HIV JournalView


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An Alternative for Peripheral Neuropathy

Hart AM, Wilson ADH, Montovani C, et al. *Acetyl-l-carnitine: a pathogenesis based treatment for HIV-associated antiretroviral toxic neuropathy*. ***AIDS. July 23, 2004;18(11):1549-1560.***

It is difficult to imagine: pain with every step, lying awake in bed, feet on fire, a tingling numbness that doesn't allow you to think of anything else. Painful distal peripheral neuropathy (PN) is a particularly insidious adverse effect of certain HIV therapies, and a common complaint in clinical practice.

To a great extent, the incidence of antiretroviral-related PN has been pegged to the popularity of the deoxynucleotide analogue agents -- stavudine (d4T, Zerit), didanosine (ddI, Videx) and zalcitabine (ddC, Hivid); as use of these agents has waned, so too has the incidence of drug-associated PN. However, for various reasons, some patients still require these antiretrovirals. Therapy for painful PN has had limited success and there are no licensed effective therapies to date. Once the cornerstone of therapy, tricyclic antidepressants have given way to anticonvulsants such as gabapentin (Neurontin) and lamotrigine (Lamictal). Yet, for many PN sufferers, these agents -- even in combination with narcotic analgesics -- provide less than complete relief and add additional pill burden to standard HIV regimens. Withdrawal of the offending antiretroviral is often possible, although, in some cases, there is the risk of loss of control of HIV viremia. Further, the heavy reliance on stavudine in the developing world insures that PN may become a major issue in the management of HIV in these areas. Therefore, an effective therapy for relief of antiretroviral-associated PN remains an important priority.

The etiology of treatment-associated PN is thought to be rooted in the mitochondrial toxicity of certain antiretrovirals. With a drug-mediated reduction in neuronal mitochondrial DNA, disruption of oxidative metabolism within these organelles ensues. Neurons, with their long axons, become unable to meet the demands of their unique metabolism and eventually wither. Biopsies of epidermis confirm that patients with PN have fewer peripheral nerves than those without PN. This putative mitochondrial toxicity mechanism has sparked investigations into therapeutic approaches that aim to protect mitochondrial function.

Acetyl-L-carnitine (ALCAR) is an integral transport molecule for free fatty acids as well as an acetyl-group donor in high-energy metabolism and free fatty acid beta-oxidation within

mitochondria. In addition, ALCAR has been shown to promote nerve regeneration and to be neuroprotective in patients with diabetes, preventing development of PN and reducing pain scores in those with the sensory neuropathy. Less is known about the effect of ALCAR in antiretroviral-associated PN.

To assess the efficacy of ALCAR, researchers in the United Kingdom administered the drug orally at 1500 mg twice a day for up to 33 months in 21 patients who had established antiretroviral-associated PN and were not on other PN therapies. In addition, 5 HIV-uninfected individuals who did not have PN were recruited as controls. Nerve biopsies were performed in both subjects and controls. The subjects were fairly antiretroviral experienced and had a median exposure to 6 antiretrovirals in the past. The median viral load was <400 copies/mL and the median CD4+ cell count was 286 cells/mm^3. All had grade 1 or higher PN and most required some form of analgesic, although only 3 subjects were taking narcotics. The median duration of PN was 11 months.

Among the 21 subjects, 15, including 2 of the 3 subjects who had grade 3 PN at entry, had improvement in their neuropathy by standard adverse event grading score. More detailed pain or quality of life scores were not reported. One subject had worsening of PN on treatment; 3 subjects switched from stavudine or didanosine to an alternative antiretroviral during the study. Whether these subjects were responders was not described. Those who stopped ALCAR had worsening of symptoms in this open-label study. Apparently, ALCAR was well tolerated.

Biopsies of the skin from the most effected leg were performed at baseline in all subjects and in the 5 controls. Eleven subjects had a follow-up biopsy. The controls had normal cutaneous innervation patterns. The subjects with PN had almost complete absence of nerve fibers in the epidermis, subepidermal plexus and around the sweat glands. The use of ALCAR by those with repeat biopsies at 6 months led to marked normalization of the innervation of these structures. Quantification of fiber types was accomplished by immunostaining and dramatic increases in small sensory fibers in particular were found.

