HIV, antiretrovirals and aging

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Created *2011/07/01 - 4:27pm*
1 July, 2011 - 16:27 ? moderator

People with HIV on antiretroviral treatment or at the point where antiretroviral treatment is recommended need not be alarmed by a study that received wide media coverage this week. Antiretrovirals save lives. Their benefits far outweigh their risks.

On Sunday 26 June scientists from Newcastle University in the UK issued a press statement explaining that they had found evidence that a class of antiretroviral (ARVs) called nucleoside reverse transcriptase inhibitors (NRTIs) could theoretically contribute to accelerated aging in people with HIV. Their paper was published in the prestigious scientific journal, Nature Genetics. The press statement was picked up by the SABC and was the top item on radio news on Sunday evening. It has subsequently received wide media coverage in South Africa and elsewhere.

We are concerned that this report has caused unnecessary anxiety in people with HIV who are taking ARVs or will soon be starting ARV treatment. NRTIs are a crucial part of ARV treatment regimens across the world, in both rich and poor countries.

The term *accelerated aging* refers to evidence that people with HIV may have higher rates of non-AIDS illnesses, such as heart disease, dementia, bone fractures and certain cancers than HIV-negative people of the same age.

The study examined 33 people with HIV under 50 and compared them to 10 HIV-negative people who were slightly younger on average. It found that people on NRTIs had a higher frequency of genetic mutations in their mitochondrial DNA of a type known to accumulate during normal aging in HIV negative people.1 The study does not show that NRTIs caused these mutations, but rather that in some study participants, use of the drugs was associated with an increase in their frequency above what would be expected among HIV negative people of similar age.

It is suspected by some scientists that the increased frequency of mutations in mitochondrial DNA that occurs as people get older plays a causative role in aging, but others believe they are a consequence of aging. As the Nature Genetics paper states: ?it is still not clear whether the DNA mutations are a cause or a consequence of aging in humans.?

The study was very small and did not compare health outcomes between the study volunteers. A study like this cannot exclude the possibility that factors unrelated to HIV or ARVs were responsible for its findings.
People with HIV and their carers should be aware of the following:

- The association between NRTIs and mitochondrial DNA mutations found in this study have been known since at least 1998.2 This study provides a small piece of evidence in an ongoing complex scientific discussion.
- HIV itself causes damage to mitochondrial DNA.3
- Nothing in this study contradicts the fact that the benefits of ARVs far outweigh their risks.
- If you live with HIV and your CD4 count is below 350 cells/mm3, delaying ARV treatment will almost invariably leads to an array of illnesses and ultimately death. However, by starting ARV treatment you are very likely to restore your health so that you are able to lead a full life with almost normal life-expectancy.
- Studies show that people who have had a CD4 count below 200 cells/mm3 are more likely to have signs of

accelerated aging than people who have started treatment before reaching this point.[4]

- The optimal CD4 count at which to start ARV treatment is not yet known, but there is clear evidence from clinical trials and observational studies that it is at least 350 cells/mm3. There is emerging evidence from observational data that starting ARV treatment with a CD4 count greater than 500 cells/mm3 is beneficial, but this is unclear and will have to be determined by clinical trials. Two clinical trials, START and TEMPRANO, are looking at this and will report results in the next two to four years.[5]
- There is clear evidence from the HPTN 052 trial that if you are on ARV treatment at any CD4 count below 550 cells/mm3, you will be less likely to infect your sexual partners.
- ARVs, like all effective chronic medicines, have short and long-term side-effects. Accelerated aging is a concern for people with HIV and is a research priority. However, the extent to which HIV infection or ARV treatment is a cause of accelerated aging is an unresolved scientific question. If you are on ARV treatment it does not mean you are likely to age prematurely. If you are showing signs of accelerated aging, there are often medical interventions that can improve your quality of life.
- To the extent that ARVs may be associated with accelerated aging, the Nature Genetics study indicates that this would be more likely to happen in people with complicated treatment histories. This is often associated with starting ART at a very late stage of HIV infection or having to switch regimens frequently because of side effects.
- There are no implications for ARV guidelines for any country that follow from the Nature Genetics study.

In a statement below, we consider the Nature Genetics study in more detail.

[END OF MAIN STATEMENT]

Mitochondrial aging and NRTIs: a technical note

The study by Payne *et al.* examined 21 patients with a history of ART, 11 patients with HIV but who were still ART-naive and ten age-matched HIV-negative controls.[6] Skeletal muscle was extracted from each of the subjects and examined for genetic mutations.

