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Statins as Antiviral and Anti-inflammatory Therapy in HIV Infection

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Human immunodeficiency virus (HIV) infection is a disease associated with chronic inflammation and immune activation [1]. Antiretroviral therapy reduces inflammation, but not to levels in comparable HIV-negative individuals. Thus anti-inflammatory treatments might provide additional benefit and improve HIV outcomes [1]. One such treatment is the use of statins which have been suggested to have antiviral, anti-inflammatory and immunomodulatory effects but the significance of these effects in HIV infection remains ambiguous.

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors ("statins") have been found to inhibit several pro-inflammatory processes and suppress immune activation independent of their cholesterol-lowering effects [1]. They decrease pro-inflammatory cytokine levels and acute phase proteins [2,3], and also appear to have cellular immunological effects [4], and repress the activation of T lymphocytes [2,5,6].Statins are currently used in HIV-positive individuals to reduce the hyperlipidemia that is frequently induced by antiretroviral treatment [8]. The availability of generic formulations and the results of recent studies revealing a benefit to statin use in the primary prevention of coronary artery disease, a common complication in HIV-infected patients, make the continued study of statins as disease-modifying agents in HIV-infected individuals particularly attractive [2].

Statin compounds exhibit anti-inflammatory and antiviral effects in vitro [5,9-12]. Statins have been found in some, but not all, studies to inhibit HIV replication in vitro through an unclear mechanism [8,11,13,14]. In vitro models suggest that virions derived from cholesterol-depleted cells demonstrate reduced infectivity in vitro [9], and disruption of lipid rafts with cholesterol-depleting agents, such as statins, reduces HIV-1 particle production [9]. In addition, statins have demonstrated effects on protein prenylation and inhibit lymphocyte function antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1) interactions that influence viral entry and exit [9-12,15]. Conversely, statins may perturb the activation of immune cells and increase HIV transcription [10]. Nabatov et al. reported that statins disrupt CCR5 and RANTES expression levels in CD4+ T lymphocytes in vitro and preferentially decrease infection of R5 versus X4 HIV-1 [17]. Finally, statin-induced increase in intracellular Gag and decrease in virus release from chronically HIV-1 infected cells, and diminished geranylgeranylation may be principal mechanisms of statin-induced inhibition of virus release [14]. However, the effect of statins in chronically HIV-1-infected cells and its precise mechanism remain to be uncovered.

On the other hand, several groups have reported preliminary data on the failure of statins to control HIV replication *in vivo*(8;18;19) (1;20) and have yielded conflicting results (8;10;18;19;21). The only randomized trial to address this issue, however, found that atorvastatin therapy begun at the time of interruption of antiretroviral therapy did not affect the rate or magnitude of rebound HIV viremia [22]. In a recent study of HIV-infected adults not receiving antiretroviral therapy,atorvastatin had no effect on plasma HIV RNA load despite good adherence to therapy [1]. If additional observational data support the inhibitory effect of statins on HIV-1, further randomized clinical trials would be warranted to confirm this association.

Levels of T lymphocyte activation are associated with more rapid

progression of HIV disease in untreated adults [23]. Ganesan et al [1], also found that atorvastatin caused statistically significant reductions (2.5%–5.0%) in markers of immune activation (HLA-DR and CD38) on both CD4+ and CD8+ T lymphocytes which did not correlate with changes in LDL cholesterol levels [1]. Finally data from this study suggested that the effects on cellular activation are perhaps less dependent on the extent of cholesterol depletion, but rather depend on the nonlipid effect of statins [1]. However it is not clear whether the decreases in T lymphocyte activation observed among those subjects who received atorvastatin are clinically significant since the magnitude of change in these levels that is associated with clinically relevant differences in the rates of HIV disease progression is unknown.

Statin use was also associated with significantly lower hazard of dying in HIV-infected patients who were being effectively treated with antiretroviral therapy as determined by virologic suppression [24]. Even if statin use is clinically causing a reduced mortality, it could be due to reasons other than an effect on inflammation and immune activation. However, it is certainly possible that statins were used selectively in patients with a better survival prognosis and that there are unmeasured confounders that would explain the results of this study.

Most studies that have determined the effect of statins in HIV infection have several limitations. Levels of inflammatory serum proteins, such as C-reactive protein, were not measured in all studies. There have been differences in the types of antiretroviral regimens and differences in activity for specific statins between different studies. Most studies have not included a comparator arm, and were not designed to demonstrate clinical benefit and investigate both virologic and cellular immune activation outcomes. Moreover, the duration of statin exposure was relatively short, so it is not known whether the anti-inflammatory effects observed would be sustained with longer statin exposure. Finally, the ability to discern a difference in HIV-1 RNA level after treatment with a statin in these studies may have been limited by the small sample size, as well as the nonrandomized, open-label, and observational nature of most of these studies.

In conclusion, statins are lipid-lowering, anti-inflammatory, and potentially antiretroviral drugs and a logical therapy to assess for a possible salutary effect on HIV disease progression and outcomes. The ambiguity in the antiviral mechanism of statins and the lack of clinical studies specifically designed to evaluate their effects on HIVinfected patients impedes a correct evaluation of the potential benefits of this treatment. A very large study would probably be required to determine whether the potentially positive effects of statin therapy on inflammatory biomarkers will translate into less HIV disease

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progression and fewer cases of inflammatory non–AIDS-related illnesses, such as cardiovascular disease. Large studies with longer durations of follow-up that are designed to evaluate the potential effects of statins are needed to investigate any clinical benefit of this drug for HIV-infected patients [1].

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