integrated Clinical Systems (CNICS) Cohort

by Jeannette Aldous, M.D.

In the past decade, significant advances have been made in availability, efficacy and tolerability of HIV antiretroviral medications (ARVs); treatment outcomes have improved and patients are having more success on therapy. However, it is important that research continues to evaluate both the improvements and shortfalls. Determining trends in ARV use, resistance, and clinical outcomes has important implications for understanding to what degree advancements in HIV medicine are translating to clinical success and identifying areas where further focus is needed to improve outcomes.

The CNICS Cohort is a multi-center collaboration that collects real-time clinical data on HIV patients from large urban HIV clinical care centers, including the UCSD Owen Clinic. The UCSD CNICS research group recently presented data from this cohort at the XVIII International HIV Drug Resistance Workshop. The study evaluated the prevalence of multi-class anti-retroviral treatment experience and treatment failure at 2-year intervals from 2000-2008. Extensive multi-class experience included “triple-class exposure” (≥ 2 NRTIs, ≥ 1 NNRTI, and ≥ 2 PIs) and “four-class exposure,” (triple-class exposure plus one of the new classes of ARV drugs (Integrase inhibitors -, Fusion inhibitors -, or CCR5 inhibitors). Treatment failure was defined as having an HIV viral load over 200 copies/ml after less than 24 weeks on therapy.

The study included 2000-4000 patients at each of the intervals from 2000-2008. Extensive ARV exposure increased consistently; 3-class exposure rose from 23% in 2000 to 35% in 2008. 4-class exposure was uncommon, but increased from 0.3% to 5.3%. The percentage of patients experiencing treatment failure decreased over the same period, dropping from 30% in 2000 to 11% in 2008. Risk factors associated with treatment failure were multi-class exposure, over the age of 40, lower CD4 count, and African American race.

What does this mean? The good news is that the prevalence of treatment failure has declined significantly in the past 8 years. Interestingly, the decline in treatment failure began before the introduction of the newest ARVs, suggesting that access to new drugs does not solely

explain the decline. Presumably the trend is due to a combination of improvements in treatment regimens, patient monitoring, and clinical care. However, the prevalence of exposure to multiple classes of ARVs has also increased at a steady rate. Thus, contrary to what we might have expected with regimens that are more tolerable and easier to adhere to, patients continued to cycle through multiple ARVs over time. Interestingly, a sub-analysis showed that the number of people who were failing their regimen prior to changing to a new regimen was going down over time, suggesting that *patients were changing regimens for reasons other than treatment failure.*

Potential explanations for increases in regimen switches, despite decreasing treatment failure, might include toxicity, ease of dosing, increased choices, pharmaceutical marketing or patient/physician preference. With our current data it is not possible to determine which (if any) of these factors has the greatest influence. But regardless of the reasons, this result demonstrates that despite the significant improvements in treatment outcomes, patients continue to require changes in regimens which may lead to a persistent need for new ARV options in the future.

Another troubling outcome was the greater risk of treatment failure in African-American patients. In 2000, 41% of African Americans experienced treatment failure compared to 25% of Caucasians. In 2008, the difference was 20% versus 10%. These disparities need further investigation, particularly in light of CDC data showing that African Americans bear a disproportionate burden of the HIV epidemic, representing nearly half of new U.S. HIV/AIDS cases.

Further analysis from this cohort will be performed to explore the causes of multi-class ARV exposure and failure, along with the impact of the newest ARV drugs. Additional investigations into the prevalence of HIV drug resistance and the clinical consequences of ARV resistance are ongoing. Future analyses will also specifically focus on disparities in outcomes for minority patients. The large and diverse CNICS cohort, representing patients in real-life clinical care (as opposed to a more constrained clinical trial setting) has the potential to reveal a wealth of information about trends and future needs in HIV clinical care.

UCSD Antiviral Research Center (AVRC)

Study List Winter 2010



(619) 543-8080

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Antiretroviral Studies – Treatment Naïve

Study	Number	Design	Criteria
Comparison of NNRTI-sparing initial regimens	ACTG 5257	Open label ATV/RTV + Truvada (TDF/FTC) vs. DRV/RTV + Truvada vs. RAL + Truvada.	Treatment naïve HIV RNA > 1000
Comparison of initial regimens	CCTG 589	Open label RAL + Kaletra (LPV/RTV) vs. Atripla (EFV/TDF/FTC)	Treatment naïve HIV RNA \geq 5000 CD4 \geq 50

Antiretroviral Studies – Treatment Experienced

Study	Number	Design	Criteria
Effect of adding MVC to a suppressive ARV regimen with suboptimal CD4 recovery	CCTG 590	Open label MVC added to current regimen	Undetectable > one year CD4 < 350
OPTIONS Trial—Optimized treatment that includes or omits NRTIs for highly treatment experienced patients.	ACTG 5241	Selected regimens chosen from ENF, RAL, DRV/RTV, etravirine, TPV/RTV, plus two NRTIs or no NRTIs	HIV RNA > 1000. Experience with three classes of ARVs or resistance. Currently taking a protease inhibitor. No experience with any integrase inhibitor, etravirine, or rilpivirine (TMC278).