This study provides initial evidence for the efficacy of ALCAR for antiretroviral-associated PN. The biopsy results are striking and bolster the clinical improvements observed. These exciting findings certainly support larger clinical investigation of this agent and offer renewed hope for people who are suffering from antiretroviral-associated PN. The results also suggest that this may be a potential, and maybe cheap, therapy for other mitochondrial toxicity disorders and this too requires further study.

Stable Viral Load but Evolving Drug Resistance

Kantor R, Shafer RW, Follansbee S, et al. Evolution of resistance to drugs in HIV-1-infected patients failing antiretroviral therapy. AIDS. July 23, 2004;18(11)1503-1511.

While the major goal of antiretroviral therapy (ART) is to drive plasma HIV levels to below the lower limit of an ultrasensitive assay, in real life many, if not most, patients have detectable viremia while on HIV therapy. For instance, a common clinical scenario is the patient on potent ART who has had a 2 or more log10 decline in plasma HIV RNA and has sustained CD4+ cell count increases but continues to have low-level, detectable viremia. For many clinicians, this has been the equivalent of an Olympic silver medal -- it's not gold, but it's close. However, emerging data suggest that some patients with stable, low-level viremia *do* accumulate new ART resistance.

To evaluate the risk of resistance cultivation in patients with viremia, researchers at Stanford University in California searched their database for patients with known treatment histories, 2 genotypic resistance tests performed at least 2 months apart and no change in ART during the period between the 2 genotypic resistance tests. Their search yielded 106 patients.

They found that the median duration of the ART regimen prior to the patients' first genotypic resistance test was 29 months. The median time between genotypic resistance tests was 14 months. Patients had a median exposure to 6 drugs at the time of the first genotypic resistance test and almost 73% of the patients were protease inhibitor (PI) experienced. There was little, if any, ritonavir (RTV, Norvir)-boosted PI use.

For the first genotypic resistance test, the median viral load and CD4+ cell count were 3.7 log10 cpm and 336 cells/mm^3, respectively. At the time of the second genotypic resistance test, these were 4.0 log10 cpm and 339 cells/mm^3, respectively, which was statistically significant only for the change in viral load.

In the period of time between the 2 genotypic resistance tests, 75% of the patients had developed a new drug resistance mutation. There were PI mutations in 62% of those on PIs, nucleotide reverse transcriptase inhibitor (NRTI) mutations in 42% of those on drugs of this class and non-nucleotide reverse transcriptase inhibitor (NNRTI) mutations in 29% of those on efavirenz (EFV, Sustiva, Stocrin) or nevirapine (NVP, Viramune).

Among patients with a viral load of less than 5000 cpm at first test, 37% developed new drug resistance, as did 12 of the 13 patients who maintained a viral load of 50-999 cpm. Conversely, 21% of the patients "lost" resistance mutations from the first to the second genotypic resistance test (i.e., these mutations were no longer detected, although they were almost certainly still present). The total number of drugs predicted by resistance testing to be "resistant" increased from a median of 8 to 10.

Interestingly, there was no major difference in the acquisition of new resistance mutations between patients who experienced virologic and/or immunologic improvement in between assays and those who did not. Not surprisingly, patients who had fewer resistance mutations at the time of their first genotypic test were more likely to develop new mutations -- probably because those with lots of resistance at baseline already developed their resistance mutations. Further, longer time between assays was associated with an increased risk of resistance.

These results are cause for concern. While, reassuringly, CD4+ cell counts and viral loads changed little while ART was continued and viremia remained detectable, drug resistance increased in the great majority of patients nonetheless. Similar results were presented at the International AIDS Conference in Bangkok.[1]

Clinicians confronted with a patient who has reduced but persistently detectable viremia must balance these findings with other factors. This includes a consideration of available treatment options as well as patient willingness to change therapy that, by clinical criteria are successful, as evidenced by rising CD4+ cell count and reduced viral load. Chasing viral load to undetectable is not without its own risks (i.e., toxicity, poor adherence) and whether in this case the enemy of "good enough" is "even better" needs to be considered and certainly studied prospectively. I must admit I am now eyeing my persistently viremic, ART-receiving patients less sanguinely than before and have begun to intensify therapy when possible.

