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AVRC Mission Statement

To develop and perform high quality research protocols that enhance the overall management of HIV infection while respecting and supporting the best interests of our clients. We maintain a safe, caring, and confidential environment.

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How Past ART During Pregnancy Affects Current Treatment Decisions: A New Clinical Trial for Women

by Constance A. Benson, M.D.

As antiretroviral treatment (ART) choices and the prospects for long-term good health continue to improve for HIV-infected women, many are reconsidering their options for having children. When considering pregnancy, HIV-infected women (and their healthcare providers) should ensure that they are maintaining a stable, undetectable viral load on ART prior to becoming pregnant, and that any ART-related side effects that might affect pregnancy or the woman's health are evaluated and controlled. When HIV-infected women do become pregnant, it is important to understand that decisions about

treatment for HIV infection will affect both the mother and her infant.

Decisions regarding the initiation of ART for maintaining health are the same for pregnant women as for non-pregnant women, although there are decisions to be made about specific anti-HIV drugs that might affect the health of the baby or might influence the risk of HIV transmission to the baby. For HIV-positive women not on ART who

become pregnant, an extensive evaluation of their medical history, previous pregnancies, current medications, previous anti-HIV drug treatment, CD4+ T cell count, HIV viral load, and stage of pregnancy are all important when deciding what to do about ART. The 3-part ZDV prophylaxis regimen, alone or in combination with other antiretroviral drugs, should be offered to all

One major concern regarding short courses of ART during pregnancy is the potential for selection of drug-resistant HIV strains that could interfere with future treatment responses.

pregnant HIV-infected women to prevent HIV transmission to the infant. This regimen consists of oral ZDV starting at 14-34 weeks of gestation, intravenous ZDV during labor and delivery, and oral ZDV (2 mg/kg body weight every 6 hours) to the newborn starting at 8-12 hours after birth and continuing for 6 weeks.

Following delivery of the baby, current recommendations are that for women who do not otherwise need ART for their own health, ART should be discontinued, and they should be monitored off ART until their health status changes. Initiation of ART is generally recommended when the CD4+ T cell count declines below 350 cells/ μ L and the HIV RNA

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viral load increases above 100,000 copies/ml. Therefore, many healthy HIV-infected pregnant women receive ART during pregnancy only to prevent transmission of HIV to the baby, and then stop ART after delivery.

One major concern regarding short courses of ART during pregnancy, particularly if drugs with low barriers to resistance (such as nevirapine or lamivudine) are used, is the potential for selection of drug-resistant HIV strains that could interfere with future treatment responses. Selection for drug-resistant variants can occur rapidly when ART is only partially suppressing HIV replication. For example, published information suggests that following a single dose of nevirapine used for prevention of mother to child transmission (pMTCT) of HIV in developing countries, 30%-50% of women have significant HIV drug resistance mutations to nevirapine using standard genotypic resistance tests, but up to 100% may actually have mutations detected when more sensitive drug-resistance assays are used. These mutations can be "archived," that is, present in a latent state in reservoirs outside the blood stream, as low-level minority viral variants. The likelihood of detecting these minority variants or archived mutations acquired during prior pregnancy ART decreases over time off therapy. Thus, standard testing for drug resistance at a later time when these women

Clinical Trial for "Nearly Naive" HIV+ Women ACTG A5227

This new clinical trial will investigate the efficacy of antiretroviral treatment for women who have prior short-term experience ("nearly naive") with antiretroviral therapy for the prevention of mother-to-child HIV transmission (pMTCT).

A5227 is an open label study of Efavirenz + Truvada (TDF + FTC) or any standard of care regimen chosen by the participant and her primary care provider. Efavirenz + Truvada will be provided by the study.

Inclusion Criteria

- * Women age 16 or older
- * Past pMTCT treatment for less than 40 weeks
- * Currently off treatment for at least 24 weeks before enrollment
- * HIV RNA > 500 copies/mL

For more information, please contact the AVRC screening coordinator at (619) 543-8080.

need to restart ART for their own health is unlikely to be helpful in determining the best treatment for them.