Acute / Early Infection Studies

Study	Number	Design	Criteria
Standard of care (SOC) vs. SOC plus MVC in patients with acute HIV infection	Acute R-5	Randomized, placebo-controlled trial of ATV/RTV + Truvada (TDF/FTC) vs. ATV/RTV + Truvada + MVC.	Acute HIV infection
Partner HIV transmission study (Partner Early Test)	AEH 027	Observational study of factors related to the transmission of HIV infection.	Partners of those taking The Early Test (nucleic acid testing)
Primary HIV infection study (First Choice Program)	AEH 020	Observational study of factors related to the acquisition of HIV infection	Acute and early (< 3 months) HIV infection. Treatment naïve

Abbreviations ART = antiretroviral therapy ARV = antiretroviral CSF = cerebrospinal fluid HAART = highly active antiretroviral therapy
HCV = hepatitis C virus HPV = human papillomavirus NRTI = nucleoside reverse transcriptase inhibitor
NNRTI = non nucleoside reverse transcriptase inhibitor PI = protease inhibitor TB = tuberculosis

Antiretroviral drugs ATV = atazanavir DRV = darunavir ENF = enfuvirtide EFV = efavirenz FTC = emtricitabine LPV = lopinavir
MVC = maraviroc RAL = raltegravir RBV = ribavirin RTV = ritonavir TDF = tenofovir TPV = tipranavir

Complications and Co-Infection Studies

Study	Number	Design	Criteria
Safety and efficacy of boceprevir in patients co-infected with HIV and HCV	Schering-Plough P05411	Step 1: Peginterferon (Peg-IFN) plus RBV for 4 weeks Step 2: Then add boceprevir vs. placebo for 44 weeks	Must be on ART for HIV. HIV RNA < 50. CD4 ≥ 200. HCV genotype 1, HCV treatment naïve.
Duloxetine and methadone for treatment of neuropathy	ACTG A5252	Placebo-controlled study with 4 weeks of duloxetine, 4 weeks of methadone, 4 weeks of both, and 4 weeks of neither, with the 4-week cycles in randomized order.	HIV-associated neuropathy. On current ARV regimen for at least 30 days.
Mefloquine for the treatment of progressive multifocal leukoencephalopathy (PML)	Biogen 111JC101	Mefloquine + local standard of care vs. local standard of care only. All participants will have the option of receiving mefloquine after 8 weeks.	Onset of PML symptoms within last 3 months
Comparison of regimens among HIV-infected high-risk PPD TB skin test reactors who require treatment of latent infection to prevent TB	ACTG A5259	Weekly rifapentine + isoniazid for 3 months vs. daily isoniazid for 9 months	HIV-positive and HIV treatment naïve. No active TB and TB treatment naïve. PPD skin test reactors at high risk for developing TB.
Pioglitazone prior to HCV treatment in those with insulin resistance and non-response to HCV therapy	ACTG A5239	Pioglitazone for 24-28 weeks, then add peginterferon (Peg-IFN) + RBV. Open label, pilot study.	HIV/HCV co-infection (HCV genotype 1). CD4 > 200. Must have insulin resistance and non-response to previous therapy with Peg-IFN/RBV. Must be on stable or no anti-retroviral therapy for 12 weeks.

Studies for Women

Study	Number	Design	Criteria
The HPV recombinant vaccine (gardasil) in HIV-positive women	ACTG A5240	All participants vaccinated at weeks 0, 8, and 24.	Females, age 18-45 (HIV-positive). No history of cervical cancer, no genital warts within 6 months, no prior HPV vaccinations. Either HIV RNA > 10,000 or CD4 < 350.

Other Studies

Study	Number	Design	Criteria
Chloroquine for reducing HIV-associated immune activation	ACTG A5258	Crossover design to evaluate the effect on CD8 T-cell activation of 12 weeks chloroquine vs. placebo.	HIV RNA > 20,000. CD4 > 400. Ages 18-65. Treatment naïve or off ART for 6 months, and unlikely to start ART for 6 months.
Zostavax (live herpes zoster vaccine) in HIV infected adults	ACTG A5247	Zostavax vs. placebo.	Undetectable HIV RNA. CD4 between 200 and 350. CD4 nadir (lowest ever) not less than 100. On stable ART.

Click on these links for related studies:

[HIV and Malignancy Studies](#)

[HNRC Studies \(HIV Neurobehavioral Research Center\)](#)

[Mother/Child/Adolescent Studies](#)

AVRC Programs, Events, and Announcements



is now located at:

220 Dickinson Street, Suite A
San Diego, California 92103

We're just beyond UCSD Medical Center on Dickinson
near Front Street.

Telephone: (619) 543-8080
New fax# : (619) 543-5066

AVRC Community Advisory Board (CAB) meeting (CAB) on January 4, 2010



Topic: *HIV and Hepatitis C Co-Infection: Updates and Current Studies
with Dr. David Wyles*

CAB meetings are usually held the first Monday of every month, and no RSVP is required. A light meal is served. If you would like to get monthly email reminders about CAB meetings, please contact Jack Degnan at jdegnan@ucsd.edu.

The HIV Early Test and the First Choice Programs

The AVRC is offering the Early Test (an HIV antibody test + nucleic acid testing), which looks directly for the virus. The advantage of the Early Test is that you can test one week after an exposure. For those who test positive, the First Choice Program can assist with notifying partners and accessing community medical and social services.

The test is free, confidential and offered by appointment Monday through Friday. It is also offered during the evenings and one Saturday per month. Call (619) 543-8080 to make an appointment or visit the Early Test website at theearlytest.ucsd.edu.



Antivirals for Starters Offered on January 27, 2010

Starting antivirals for the first time is a big step, so it is important to learn all you can. This lecture is given by the AVRC physicians every other month. The lecture will cover the classes of medications, when to start, drug resistance, the importance of adherence, and side effects. To sign up, call Jack Degnan at (619) 543-8080.

The Early Intervention Program (EIP)

EIP is a brief primary care program to help those without health insurance and who are currently not in need of antiretroviral medications. The program provides medical evaluation, laboratory monitoring, psychological services,