Niacin Revisited

Gerber MT, Mondy KE, Yarasheski KE, et al. Niacin in HIV-infected individuals with hyperlipidemia receiving potent antiretroviral therapy. Clin Infect Dis. August 1, 2004;39(3)419-425.

Niacin (Niacor, Niaspan) is an effective lipid-lowering therapy in HIV-uninfected patients that, like statins, can lower low-density lipoprotein (LDL) cholesterol but can also raise high-density lipoprotein (HDL) cholesterol and reduce triglycerides. The use of traditional niacin has been limited by its toxicities, which include cutaneous flushing and insulin resistance. Extended-release niacin (niacin ER) has been associated with lower rates of flushing and improved hepatic safety. However, use of this agent in the setting of HIV-associated dyslipidemias has been cautious, as there remains the potential for hyperglycemia with niacin ER.

In this pilot study, Gerber and colleagues at Washington University administered 2000 mg of niacin ER to 14 patients receiving highly active antiretroviral therapy (HAART) -- PI or NNRTI based -- who had fasting triglyceride levels $\geq$200 mg/dL and/or direct LDL cholesterol $\geq$130 mg/dL. All subjects were to follow a National Cholesterol Education Program (NCEP) Step I diet that began 4 weeks prior to niacin ER administration. Simultaneously, all lipid-lowering agents were discontinued.

Niacin ER was started at a dose of 500 mg daily, increased to 1000 mg at week 2 and titrated by 500-mg increments every 4 weeks up to 2000 mg daily, with the aim of driving triglyceride levels below 200 mg/dL or to the NCEP goal for LDL cholesterol. Aspirin was recommended 30 minutes before niacin ER dosing as a prophylaxis against flushing. Niacin ER was stopped after 14 weeks. Numerous evaluations were conducted during the study, such as lipid profiles that included direct LDL cholesterol measurements and 5-hour, 11-point oral glucose tolerance testing.

The 14 subjects were all male and, save for one, all white. The median age was 48.9 years and the median baseline CD4+ cell count was 421 cells/mm^3. Only 4 subjects were taking statin therapy at baseline (2 of whom were also on a statin). The efficacy results of the study are presented below. Recall that study entry is 4 weeks prior to administration of niacin ER and is

when the NCEP diet commences. Median values are presented.

	Before Start of NCEP Diet (Week 0)	Before Start of Niacin ER (Week 4)	At End of Niacin ER Therapy (Week 18)	4 Weeks After Niacin ER Stopped (Week 22)	*P* Value Week 4 vs. Week 18
Total Cholesterol	251	245	220	246	**.005**
Triglycerides	527	489	406	460	**.041**
HDL-C	37	39	39	38	.592
LDL-C	121	114	123	121	.505
Non-HDL-C	209	200	177	207	**.006**

Of the 14 subjects enrolled, 12 completed the study. The 2 patients who did not complete the study were both hospitalized -- one for exacerbation of preexisting heart failure and the other for pneumonia. Six (43%) of the subjects reported adverse effects from therapy, mostly flushing, itching or headache -- none of which led to treatment discontinuation and, generally, the symptoms improved during the course of the study. There were no significant changes in hepatic transaminases, uric acid, CD4+ cell count or HIV viral load.

Eleven subjects underwent an oral glucose tolerance test (OGTT). Incredibly, 6 of the 11 subjects were found to be glucose intolerant (2-hour OGTT value $\geq$140 mg/dL) at the start of treatment with niacin ER. After 14 weeks of niacin ER, 3 additional subjects met the criterion for glucose intolerance while 2 subjects with glucose intolerance at the start of therapy had 2-hour levels below 140 mg/dL (113 mg/dL and 136 mg/dL) at the end of treatment. Based on the homeostasis model of insulin resistance (HOMA-IR), insulin sensitivity was found to be significantly reduced after niacin ER therapy. No subject developed frank diabetes.

