Madhavi Parekh, PGY2
ICCR IRB Proposal
12.18.08

The Effect of Highly Active Antiretroviral Therapy (HAART) on Adrenocortical Function in Patients with Aquired Immunodeficiency Syndrome (AIDS)

1. Study Purpose and Rationale

Adrenal dysfunction is the most common endocrine disorder in patients with Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS). Adrenal insufficiency has a very broad range of clinical implications, but is a potentially life threatening condition if unrecognized, marked by adrenal crisis or cardiovascular collapse. While the mechanism of adrenal insufficiency in patients with HIV/AIDS has not been adequately studied, potential etiologies include direct involvement by HIV, opportunistic infections, AIDS-related malignancies, and various medications, indicating likely primary adrenal insufficiency (at the level of the adrenal gland). Pathologic data (via post-mortem analysis) suggests direct adrenalitis caused by various opportunistic infections, notably cytomegalovirus (CMV), *mycobacterium avium-intrarcellulare* (MAI), tuberculosis, cryptococcosis, histoplasmosis, blastomycosis, toxoplasmosis, lymphoma and Kaposi's sarcoma.[i,ii] Autopsy studies have also noted adrenal necrosis in patients with HIV/AIDS, commonly seen in patients with pathologic evidence of concurrent CMV disease.[iii,iv] Certain medications used for AIDS-related illnesses can also contribute to an underlying adrenal disorder, including: ketoconazole (directly inhibits steroidogenesis), rifampin, megestrol acetate (has intrinsic glucocorticoid activity and prolonged use can result in secondary adrenal insufficiency).[v]

The diagnosis of adrenal insufficiency can be difficult given its often insidious nature and vague clinical characteristics. Clinical manifestations of chronic insufficiency include: fatigability, weakness, anorexia, fever, nausea, and vomiting, all of which are non-specific and can easily overlap with AIDS-related symptoms. Clinically severe or acute adrenal insufficiency (resulting in life threatening hypotension) is thought to be uncommon in patients with HIV/AIDS, but these patients are at increased risk of developing severe symptomatology given their propensity to develop severe illnesses and potentially precipitate adrenal crises.[vi]

Numerous studies have examined adrenal function in patients with HIV, but have demonstrated varying results. Smaller studies (n<25) of patients with HIV (without AIDS) have found subnormal cortisol responses to ACTH stimulation in approximately 25% of patients,[vii,viii] while studies looking at patients with clinical AIDS had higher rates of subnormal responses to ACTH stimulation (as high as 54% of patients).[ix] More recently, a study looking at 104 HIV-infected patients (32 with HIV alone, 72 with AIDS), demonstrated adrenal insufficiency by low-dose cosyntropin stimulation test in 21% of all patients (9% in those with HIV alone and

26% of those with AIDS). Greater than 50% of all study participants were completely asymptomatic, and of patients with symptoms of adrenal insufficiency (weight loss, diarrhea, anorexia, dizziness, hyperpigementation, vomiting), none were found to have subnormal cortisol levels after cosyntropin stimulation, suggesting clinical features of adrenal insufficiency are difficult to assess in this population and potentially that all patients with HIV may warrant assessment of adrenal function.[x]

As suggested by these few studies, patients with AIDS have a higher incidence of adrenal insufficiency than patients with HIV alone. While there are many possible etiologies of adrenal insufficiency in patients with AIDS, the mechanism remains unclear yet, and perhaps this disorder can be treated as an AIDS-related illness. The advent of highly active antiretroviral therapy (HAART) therapy, which causes both an immunologic response (manifested by a sustained elevations in CD4 lymphocyte counts) and a virologic response (nearly complete suppression of HIV viral replication) in patients with AIDS, has resulted in a reduction in AIDS-related illnesses (opportunistic infections, AIDS-related malignancies). Along these lines, HAART may also treat HIV-related adrenocortical dysfunction.

Therefore, the purpose of this study is: to determine if adrenocortical function improves in patients with diagnosed AIDS and adrenal insufficiency with HAART therapy.

Study hypothesis: adrenocortical function (as determined by low-dose cortrosyn stimulation test) will improve in patients diagnosed with AIDS after 6 months of treatment with HAART.

2. Study Design/Statistical Analysis

a. Design

The study will be a prospective cohort study that follows asymptomatic patients with HIV (by ELSIA and confirmatory Western Blot) and AIDS (by CD4 T-cell count of <200 or CD4 T-cell count <350 with high viral load >10-20,000 copies/ml), over a 6-month period, starting at the initiation of HAART therapy. The primary endpoint is adrenocortical function at the end of this 6-month period.

Participants will be tested for adrenal insufficiency (by low-dose cosyntropin stimulation test) at baseline, and will be included in the study if their post-stimulation cortisol at 30-60 minutes is <20mcg/dL. Patients who qualify will be separated into 2 groups, the HAART treatment (exposure) group, and control (unexposed) group (made of patients refusing HAART therapy). All patients will similarly be tested for adrenal insufficiency at baseline and at 6 months. All patients will also have a full history and physical exam at baseline and 6 months, specifically inquiring about symptoms of adrenal insufficiency (weight loss, diarrhea, anorexia, dizziness, nausea, hyperpigmentation, vomiting). A cortisol level, ACTH level, basic metabolic

panel, CD4 T-cell count and HIV viral load will also be measured at the same time points.