We do not have sufficient information about the levels of HIV drug resistance and potential compromise of future treatment options in this population, since pregnant women and women who received short-course ART only during pregnancy are often excluded from clinical trials. Preliminary information from other countries where nevirapine-containing regimens are used more frequently indicates that up to 12%-15% of women who received a nevirapine-containing ART regimen only during pregnancy had detectable HIV drug

resistance mutations in the postpartum period. Studies of treatment interruptions suggest that in a population of patients with a good response to an initial ART regimen, there is little risk of acquiring drug resistance mutations in the short term. However, this may not be directly applicable to women who have received ART for pMTCT, since ART was interrupted for only short periods of time in most research studies. Data from the Strategies for the Management of Antiretroviral Therapy (SMART) trial have suggested that despite the low risk for development of drug resistance mutations after short periods of treatment interruption, patients who repeatedly interrupt

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ACTG A5235 Studies Minocycline for the Treatment of HIV-Associated Cognitive Impairment

by Ronald J. Ellis, M.D., Ph.D.

Many people living with HIV report difficulty concentrating on mental tasks, memory loss, and mental slowness. When their mental function is measured by performance on cognitive tests, it is often found to be reduced compared to HIV-negative people of similar educational and demographic backgrounds. Sometimes these difficulties are unnoticed, and are typically not severe enough to constitute dementia, which is a general term for more severe cognitive deterioration that limits a person's ability to care for him or herself without assistance.

Despite the remarkable gains in general health attained with combination antiretroviral therapies, milder cognitive problems remain quite frequent, with recent studies indicating that about half of people living with HIV are affected. So-called mild neurocognitive impairment reduces quality of life, can lead to problems with adhering to complex antiretroviral drug regimens, and may affect employability. Numerous studies demonstrate that in those with HIV infection, the complexity of connections between brain cells (neurons) is reduced, likely a consequence of both HIV itself and chronic immune changes induced by HIV. Many researchers are convinced that the loss of neuronal connections might be slowed, or even reversed, if appropriate treatments can be found.

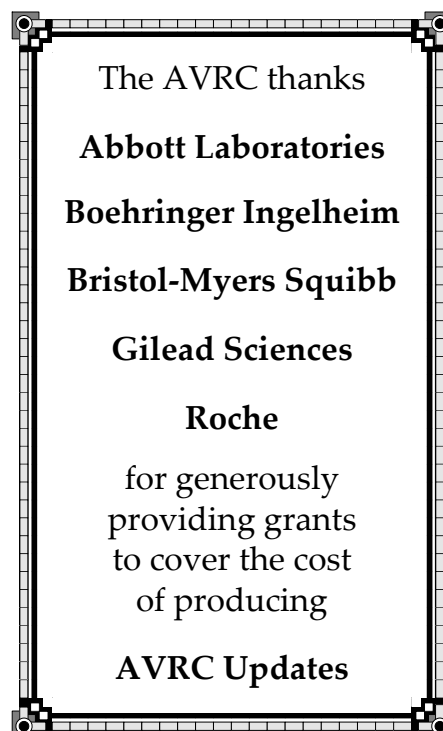
Minocycline is one such

treatment being studied at the UCSD Antiviral Research Center (AVRC) and HIV Neurobehavioral Research Center (HNRC). Many people will recognize that minocycline is an FDA-approved drug that has been used for decades to treat infections and acne. More recently, NIH-funded research has shown that in the laboratory and in animal models of HIV infection, minocycline can reduce damage to the brain induced by the virus and can help correct immune-mediated damage to the nervous system. The AVRC is collaborating with numerous other NIH-funded centers across the country to conduct the AIDS Clinical Trials Group (ACTG) A5235 study, which examines whether minocycline will help people living with HIV-related neurocognitive impairment.