Niacin ER, given its lack of drug-ART interaction and effect on HDL cholesterol and triglycerides, is an attractive therapy for HIV-associated dyslipidemia. The risk of developing or exacerbating glucose intolerance limits the attractiveness of this agent in this setting. This pilot investigation suggests that niacin ER may be better tolerated than suspected, but that caution regarding its use in those with glucose intolerance is justified. Overall, there was an increase in insulin secretion secondary to heightened beta cell sensitivity to stable glucose levels, but this insulin resistance did not lead to overt diabetes. However, keep in mind that this was a small study of relatively short duration and the maximal dose of niacin ER was not achieved until shortly before the study ended.

Further, these results can hardly be categorized as blockbuster. Since it is a small cohort, one cannot read too much into the magnitude of response seen; however, the absence of significant reductions in LDL and HDL cholesterol levels tempers enthusiasm for an agent that is designed to do just that -- especially since statins are being used with some measure of success in HIV-infected persons. But evaluation of alternatives is warranted because there are patients already receiving or who can not tolerate a statin who may benefit from niacin. For these patients, these data assuage some of the concerns regarding toxicity and provide a green light for bigger and better studies of the efficacy of extended-release niacin in HAART-treated patients.

HIV on Campus

Centers for Disease Control and Prevention. HIV transmission among black college student and non-student men who have sex with men -- North Carolina, 2003. MMWR. August 20, 2004;53(32) 731-734.

The role of men who have sex with men (MSM) and also have sex with women in the spread of HIV has received considerable attention of late. A cover story in The New York Times Magazine, an "Oprah" show dedicated to the topic and segments on the nightly news programs have introduced the term "living on the down low" to the HIV/AIDS lexicon.

The focus of attention has been concentrated on those African-American men who, although they have sex with both men and women, consider themselves straight. In urban areas where HIV infection is prevalent, there is a 14% incidence and 32% prevalence of HIV among young, African-

American MSM. Further, the dramatic increase in the proportion of African-American women in the United States who acquire HIV via heterosexual contact has led to renewed examination of the intimate behaviors of the men from whom they acquired the virus.

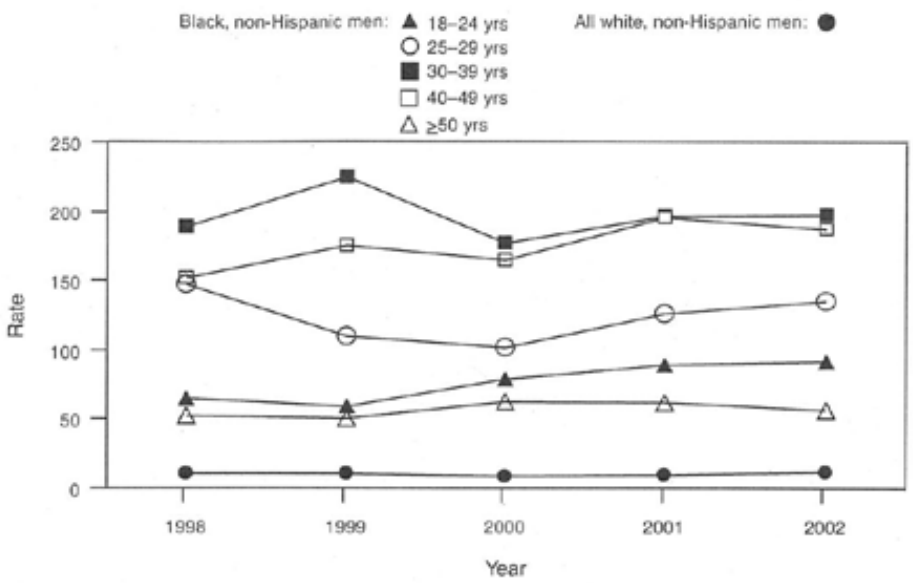
In North Carolina, a program designed to identify acute HIV infection among those presenting for HIV antibody testing, in November 2002 identified 2 male, African-American college students with acute HIV. A retrospective review of all men between 18 to 30 years of age with HIV diagnosed during January 2000 to May 2003 indicated an increase in HIV case reports among male college students, from 2 cases in 2000 to 56 cases during January 2001 to May 2003. Of these 56, a total of 49 of the cases (88%) were African-American, and nearly all were MSM, including some men who had sex with both men and women.[2]

In follow-up, a case control study was initiated to identify behavioral risk factors for HIV infection in young, black MSM. Cases were black, HIV-infected, MSM college students, age 18 to 30 years, diagnosed during 2001 to 2003. All were North Carolina residents. These cases were compared to 2 groups of HIV-uninfected controls: college students and non-students, all of whom also were also black MSM, aged 18 to 30 years, who lived in North Carolina.

