Several studies have shown that the prevalence of anaemia is high in patients with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS). Anaemia in HIV infection is associated with uniformly adverse outcomes such as opportunistic infections and neurologic deterioration and progression to AIDS. Anaemia is associated with several other consequences including fatigue, poor quality of life and increased requirement for erythropoietin therapy. Several observational studies have also reported a higher mortality in HIV infected patients from low haemoglobin levels even after adjusting for CD4 cell count and viral load. The aetiology of anaemia in HIV infection is multifactorial and typically the anaemia results from underproduction of red blood cells and frequently the laboratory features are compatible with anaemia of chronic disease with a low reticulocyte count, normocytic and normochromic red blood cells with normal iron stores and cytokine mediated poor erythropoietin response. The use of highly active antiretroviral therapy (HAART) is associated with an increase in haemoglobin concentrations and a decrease in the prevalence of anaemia. Amelioration of HIV-related anaemia with HAART has several benefits including improvements in functional status, energy levels and fatigue and overall improvement in quality of life.

Combination antiretroviral (ARV) therapy is the current standard of care for treating patients with HIV/AIDS. Use of HAART has remained the only regimen potent enough to decrease viral replication in patients with HIV/AIDS and its use has been shown to reduce anaemia by inhibiting acceleration of the disease. In resource-limited settings, combination chemotherapy consisting of 2 nucleoside analogues (reverse transcriptase inhibitors) [either zidovudine (AZT) or stavudine (d4T) along with lamivudine (3TC)] and 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) [either nevirapine (NVP) or efavirenz (EFV)] are frequently used. AZT, a nucleoside reverse transcriptase inhibitor (NRTI) is one of the earliest antiretroviral agents used as a combination in some of the HAART regimens for the treatment of HIV/AIDS, and it was the first drug which was approved by the US FDA for use in HIV/AIDS. In most of the instances, when the haemoglobin level is >8g/dl, AZT is used in the first-line drug combination as stavudine is more frequently associated with mitochondrial toxicity. Its use, however, is associated with haematological toxicity particularly bone marrow aplasia leading to varying degrees of cytopenias especially anaemia in some patients. The mechanism of this anaemia is attributed to 50-70 per cent inhibition of proliferation of blood cell progenitor cells in a time-and dose-dependent fashion. Further, laboratory studies have also shown that zidovudine exhibits cytotoxicity to the myeloid and erythroid precursors in the bone marrow at drug concentrations close to those associated with the optimal antiviral effect in vitro. This haematological toxicity is observed in most of the patients within 3-6 months and is reversible. Female gender has been found to be a risk factor for anaemia in some studies. This adverse effect of anaemia from AZT limits its use in some patients. Zidovudine has also been reported to produce pure red cell aplasia (PRCA) with a selective depletion of red blood cell line and this adverse event is also reversible. Therefore, patients who are started on AZT combination regimen for HIV/AIDS treatment, should be closely monitored during follow up for development of bone marrow toxicity. Co-trimoxazole preventive therapy has been recommended along with HAART especially in those with HIV-TB to decrease incidence of serious opportunistic infections. The impact of co-trimoxazole on haematological
cytotoxicity when it is used concurrently with AZT, should be systematically evaluated in future studies.

In this issue, Agarwal et al.\textsuperscript{15} in their retrospective study report a high incidence of ZDV-induced anaemia in HIV infected patients from eastern part of India. Zidovudine was initiated in 1256 of 2941 (42.7\%) patients between March 2005 to December 2007. Measurement of haemoglobin was done regularly in these patients. Patients were carefully excluded if they had gastrointestinal diseases, iron deficiency or vitamin B\textsubscript{12} deficiency anaemia; 203 patients (16.2\%) developed anaemia (haemoglobin <8g/dl) and 100 (7.9\%) of these had haemoglobin < 6.5g/dl. In majority of patients (94.4\%), ZDV induced anaemia occurred within 6 months of initiation of therapy and the peripheral smear showed normocytic, normochromic anaemia in almost half of the patients and in the remaining it showed macrocytic changes. Bone marrow was done only in 27 patients and was normocellular in 18 patients. Dysplastic changes were seen in myeloid (30\%) and erythroid cell lines (28\%).

Though it is a good attempt on the part of authors, the study suffers from all drawbacks such as confounding and bias of a retrospective study. This study reveals a very high incidence of anaemia supposedly related to zidovudine as haemoglobin levels rose after stopping zidovudine. Another retrospective south Indian study\textsuperscript{16} has reported a relatively lower incidence (5.4\%) of anaemia due to AZT. How do we explain these different results? These differences can be attributed to different study designs, use of different methodologies including inclusion and exclusion criteria and different cut-offs used to define anaemia.

Ideally, a very systematic, prospective, cohort study with application of stringent inclusion and exclusion criteria should be planned to find out the exact incidence of anaemia due to zidovudine. Preferably, it should be a multicenter study with adequate clinical supervision and appropriate monitoring provisions for laboratory quality control. Nutritional anaemia, multiple worm infestations which are rampantely prevalent in India should be carefully ruled out. Patients with microscopic and macroscopic blood losses, those using aspirin and other non-steroidal anti-inflammatory drugs require careful exclusion. Bone marrow examination should be done in those who develop haematological toxicity. In addition to clinical follow up, a regular monitoring of CD4 cell count and viral load for demonstrating treatment failure is essential as disease progression itself is associated with the development of anaemia.

In the meantime, what should be the strategies to deal with this type of problem in resource-limited settings? First, AZT is not too expensive and is affordable to be used in the first-line combination drugs by most resource constrained nations as a public health approach. Therefore, one can continue with the current guidelines to use it in those patients who have haemoglobin level >8g/dl and these patients should have a detailed haematological work-up at baseline and close monitoring of haematological profile during follow up, and change to other nucleoside analogue such as tenofovir or emtricitabine in case haemoglobin level falls below 8 g/dl. Second, AZT should not be used as the first-line drug and instead use d4T as the first drug and use AZT as a switch therapy after sometime and while on AZT patients should be carefully and closely monitored. While doing so one has to keep in mind the current World Health Organization Guidelines (2009) to phase out the use of d4T in combination therapy because of mitochondrial toxicity\textsuperscript{17}. Third, the use of tenofovir (TDF) or emtricitabine (FTC) as the first-line drug in combination therapy should be considered if country programmes for HIV/AIDS have enough budget to afford the cost on a long-term basis.

In conclusion, we should first try to determine the exact magnitude and predictors of AZT-induced anaemia in HIV/AIDS patients in properly planned and well-conducted prospective studies. Meanwhile, we should continue to use AZT in the first-line combination therapy in HIV/AIDS patients with haemoglobin levels >8g/dl as a public health approach since the drug is cheaper and should do a continuous surveillance for development of haematological toxicity.

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