Eligible participants will have HIV infection and progressive memory and thinking problems noticed by themselves or by someone who has known them well for years. They should be on a stable antiretroviral therapy regimen, and there are no inclusion criteria specifying HIV viral load levels or T-cell counts. This study will include neurological and physical exams, neuropsychological testing, health questionnaires, blood draws, lumbar punctures, and taking study medication. Participants will be compensated for their time, in addition to receiving free study medication.

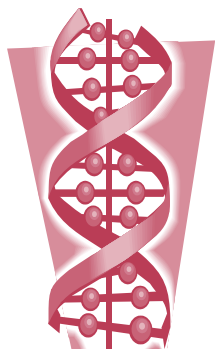
Enrolled volunteers will be randomized to receive either minocycline or a placebo for 24 weeks. Minocycline or placebo is taken as one capsule every twelve hours, at the same time every day, with or without food. At the end of 24 weeks, the participant can choose to take open-label minocycline for an additional 24 weeks. One hundred HIV-infected participants will be enrolled in this study. Most side effects from minocycline are mild and resolve on their own, and interactions with antiretroviral medications are few.

If you are interested in this study or would like more information, please call the AVRC at (619) 543-8080 and ask for the screening coordinator. ☞



Off your HIV medication?

The AVRC is seeking participants for a Phase 2a “proof of concept” study of an experimental HIV medication, KP-1461. The drug is designed to increase the mutation rate of the virus, leading to impaired viral function and replication to the point of non-viability. Participants will take KP-1461 twice daily for 124 days, and will be compensated for their time.



To qualify, candidates must:

- * be asymptomatic and off ARV treatment for at least 16 weeks
- * have had nonsuppressive exposure to or resistance to at least one PI, NRTI, and NNRTI
- * have HIV RNA level > 2,500
- * have CD4 \geq 250

For more information, please contact the AVRC screening coordinator at (619) 543-8080.

Eligible participants will be HIV-infected women age 16 and older who were treated with short-course pregnancy ART for pMTCT and do not have evidence of significant antiretroviral drug mutations associated with the two drug classes to be used in this study. Study participants will receive treatment with efavirenz (Sustiva) and a fixed dose combination of tenofovir and emtricitabine (Truvada) through the trial. Within-class drug substitutions at study entry and during the study will be allowed, at the discretion of the site investigator or clinician, and with approval from the study chair or vice chairs, however, substitute drugs will not be provided by the study. Participants will receive

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treatment have an increased risk of HIV disease progression and experience more drug-related complications than those who stay on continuous therapy. Patients in the SMART trial had more advanced HIV infection and had previously been on ART for an average duration of more than 5-6 years, so it is not clear that the results of the SMART trial are applicable to women who receive short-course pregnancy ART.

If a woman with a prior history of short-course ART requires initiation of ART, either during a subsequent pregnancy or to treat her own HIV infection, the question remains whether it is best to restart the same regimen used during the prior pregnancy, or to try to construct a new regimen by avoiding

drugs or drug classes that the woman received in the past out of concern for the possibility of resistance to the previously used drugs.

To address these issues, the AVRC is participating in a new clinical trial, the AIDS Clinical Trials Group (ACTG) protocol A5227, which studies whether the use of short-course potent ART for pMTCT during a prior pregnancy will affect the response to future treatment with a standard ART regimen of efavirenz plus fixed dose tenofovir plus emtricitabine, all first-line drugs recommended for initial ART in the U.S. If it is confirmed in this research study that women who were previously treated with short-term ART for pMTCT respond to first-line therapy the same as persons who have never received ART, then women treated during a previous pregnancy, who have generally been ineligible for inclusion in clinical trials of initial ART, could now be included in future studies.

Research Study for Lowering Cholesterol

The SABAR study will measure brachial artery reactivity after a switch to atazanavir (Reyataz).

Participants will be compensated for their time.

Design

Stay on current regimen or switch protease inhibitor to atazanavir.

Inclusion Criteria

Currently on a protease inhibitor other than atazanavir.