Face-to-face interviews were conducted to obtain epidemiological and behavioral information, data on sexual behaviors during the year prior to HIV diagnosis for the HIV-infected college students or the date of interview for HIV-uninfected college students and non-students. In addition, according to the report, 3 discussion groups were held during which approximately 60 black male and female students from 11 colleges in North Carolina discussed perceived barriers to sexual risk reduction and suggestions for prevention programs targeting college students.

Importantly, during the study, the overall rates of newly reported HIV infection in North Carolina were higher in black men in all age groups compared with white men overall (see Figure). The increase in HIV infection among black men aged 18 to 24 years increased significantly from 65 per 100,000 population in 1998 to 92 per 100,000 population in 2002 ($P<.01$).

FIGURE. Rates* of newly reported human immunodeficiency virus infection among non-Hispanic black men, by year and age group, and among all non-Hispanic white men, by year — North Carolina, 1998–2002



* Per 100,000 population.

The study recruited 17 (35%) of the 49 African-American men who were college students and identified by the state surveillance system as being HIV infected. The 2 groups of HIV-uninfected controls: 19 HIV-uninfected college students and 15 HIV-uninfected non-students were recruited during HIV pre- or post-test counseling activities at local health departments (n = 5), gay nightclubs (n = 26) and the North Carolina Pride Festival (n = 3).

The general characteristics of the 3 groups (HIV-infected MSM college students, HIV-uninfected MSM college students and HIV-uninfected MSM non-college students) were similar; however, there were higher rates of sexually transmitted diseases among the HIV-uninfected students compared to the HIV-infected group. College students, not surprisingly, were younger than non-students, and the mean number of lifetime sex partners was lower for college students (mean no. of partners was 20 for HIV-infected students and was 18 for HIV-uninfected students) than for non-students (mean no. = 13). The mean number of steady male partners during the preceding 12 months was similar for the 3 groups and the frequency of unprotected receptive anal intercourse with steady partners ranged from 38% among non-students to 56% among HIV-infected students. More non-students tended to have casual male sex partners than students. Approximately 20% of all the study participants had a female sex partner during the preceding 12 months and this did not differ between the groups. While one third of both HIV-infected and HIV-uninfected college students met sex partners on college campuses, most met their sex partners at gay nightclubs or over the Internet. Compared to non-college students, fewer college students identified themselves as gay or disclosed their sexual identity.

This report identifies several concerns. First, surprisingly, despite high-risk behaviors and high rates of prior sexually transmitted disease, HIV-infected African-American college students in this study did not perceive themselves to be at risk for HIV infection prior to their diagnosis. Second, these men did not always identify themselves as gay and a substantial proportion had sex, often unprotected, with women. Therefore, these men may be transmitting HIV to female partners.

In addition, prevention messages aimed at MSM may not be effective at reaching these men as they do not always identify as MSM. Lastly, while much attention is paid to the spread of HIV in urban settings, this study suggests that the epidemic has become well entrenched in the more rural South. As a transplanted Northerner treating HIV in North Carolina, this author can attest to the need for additional resources to develop an improved understanding of HIV transmission in the southern United States and, ultimately, effective prevention interventions for our at risk populations.

References

1. Lafeuillade A, Hittinger G, Delbeke E, Poggi C. Resistance selection in patients with stable low levels of HIV-1 viremia. In: Program and abstracts of the XV International AIDS Conference; July 11-16, 2004; Bangkok, Thailand. Abstract WeOrB1293.

2. Hightow L, Leone P, MacDonald P, et al. Are colleges high transmission areas in the rural southeast? insights from acute HIV surveillance. In: Program and abstracts of the National HIV Prevention Conference; July 27-30, 2003; Atlanta, Georgia. Abstract WO-L305.

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