The study found that in the subjects with a history of ART, particularly NRTI use, there was a statistically significantly greater amount of mutated mitochondrial DNA than in the HIV-negative controls or ART-naive HIV-positive subjects. There was no difference between the latter two groups.

Eleven of the 21 patients on NRTI-containing ART had no signs of excess mutations over what would be expected among HIV-negative individuals of similar age (0.5% or less), including six subjects who had been on treatment for over five years (in one case, 10.5 years). Several more had very minor proportion of mutations. The ?up to 10%? figure cited in the study abstract is derived from one 45-year old individual with an extensive treatment history and more than 13 years since diagnosis who showed evidence of mutations in 9.8% of muscle cells. The authors noted health problems in four of the people on ART. Most of the contribution to the statistically significant result came from three patients with long and complicated treatment histories, i.e. many ARV switches over many years.

The study was not set up in a way to examine the link between these mutations and clinical signs of aging so the relevance of these findings to clinical aging is unclear.

The finding that NRTIs are responsible for mitochondrial mutations is not new. In a 1998 paper in the journal *AIDS*, titled *Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway*, the authors state:

More than 10 years of experience with NRTI therapy has revealed important adverse effects ranging from mild (myopathy) to fatal in some cases (pancreatitis, liver failure and lactic acidosis). Behind most of these side-effects there appears to be a common mechanism: a decreased mitochondrial energy-generating capacity ? didanosine (ddI), zalcitabine (ddC), lamivudine (3TC), stavudine (D4T), and recently abacavir.....A special feature of some of these

brain barrier. ? Altogether, mtDNA appears to be extremely vulnerable to genetically and exogeneously acquired mutations. Since DNA polymerase ? appears to be the only regulating enzyme of mtDNA replication, inhibition of this enzyme with RTI might easily downregulate this replication resulting in decreased mitochondrial energy generation.

However, HIV itself causes damage to the mitochondria. This is from *Changes in Mitochondrial DNA as a Marker of Nucleoside Toxicity in HIV-Infected Patients* published in the New England Journal of Medicine in 2002:

Mitochondrial DNA:nDNA ratios were significantly lower in HIV-infected, asymptomatic patients who had never received antiretroviral therapy than in non?HIV-infected controls (P<0.001), a difference that was not explained by the lower CD4 counts in the former group. This finding is consistent with the results of recent in vitro studies in which HIV-infected cells had signs of mitochondrial necrosis. Furthermore, a mitochondria-controlled mechanism of cell death has been postulated in HIV infection.

The importance of mitochondrial DNA mutations in aging is also controversial. Many scientists believe that aging is normally due to damage to the cell's DNA, particularly telomeres. Telomeres are repetitive sequences of DNA at the end of the chromosomes. They signal to the cell reproduction process that copying should stop, else the chromosome will be merged with neighbouring chromosomes. Each time a cell replicates, the telomeres are shortened, eventually leading to them being so short that the cell cannot reproduce properly. There is evidence that both HIV and NRTIs shorten telomeres in some cells.

In conclusion, while the effects of NRTIs on mitochondrial DNA are concerning, we still know very little about the clinical consequences of this or how pervasive or serious a problem it is.

Thank you to Richard Jefferys, Simon Collins, Gregg Gonsalves, Nick Bennett and Ken Witwer for assistance with this article. TAC takes full responsibility for its contents.

Footnotes

1Mitochondria are the energy factories of cells. Their DNA is quite interesting in that it is separate from the DNA of the cell that generates each unique human being. In other words mitochondria reproduce using their own DNA, not the DNA that reproduces our cells. This is because over a billion years ago they were a separate organism that evolved to form a mutually beneficial relationship with the cells found in all complex animals and plants. We inherit our mitochondria from our mothers.

2See http://www.ncbi.nlm.nih.gov/pubmed/9792373.

3See http://www.nejm.org/doi/full/10.1056/NEJMoa012035.

4See http://www.ncbi.nlm.nih.gov/pubmed/21443771 and http://www.ncbi.nlm.nih.gov/pubmed/21628488 for examples.

5See http://dl.dropbox.com/u/193052/PrimaryDocuments/IndividualArticles/WhenToStart-TalkForSAAIDSConference2011-notes.pdf

6Nature Genetics, doi:10.1038/ng.863, published online 26 June, 2011. ☒
http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.863.html

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