HIV RNA < 500.

LDL > 130 mg/dL or fasting triglycerides > 200 mg/dL.

For more information, please contact the AVRC screening coordinator at (619) 543-8080.

Patient and Provider Perspectives on Barriers to Latino Participation in HIV/AIDS Research

by María Luisa Zúñiga, Ph.D.

UCSD Division of International Health and Cross-Cultural Medicine

In our commitment to improving the health of persons living with HIV and their families, researchers and clinicians continue to work to better understand why some groups participate less frequently in HIV clinical trials. In a study that analyzed national data, Dr. Allen Gifford and colleagues found that Latinos and African Americans are less likely to participate in HIV/AIDS research than non-Latino White persons. These findings highlight the need for communities of color—who are most impacted by HIV disease—to be better represented in clinical studies in order to assure that new treatments work effectively for all populations affected by the epidemic and that all communities have equal access to potentially valuable new treatments (AL Gifford et al., N Engl J Med, 346: 1400-

1402, 2002). We recently conducted interviews with members of Latino communities living with HIV and the health care providers who serve these communities to give us a better idea of what might be the barriers to study participation among Latinos.

From December 2003 to April 2004, we interviewed 40 HIV-positive Latinas receiving health care at San Ysidro Health Center (SYHC) and UCSD, and 14 HIV health and social service providers and clinical trials recruitment staff from UCSD, including some UCSD providers who serve patients at SYHC. All of the Latinas who were contacted about this survey agreed to participate. Latina

participants were on average 38 years old, were primarily Mexican-born (70%), and 62% preferred receiving health information in Spanish. Most Latina study participants (65%) had made at least one round trip border crossing in the last year. Sixteen of the 40 women reported having previously participated in an HIV/AIDS-related clinical trial. **All of the Latinas who had previously participated in a clinical trial said that they would participate again.** Compared to women who had never participated, women who had participated in an HIV/AIDS clinical trial were more likely to report having received HIV/AIDS clinical trials information in the past year.

The 14 health care providers and staff who were interviewed included five clinicians, five case managers, and four clinical trials recruitment staff. A majority of providers were women (90%), provided HIV services four or five days per week (70%), and had an average patient/client caseload of 136 HIV-positive persons, nearly half of whom were Latino.

In order to be able to compare opinions across the groups, we asked the same three questions of Latina

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The HIV-positive Latina participants felt that the most important barriers to clinical trials participation for Latinos are related to personal reasons, including fear, ignorance, shame (vergüenza), and denial.

Discordant Treatment Response? ACTG A5212 is for Patients with Low Viral Load and Low CD4 Count

The AVRC is seeking participants with HIV RNA < 200 and CD4 < 250 for a research study to determine if palifermin (keratinocyte growth factor) will increase CD4 count. Participants will remain on their current HIV treatment regimen.

For more information, please contact the AVRC screening coordinator at (619) 543-8080.

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participants, clinicians, and social service providers:

- 1) What do you think are the most important reasons that Latinos do not participate in HIV clinical trials?
- 2) What do you think are some of the reasons that Latinos participate in clinical trials?
- 3) In your opinion, what could be done to improve participation of Latino persons in HIV/AIDS clinical trials?

The HIV-positive Latina participants felt that the most important barriers to clinical trials participation for Latinos are related to personal reasons, including fear, ignorance, shame (*vergüenza*), and denial. When we analyzed the information more closely, we realized that many of the barriers reported by Latinas were related to HIV stigma. Only 10% of Latinas mentioned barriers such as lack of transportation and language-appropriate services. Most

Cognitive Intervention Study

- HIV is associated with cognitive impairment.
- 35% of asymptomatic HIV+ people and 50% of people with AIDS may experience cognitive impairment.
- Some people who experience cognitive symptoms are failing on their current antiretroviral regimen.



UCSD researchers are investigating the cognitive effects of physician-prescribed changes in antiretroviral medications.

