

Commentary

Antioxidant therapy for AIDS

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HIV infection is characterized by many immunological, neurological and metabolic abnormalities. The intra and extra cellular redox balance also is severely disturbed in HIV-infected individuals. The tripeptide glutathione (GSH) is the main intracellular defense against oxidative stress and regulates the cellular redox potential. Other antioxidant systems, such as thioredoxin, vitamin C, vitamin E and coenzyme Q also contribute to the antioxidant protection mechanisms of cells. An impressive number of papers has demonstrated decreased GSH levels in blood, lymphocytes or lymphocyte subsets and other tissues in both pediatric and adult HIV-infected people [1–10].

GSH fulfills important roles in the cell; besides its role in maintaining the cellular redox balance, it is essential for synthesis of DNA precursors, reduces protein disulfides and protects the cell against deleterious influences of reactive oxygen intermediates (ROI). More specifically, essentially all aspects of lymphocyte function depend on sufficient levels of intracellular GSH (for references, see for instance [3]).

It seems therefore logical to try to restore GSH to adequate levels during HIV disease. This notion becomes even more attractive, when one takes into account that a wide variety of antioxidants, including GSH replenishing drugs have been shown to inhibit HIV replication *ex vivo* [11–13]. Among these compounds, N-acetylcysteine (NAC), sometimes in combination with vitamin C or E, has been the drug of choice. This is not surprising, given the known GSH replenishing properties, low cost and low toxicity of NAC.

Several groups have proposed GSH replacement therapy for HIV disease, and recently the first clinical studies have been completed [14–17]. Two sizeable clinical trials have also been completed recently [15,16], one of which is

published in this current issue of the *European Journal of Clinical Investigation* [16]. In addition, a small pilot study of high dose NAC in combination with vitamin C is also published in this issue [17].

During the latter study on 8 patients, the group of Muller *et al.* used a combination of NAC and vitamin C for 6 days [17]. The aim of the study was to investigate the effect of antioxidant treatment on several immunological parameters in HIV-infected individuals. Although obviously very small in design, this pilot study showed some remarkable results. The short-term treatment with antioxidants decreased HIV RNA in plasma and led to a remarkable 20–30% increase in CD4+ lymphocyte count. In addition, GSH levels were increased in CD4+ T cells and lymphocytes showed enhanced proliferation in a standard mitogenic stimulation assay.

The two other reports concern placebo-controlled, double-blind clinical trials performed by the two laboratories that originally reported on the importance of low GSH for the pathogenesis of AIDS [15,16]. The German group led by Wulf Droge reported their findings very recently in the *Journal of Molecular Medicine*, whereas de Rosa *et al.*, the American group, report their findings in this issue of *EJCI*. The American trial set out to discover if oral administration of NAC would restore GSH levels in T cells and whole blood of 61 HIV infected subjects (31 in the NAC-arm, 30 in the placebo arm) [16]. This was indeed the case, demonstrating that NAC is bio-available to replenish GSH in HIV-infected individuals. This conclusion differs from earlier reports where bioavailability was estimated to be low [18], however, because as NAC is a GSH prodrug, plasma NAC concentrations are of little relevance for assessment of bio availability. Because the relevant measurements were not done in this previous report, the two reports in this issue of *EJCI* [16,17] now settle this controversy and show that NAC is functionally bio available in HIV infected patients.

The American trial did not investigate virological or immunological parameters, but did look at 2–3 years survival, which increased dramatically in patients who took NAC. In contrast, the German trial investigated several metabolic and immunological parameters, without investigating GSH levels in blood or T cells [15]. This trial

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separated patients on receipt of antiretroviral therapy (ART). Thirty-two patients receiving ART and 20 without ART were analysed in this trial. NK cell lytic activity and T cell function (proliferation upon mitogenic stimulation and responses against tetanus toxin) were dramatically increased in patients receiving NAC. In contrast to the pilot study from Muller *et al.* this study did not see significant changes in viral load (plasma RNA). This improvement in immunological function is most likely due to replenishment of GSH as GSH depletion significantly inhibits T and NK cell function. The differences in viral load outcome probably reflect differences in dosage, as in the pilot study very high doses, initially given IV, were used.

Several other reports on clinical use of NAC for HIV disease have been published [14,19–21]. In these studies fairly low doses of NAC and/or short periods of treatment were used; nevertheless most of these studies have also been promising, although some failed to detect any effects. Of note in this context is the study by Akerlund *et al.* as it is another placebo-controlled double-blind trial where NAC was used during HIV infection [14]. Although GSH levels were not determined, this study showed increased cysteine levels after NAC treatment. As the plasma cysteine supply is a rate-limiting step in GSH synthesis, this finding is consistent with the increased GSH levels reported by De Rosa *et al.* [16].

In conclusion, several reports have now provided evidence that therapy with NAC alone or in combination with other antioxidants restores GSH levels and improves immune function in HIV-infected individuals. Some of the beneficial effects of this treatment may also be caused by alleviating wasting and improving liver function. A large clinical trial of NAC for treatment of HIV disease, measuring metabolic, immunological and viral parameters is thus in place.

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