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Starting treatment at higher CD4 cell counts reduces risk of peripheral neuropathy, anaemia and kidney disease

Michael Carter, Thursday, January 10, 2008

Starting antiretroviral therapy with a CD4 cell count above 200 cells/mm³ reduces the risk of peripheral neuropathy, anaemia and kidney problems developing, according to a large US study published in the January 1st edition of the *Journal of Acquired Immune Deficiency Syndromes*.

These three conditions were selected by the investigators because they can be both symptoms of advanced HIV disease and side-effects of antiretroviral therapy. There is increasing evidence that initiating anti-HIV treatment at higher CD4 cell counts (350 cells/mm³) can reduce the risk of serious illnesses such as heart, liver and kidney disease and this was one of the reasons why US and European HIV treatment guidelines were recently changed to recommend that anti-HIV treatment be started in patients with a CD4 cell count of 350 cells/mm³.

Some doctors think that there could be advantages to starting treatment at even higher CD4 cell counts (500 cells/mm³). The current study found some evidence to support this strategy as patients who initiated therapy when their CD4 cell count was above 350 cells/mm³ did not have an elevated risk of developing peripheral neuropathy, anaemia or kidney disease compared with untreated people, suggesting that treatment is not increasing the risk of serious adverse events in this group of patients.

The benefits of antiretroviral therapy are now well known, with study after study showing significant and sustained falls in HIV-related illness and death since the introduction of potent anti-HIV therapy in the mid-1990s. But anti-HIV therapy can cause long-term side-effects. Some research has even suggested that such side-effects now cause more illness in HIV-positive patients than HIV-related disease.

Treatment guidelines currently recommend that anti-HIV treatment should be started when an individual's CD4 cell count is in the region of 350 cells/mm³. But there is some good evidence that starting therapy with a CD4 cell count of 500 cells/mm³ leads to a small, but nevertheless significant, reduction in the risk of HIV-related illness and death. But treatment at such a high CD4 cell count isn't currently recommended, not least because there are still concerns about the long-term toxicities of anti-HIV therapy.

Investigators therefore conducted a prospective unrandomised study involving over 2,000 patients starting anti-HIV therapy to see if starting anti-HIV therapy at higher CD4 cell counts was associated with a risk of peripheral neuropathy, anaemia and kidney disease.

The patients, 80% of whom were male and 60% white, came from the HIV Outpatient Study (HOPS) cohort and were followed for a mean of three years.

A low CD4 cell count was consistently associated with an increased risk of the three health problems being examined.

In the investigators' initial 'univariate' analysis the factors associated with peripheral neuropathy were a baseline viral load above 35,000 copies/ml; a baseline CD4 cell count below 200 cells/mm³, and older age.

Factors associated with anaemia were female gender, black race, a baseline CD4 cell count below 200

cells/mm³ and haemoglobin below 14.4g/dl.

And the factors associated with new kidney problems were older age, black and Hispanic race, a baseline CD4 cell count below 200 cells/mm³ and baseline creatinine clearance below 108.9ml/min.

Incidence rates for each of the health problems being examined were also consistently higher amongst patients who started anti-HIV therapy with a CD4 cell count below 200 cells/mm³ than in patients who initiated treatment when their CD4 cell counts were in the 200 – 349 cells/mm³ and the 350 cells/mm³ and above strata.

The investigators also found that the incidence rates of these health problems were highest in the first six months of follow-up after the initiation of antiretroviral treatment.

Although treatment with d4T and ddI were associated with peripheral neuropathy and AZT with anaemia, the investigators found that even if a patient received therapy with these drugs, their risk of developing such conditions was much lower if they started treatment at a higher CD4 cell count.

In multivariate analysis, factors significantly associated with peripheral neuropathy were older baseline age (each ten year increment, $p < 0.001$), use of d4T and ddI (both $p < 0.001$) and a CD4 cell count below 200 cells/mm³ ($p < 0.001$).

Multivariate analysis also showed that a CD4 cell count below 200 cells/mm³ was a risk factor for anaemia ($p = 0.03$), as was the use of AZT ($p = 0.017$), low baseline haemoglobin ($p < 0.001$) and female gender ($p = 0.017$).

And the risk factors for incident kidney disease were, once again, a baseline CD4 cell count below 200 cells/mm³ ($p < 0.001$), increasing age ($p = 0.003$), female gender ($p = 0.025$), non-white race ($p = 0.01$), and poor creatinine clearance at baseline ($p < 0.001$).

To better understand the role of CD4 cell count in the development of these health problems, the investigators performed another set of analyses that controlled for the other significant predictors. This showed patients with a baseline CD4 cell count below 200 cells/mm³ (compared to patients to those with a baseline CD4 cell count between 200 and 349 cells/mm³) were a statistically significant 54% more likely to develop peripheral neuropathy ($p < 0.001$), 68% more likely to develop anaemia ($p = 0.03$) and 122% more likely to develop kidney disease ($p < 0.001$).

Finally, the investigators looked at the incidence of these health problems in a cohort of 895 patients. These patients were stratified by baseline CD4 cell count (201 – 350 cells/mm³; 351 – 500 cells/mm³ and 501 – 700 cells/mm³) and the incidence of the health problems was compared by CD4 cell strata and according to whether or not a patient started anti-HIV therapy.

The incidence of all three health problems was lower in patients with higher CD4 cell counts. Furthermore, the health problems occurred less frequently for patients who initiated anti-HIV treatment in all CD4 strata (with the exception of anaemia in the 201 – 350 cells/mm³ stratum). However, none of the differences was statistically significant.

“Our data demonstrate that initiating effective antiretroviral therapy at a CD4 cell count above 200 cells/mm³ ameliorates the risk of three important adverse conditions associated with HIV infection and frequently attributed to toxicity-related side effects of antiretrovirals and that there was no increased risk for these conditions when treatment was initiated at CD4 cell counts above 350 cells/mm³”, comment the investigators.

Because of small numbers the investigators were unable to say if the patients who started anti-HIV therapy with a CD4 cell count of 500 cells/mm³ or above had any additional protection against these important illnesses. Nevertheless they conclude, “considered together with the evidence of decreased mortality and slower progression to AIDS among patients initiating therapy at progressively higher CD4 cell counts, our findings may be particularly relevant as recommendations to defer treatment in patients with CD4 cell counts above 350 cells/mm³ are reviewed and considered.”

Reference

Lichtenstein KA et al. *Initiation of antiretroviral therapy at CD4 cell counts \geq 350 cells/mm³ does not increase incidence or risk of peripheral neuropathy, anemia, or renal insufficiency.* J Acquir Immune Defic Syndr 47: 27 – 35, 2008.

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