For more information, call Teresa at the HIV Neurobehavioral Research Center at (619) 543-5045.

providers, on the other hand, thought that system-level barriers such as transportation and language barriers were the most important barriers to Latina participation and they did not mention stigma as the most important barrier.

Latina participants and the providers felt that Latinos participate in clinical trials in order to take care of themselves and as an opportunity to access HIV treatment. Latina respondents felt that providing more information about clinical trials would help increase participation. From the provider

perspective, recommendations included reducing language barriers, for example, hiring more bilingual/bicultural clinical staff and recruitment staff.

We used the information that we learned in those initial interviews to design the second phase of our study, in which we conducted additional interviews with patients and providers to ask more specifically about the nature of barriers to participation in HIV/AIDS clinical trials and what we can do to remove these barriers. This past year, with the help of patients, administrators, and clinicians at SYHC and UCSD, we have interviewed 14 HIV physicians and pharmacists about Latino clinical trials participation and have conducted four focus groups with over 40 Latinas and Latinos living with HIV/AIDS. We are in the process of better understanding the information and summarizing what we have learned. To date, we have observed that improving access to clinical trials physical locations, reducing stigma, and improving patient-provider communication and trust are important topics to both

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The Early Test Coming Soon to the AVRC

The UCSD Antiviral Research Center will soon be offering The Early Test, which provides rapid HIV antibody testing followed by nucleic acid testing (NAT). NAT can detect HIV infection as early as one week after exposure. The Early Test is already available as a pilot program at a few HIV testing sites and has been recently funded to expand to San Diego County HIV test sites in the future.

The Early Test will be offered at the AVRC for partner pairs who test together and for individuals with recent high risk exposures. For more information, please call the AVRC at (619) 543-8080 and ask for The Early Test program.

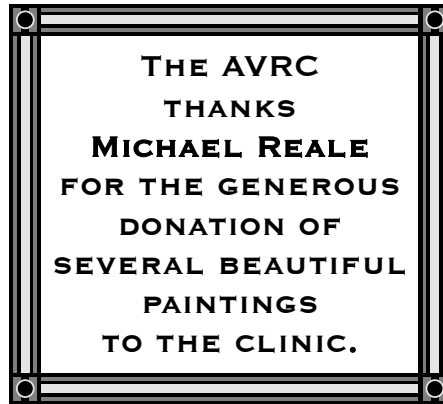


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clinicians and patients.

These studies suggest that although there is wide agreement among patients and providers on recommendations to improve Latino participation in HIV/AIDS clinical trials, there is also a need for awareness of potential differences in how patients and clinicians view barriers to clinical trials participation. For example, we are learning that HIV stigma has a powerful impact on Latino patients living with HIV, including access to HIV/AIDS care and clinical trials (in press with the *Journal of Women's Health*, ML Zúñiga et al., "Perceptions of barriers and facilitators to clinical trials participation in HIV-positive Latinas"). Improving our mutual understanding of potential barriers to HIV clinical trials from



the patient and provider perspective is important to bridge gaps in communication across the entire team devoted to achieve the best health for patients living with HIV/AIDS.

This work would not have been possible without trust and support from patients, providers, and staff from SYHC, the UCSD Mother, Child, and Adolescent Program, the HNRC and AVRC, and the exceptional dedication and contributions of Ms. Estela Blanco, the study's coordinator. For more information about these findings or our ongoing studies, please contact Ms. Blanco at (619) 681-0641. ✉

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study treatment for 48 weeks, during which time they will be evaluated with viral load, CD4+ T cell counts, and safety laboratory testing. Both conventional and highly sensitive drug resistance testing will be done to assess the presence of drug resistant HIV strains prior to starting ART and the potential impact of any drug resistance mutations present on the response to treatment. We hope to enroll up to 10 women at the AVRC and up to 118 women nationally in this study. The results of this study will have important implications for how to manage ART for HIV-infected women who have been or may become pregnant. For more information or to screen for this study, please call the AVRC screening coordinator at (619) 543-8080. ✉

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