SYSTEMATIC REVIEW OF COMBINATION ANTIRETROVIRAL THERAPY WITH DIDANOSINE PLUS HYDROXYUREA: A PARTIAL SOLUTION TO AFRICA'S HIV/AIDS PROBLEM?

We do not agree with the conclusion of Sanne and colleagues that didanosine and hydroxyurea is a safe, effective, and economically relevant alternative to existing antiretroviral regimens for poor-resource patient populations.[1]

So far randomized clinical trials have not been able to demonstrate a clear benefit from hydroxyurea-containing regimens. Hydroxyurea reduces the viral load, but it is unclear whether this parameter is a good surrogate marker for evaluating the efficacy of this drug. Hydroxyurea may be harmful because it is cytostatic and reduces the CD4+ lymphocyte count.[2] Moreover, it increases the toxicity of didanosine, leading to a higher incidence of peripheral neuropathy and pancreatitis.[3,4] It certainly should not be used in pregnant women or women at risk of becoming pregnant. One randomized trial (the AIDS Clinical Trial Group [ACTG] 65025 study) was prematurely stopped because of high rates of drug toxicity in the hydroxyurea arm. Among 68 patients randomized to the hydroxyurea arm, three deaths related to complications of pancreatitis were reported.[5] For these reasons we believe it is premature to recommend the use of hydroxyurea in daily clinical practice, even in countries with poor resources. However, we agree that additional randomized trials using hydroxyurea are needed to define the potential role of this drug in the treatment of human immunodeficiency virus (HIV). Such trials should include a sufficiently large number of participants who are followed for long enough to detect a significant difference in clinical outcome. Recently the prices of antiretrovirals have dropped sharply, and highly active antiretroviral treatment (HAART) regimens have been offered at U.S. $1 to $2 a day.[6] Such treatment regimens are known to be highly efficacious; therefore, new alternative treatment strategies should be compared with classic HAART regimens in clinical trials before proposing their use on the basis of economic arguments alone.

R. Colebunders, MD, PhD
E. Florence, MD
Institute of Tropical Medicine
Antwerp, Belgium
B. Ostyn, MD
University Hospital,
Antwerp, Belgium

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RESPONSE

In the context of human immunodeficiency virus (HIV) infection, some treatment is better than no treatment. Whereas we agree with some points raised by Colebunders and colleagues regarding the use of didanosine (ddI)-hydroxyurea for HIV infection, we believe that in poor countries of the world this drug combination has provided, and continues to offer a useful alternative to other antiretroviral regimens. In several independent studies hydroxyurea has been shown to inhibit HIV-1 DNA synthesis in infected quiescent and activated primary human lymphocytes and macrophages, by stimulating the immune system and increasing the percentage of naive cells and the percentage of cells capable of responding to antigen.[1] In combination with a reverse transcriptase inhibitor with or without a protease inhibitor, HIV suppression may occur as efficiently as with standard highly active antiretroviral therapies (HAART). In addition to its consistent short-term reduction on HIV-1 RNA levels, the long-term safety and antiretroviral activity of ddI-hydroxyurea have been documented for periods up to 25 months without evidence of viral rebound.[2] Didanosine-resistant HIV-1 mutants retain sensitivity to ddI in the presence of hydroxyurea. Furthermore, by exerting a cytostatic effect on CD4+ and CD8+ T lymphocytes, hydroxyurea may actually reduce HIV-1 replication by decreasing CD4+ T-cell proliferation and preventing the