AIDS brief

AZT associated with poorer immunological recovery in people taking first-line HIV treatment in southern Africa

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AZT-based antiretroviral therapy is associated with lower increases in CD4 cell counts than other HIV treatment regimens, according to a study published in the online edition of *AIDS*.

Investigators analysed immunological outcomes in over 72 000 people starting first-line treatment in southern Africa. People taking AZT (zidovudine, Retrovir and various generic versions) had significantly lower increases in CD4 cell counts 1 year and 5 years after initiating therapy, and were also more likely to remain severely immunosuppressed than individuals taking an alternative drug.

World Health Organization (WHO) guidelines for first-line antiretroviral therapy in resource-limited settings recommend that treatment should be based on nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbones of AZT and 3TC (lamivudine, Epivir), or tenofovir (Viread) and 3TC.

It is well known that AZT is associated with an increased risk of a range of long-term side-effects, especially anaemia. Some studies have also shown that people treated with AZT have smaller increases in CD4 cell count compared with individuals taking alternative NRTIs. However, these studies were small and had short duration of follow-up.

Viral load monitoring is not routinely available in many resource-poor countries. This means that decisions regarding switching to second-line HIV treatment regimens are made after considering clinical symptoms and immunological data.

If AZT is associated with an impaired CD4 cell count, it could mean that some people are changing their treatment unnecessarily.

An international team of investigators therefore examined changes in the CD4 cell counts of 72 500 people starting first-line HIV therapy in Botswana, Lesotho, South Africa and Zambia. They compared immunological restoration 1 year and 5 years after the initiation of treatment between individuals treated with AZT and those taking an alternative NRTI. The association between AZT therapy and the persistence of severe immune suppression (a CD4 cell count below 100 cells/mm^3) after 1 year of treatment was also explored.

'Our study is unique regarding its size and length of follow-up,' comment the investigators. 'It involved a large number of patients from a wide range of settings in southern Africa and described immunological recovery over 5 years after the initiation of ART.'

Just over a quarter (27%) of people started treatment that included AZT. The median baseline CD4 cell count was 134 cells/mm^3; median baseline haemoglobin was 11.3 g/dl; 60% of participants were female; and the median age was 36 years.

There were significant baseline differences between the AZT-treated individuals and those taking alternative drugs. Participants taking AZT had higher baseline CD4 cell counts (150 v. 128 cells/mm^3, $p<0.001$) and higher baseline haemoglobin (12 v. 11 g/dl, $p<0.001$) and were less likely to be female (52 v. 63%, $p<0.001$). Approximately a third of participants starting treatment with AZT received virological monitoring during follow-up, compared with 39% taking an alternative drug ($p<0.001$).

Total follow-up time was 35 000 and 68 400 person-years for the AZT and non-AZT groups, respectively.

For most of the first year of treatment, CD4 cell gains were similar between the 2 groups.

Differences soon emerged. After 1 year and 5 years of therapy, participants on AZT had estimated CD4 cell counts of 301 cells/mm^3 and 386 cells/mm^3, while those not taking AZT had counts at these time points of 317 cells/mm^3 and 442 cells/mm^3.

The difference between the treatment groups was most pronounced for participants who started therapy when their CD4 cell count was below 100 cells/mm^3, with participants taking AZT having a count that was 66 cells/mm^3 lower after 5 years compared with individuals taking an alternative NRTI.

Viral load monitoring was available in Botswana and South Africa. This showed that 39% of people taking AZT and 20% of non-AZT participants had at least one detectable viral load result ($p<0.001$).

Among people with a fully suppressed viral load, the CD4 cell counts of AZT- and non-AZT-treated individuals were similar after 1 year of treatment. However, by year 5 there was a difference of 21 cells/mm^3 favouring non-AZT drugs.

A total of 14 529 people started therapy with a CD4 cell count below 100 cells/mm^3. After 1 year of treatment, 11% of participants taking AZT, compared with 8% of those taking an alternative drug, still had a CD4 cell count below this level ($p<0.001$). In adjusted analysis, the investigators showed that people treated with AZT were significantly more likely to experience severe impairment of immunological recovery than individuals taking other first-line drugs (aOR = 1.40; 95% CI 1.22 - 1.61).

'The reasons for the association of AZT with poor immunological recovery are poorly understood,' note the authors. 'The most likely explanation is related to the well-known bone marrow suppression caused by AZT.'

They believe their results are significant for two reasons. First, poor immunological recovery is associated with an increased risk of serious illness and death. Second, 'a CD4 cell count persistently below 100 cells/mm^3 is one of the criteria used to diagnose immunological failure … many patients who remain under this threshold during ART are switched to a PI-based regimen, despite possible virological efficacy of the first-line regimen.'

Wandeler G, et al. AZT impairs immunological recovery of first-line ART: Collaborative analysis of cohort studies in Southern Africa. AIDS 2013;27, online edition. [http://dx.doi.org/10.1097/QAD.0b013e328362d887]

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