HAART therapy will be chosen and tailored by the primary HIV provider, and therefore will be managed outside of the study. Patients will be removed from the study if they are hospitalized during the course of the trial, or need steroid treatment for another reason, or need acute adrenal replacement therapy during the 6-month period (in the setting of severe illness or overt adrenal crisis).

b. Analysis

An unpaired t-test will be used to compare the mean difference between adrenocortical function of patients receiving HAART and those not exposed to the therapy. As aforementioned, patients who are removed from the study for a variety of reasons will not be included in the final comparison. This study will be conducted from 2009-2011. Ideally, patients would be randomly assigned to either group (treatment/exposure vs. no treatment/exposure), but given the fact that denying a patient treatment for HIV is ethically unacceptable, control subjects will be self-selecting. Assuming 200 new patients diagnosed with AIDS presenting to the clinic for the first time during a 12-month period, and assuming approximately 20% of new patients will not be started on HAART (self-selected), and that 25% of patients approached will have measurable adrenal insufficiency, the study will have 80 patients in the treatment (exposure) group and 20 patients in the control group (over a 2 year period). Using these assumptions and a standard deviation of 5 (as suggested by the data in Gonzalez-Gonzalez, et al.),[10] this will give me 80% power at α=0.05 to detect a mean difference of 2.3mcg/dL between groups.

3. Study Procedures

This study will utilize a low-dose cosyntropin test: 10μg of synthetic ACTH is administered via peripheral IV followed by a serum cortisol level measurement between 30-60 minutes after the injection. Other serum laboratories (basic metabolic panel, CD4 T cell count, HIV-1 viral load) will also be drawn at this time.

4. Study Subjects

a. Inclusion criteria
   i. Patients with HIV (by ELSIA and confirmatory Western Blot) and AIDS (by CD4 T-cell count of <200 or CD4 T-cell count <350 with high viral load >10-20,000 copies/ml) who have not yet been treated with HAART.
   ii. Patients

b. Exclusion criteria
   i. Patients who have been on any form of antiretroviral therapy in the past.
   ii. Patients on chronic steroids for any reason.

iii. Patients who are acutely ill necessitating inpatient hospitalization (which would include patients with potentially profound adrenal insufficiency).

5. Study Location

Patients would be recruited at the outpatient HIV clinic at the Harkness Pavilion of Columbia Presbyterian Medical Center. As mentioned above, approximately 150-200 new patients with HIV and AIDS are seen in this clinic each year.

6. Confidentiality

Given the sensitive nature of this patient population's information, particular care will be taken in maintaining the confidentiality of all participants. All participants will be coded numerically for recordkeeping and all identifying information will be kept in a secure location (both paper and electronic), only available to study investigators.

7. Potential Risks and Benefits

Risks are minimal to the participants in this study, and include discomfort at the IV site or with peripheral blood draws. A major benefit of this study is the determination of adrenal insufficiency in this patient population. In the event of severe illness in any of the participants, adrenal replacement therapy may help overcome the acute event. Participants will all receive alert bracelets allowing health professionals to know of their condition in the event of emergency.

---

[i] Glasgow, BJ, et al. "Adrenal pathology in the acquired immune deficiency syndrome." American Journal of Clinical Pathology 84: 594-97. 1985.

[ii] Giampalmo, A, et al. "AIDS Pathology: various critical considerations." Pathologica 82: 663-77. 1990.

[iii] Niedt, GW, and R. A. Schinella. "Acquired Immunodeficiency Syndrome. Clinicopathologic study of 56 autopsies." Arch Pathol Lab Med 109: 727-34. 1985

[iv] Tapper ML, et al. "Adrenal necrosis in the acquired immunodeficiency syndrome." Ann Intern Med 100: 239-241. 1984.

[v] Zapanti E, et al. "Dysfunction of the hypothalamic-pituitary-adrenal axis in HIV infection and disease." Hormones. 7(3):205-16. 2008.

[vi] Eledrisi, M, A Verghese. "Adrenal insufficiency in HIV infection: a review and recommendations." American Journal of Medical Sciences. 321(2): 137-144. 2001.

[vii] Azar S, J Melby. "Hypothalamic-pituitary-adrenal function in non-AIDS patients with advanced HIV infection." American Journal of Medical Sciences. 305:321-5. 1993.

[viii] Findling J, et al. "Longitudinal evaluation of adrenocortical function in patients infected with the human immunodeficiency virus." Journal of clinical endocrinology and metabolism. 79:1091-6. 1994.

[ix] Membreno L, et al. "Adrenocortical function in acquired immunodeficiency syndrome." Journal of clinical endocrinology and metabolism. 65:482-7. 1997.

[x] Gonzalez-Gonzalez, J, et al. "Prevalence of abnormal adrenocortical function in human immunodeficiency virus infection by low-dose cosyntropin test." International journal of STD & AIDS. 12: 804-810. 2001.