CRC IRB proposal
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A. Study purpose and rationale

In addition to susceptibility to a myriad of opportunistic infections, people with HIV/AIDS can develop often debilitating central nervous system (CNS) dysfunction, termed HIV-Associated Neurocognitive Dysfunction (HAND)[1]. Interestingly, these neurologic effects are thought to be mediated at least in part by direct effects of the HIV virus on cells in the brain, rather than immunosuppression and subsequent infection[2]. At its worst, HIV can cause encephalitis and HIV-associated dementia (HAD), the prevalence of which has decreased dramatically since the advent of antiretroviral therapy (ART). Although HAD is no longer common, milder forms of CNS dysfunction are seen frequently among HIV-infected patients, with prevalence approaching 40% in some studies[3-5].

HIV Associated Neurocognitive Dysfunction (HAND) can be divided into three categories based on severity[6]. HAD is the most severe form, and is characterized by scores greater than two standard deviations (SD) below the mean on neurocognitive tests in at least two cognitive areas, with marked difficulties in performing Activities of Daily Living (ADLs). Mild Neurocognitive Disorder (MND) is diagnosed if patients score between one and two SD below the mean in at least two cognitive areas with some impairment in ability to work or perform ADLs. Finally, a diagnosis of Asymptomatic Neurocognitive Impairment (ANI) can be given to patients with the same cognitive deficits as those with MND but without any clear functional impairment.

Given that neurocognitive impairment in people with HIV does not appear to be due to opportunistic infection, the risk factors for development of neurocognitive impairment are unclear. Many theories have been proposed to explain the prevalence of HAND in patients on ART, including persistent, toxic immune activation in the brain, lack of efficacy of ART in the CNS, neuro-toxicity of antiretroviral medications, and permanent residual damage from early viremia[1,7,8]. Multiple retrospective studies have demonstrated a correlation between CD4 nadir and HAND, even after people have started ART with recovery of CD4 count[3,4]. Ellis and colleagues did not find an upper threshold for CD4 nadir at which people with HIV were no longer at risk for HAND[3]. However, there have not been any prospective, long term studies investigating development of HAND in relation to CD4 count.

Another topic of significant debate is when to initiate ART. Increasingly, evidence suggests that earlier initiation of ART (i.e. at a higher CD4 count) decreases HIV-related morbidity and mortality while also decreasing rates of transmission. Current guidelines from the Department of Health and Human Services recommend ART initiation for all patients with CD4 counts <500 cells/mm^3 based on the results of randomized controlled trials and observational cohort studies (level of evidence AII). There is growing evidence that even earlier initiation of therapy and reduction in viremia could decrease the development of non-AIDS defining diseases, including neurologic complications of HIV, at the same time as new, more effective and better tolerated antiretroviral agents are becoming available[9]. Downsides to earlier ART initiation include increased drug-related complications, decreased adherence in asymptomatic patients, and increased development of drug resistant virus.

This goal of this study is to determine whether initiation of ART at the time of HIV diagnosis decreases neurocognitive dysfunction. Additionally, this prospective trial will allow tracking of development of HAND over time in HIV+ subjects over time, both on and off ART.

B. Study design and statistical analysis

This study is a randomized control trial comparing cognitive impairment in HIV+ people who are initiated on ART at diagnosis to people initiated on ART when their CD4 count is <500 cells/mm^3.

Patients newly diagnosed with HIV in the last two months, with CD4 count ≥650 cells/mm^3, and with neuropsychiatric test scores below the normalized mean will be randomized to an early initiation group or a delayed initiation group in a 1:1 ratio. Subjects in the early initiation group will start ART following initial routine blood tests, including viral resistance testing. CD4 counts in the subjects in the delayed group will be measured every three months, and ART will be initiated in these subjects after two consecutive CD4 counts ≤500 cells/mm^3. The study will be double-blind. An independent physician will determine the initial anti-retroviral regimen according to published guidelines and each subject's viral resistance profile. This physician will also receive the results of quarterly HIV RNA levels and will adjust antiretroviral regimens as needed to achieve viral suppression. Subjects in both the delayed and early treatment groups will receive monthly supplies of pills (either placebo or antiretroviral medication) and so will be blinded to both the identity of the medication and any adjustments in that medication.

The primary outcome of the study will be decline in score on neuropsychiatric testing between entry and the end of the study, three years after enrollment. Neuropsychiatric testing will be performed at randomization and annually thereafter on all subjects for a total of three years. Results of neuropsychiatric testing will be scored using normative data. We hypothesize that the change in neuropsychiatric test score from enrollment to three years will decrease by at least one standard deviation in the early ART initiation group compared to the delayed group. With 50 patients in each arm, we will have 80% power to detect a difference between groups of 57% of the standard deviation at $p<0.05$.

We will also plot the progression of neurocognitive dysfunction over time and calculate the rate of change for each subject. We will then be able to determine whether the rate of decline in neurocognitive function is slower for subjects in the early ART initiation arm compared to the delayed arm.

C. Study procedure

No procedures will be done.

D. Study drugs

Subjects will be given FDA-approved antiretroviral drugs. Recommended starting regimens are efavirenz/tenofovir/emtricitabine, ritonavir-bosted atazanavir plus tenofovir/emtricitabine, ritonavir-boosted darunavir + tenofovir/emtricitabine, and raltegravir + tenofovir/emtricitabine. Other acceptable regimes can also be used[9].

E. Medical Device

No medical devices will be used in this study.

F. Study questionnaires
No questionnaires will be used in this study.

G. Study Subjects

Inclusion criteria:

- CD4 count ≥650 cells/mm^3 at enrollment
- 18 years of age or older
- Caucasian or African-American

Exclusion criteria:

- Known neurologic disease, current diagnosis of major depression or current substance abuse, Hepatitis C
- History of an AIDS-defining illness
- Co-infection with Hepatitis B
- Pregnancy

H. Recruitment of subjects
Subjects will be recruited from CPMC inpatient and outpatient facilities at the time of HIV diagnosis.

I. Confidentiality of study data
Participants in this study will be given a unique identifier and all of their identifying information will be coded and safeguarded to protect confidentiality. Study data will be secured and will only be accessible to the investigators.

J. Potential conflict of interest
No conflict of interest

K. Location of study
The study will take place at Columbia Presbyterian Medical Center.

L. Potential Risks
Potential risks to study subjects are side effects due to antiretroviral medications, including nausea, diarrhea, abdominal discomfort, dyslipidemia, lipodystrophy, and elevations in liver function tests.

M. Potential benefits
Potential benefits to subjects include decreased likelihood of neurocognitive impairment and decreased overall HIV-related morbidity and mortality,

N. Alternative therapies
No experimental therapy will be used

O. Compensation to subjects
No compensation will be provided to subjects.

P. Costs to subjects
No additional costs to subjects.

Q. Minors as research subjects
None of the research subjects will be minors.

R. Radiation or radioactive substances
No radiation or radioactive substances involved in this study.

References

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