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# Low level detectable viral load while taking HIV treatment is associated with poorer medical outcomes

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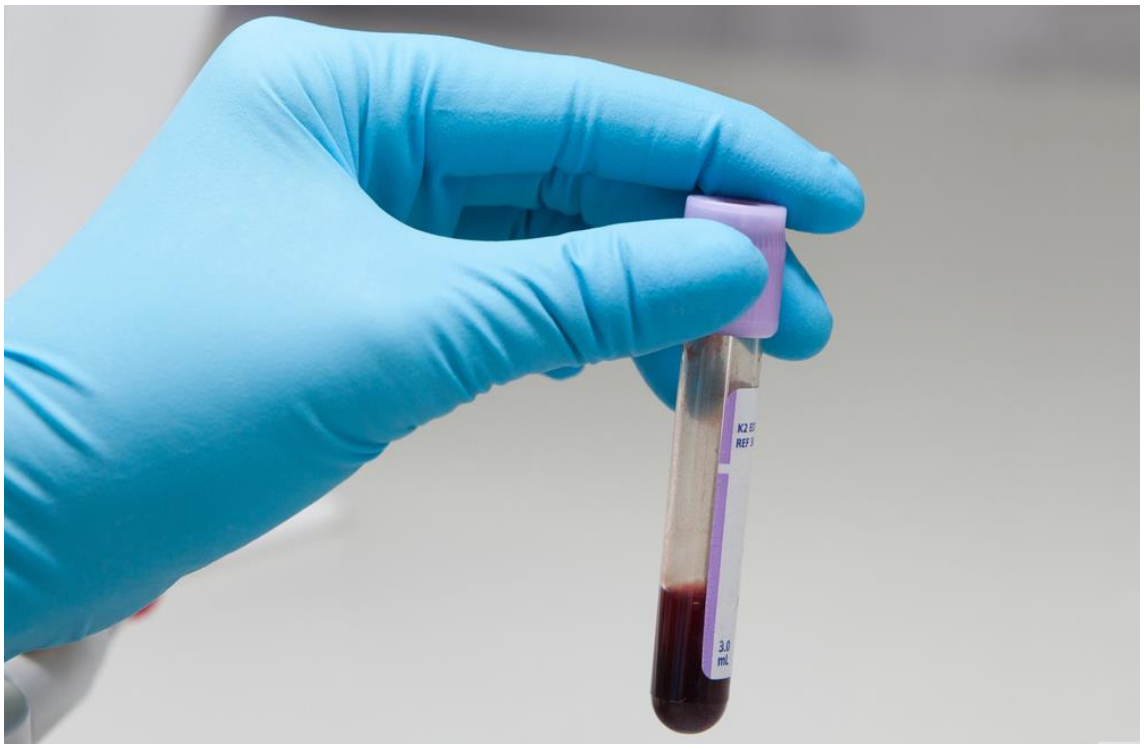

New research has underlined the importance of having an undetectable viral load while taking antiretroviral therapy (ART). Published in *Clinical Infectious Diseases*, the study showed that individuals with a persistent low-level viral load (50-999) had a higher risk of all-cause mortality compared to people with viral suppression (a viral load below 50). They also had more serious illnesses such as heart disease and some cancers.

The research involved a retrospective analysis of the medical records of approximately 7000 individuals who received ART in Sweden between 1996 and 2017. A team of researchers, led by Dr Olof Elvstam of Lund University, Malmo, compared the risk of mortality, developing an AIDS-defining illness or a serious non-AIDS-related event (such as heart, liver, and kidney disease) according to according to viral suppression.

“Low level viraemia 50-999 copies/ml during combination ART was independently associated with increased all-cause mortality,” write Dr Elvastram and colleagues. “Furthermore, persons with low level viraemia in the higher stratum (200-999 copies/ml) had a higher risk of serious non-AIDS events, whereas low level viraemia was not linked to AIDS-defining conditions.”

## Glossary

viraemia

virological suppression

AIDS defining condition

cardiovascular

detectable viral load

Improvements in treatment and care mean that many people living with HIV now have an excellent prognosis. HIV-positive people who are treated with ART can have a life expectancy that is close to that observed in the general population. Nevertheless, overall mortality rates remain higher, with many of the excess mortality risk due to serious non-HIV-related diseases.

The goal of ART is suppression of viral load to undetectable levels – often defined as below 50 copies/ml. However, up to 10% of people taking ART have a persistent viral load above the threshold of detection. A viral load over 1000 while taking ART has an established association with poorer outcomes, including elevated mortality rates.

However, the association between a persistent low-level viral load (or low-level viraemia) and the risk of developing serious illnesses or death is less clear. To get a clear understanding of this question, Dr Elvastram and colleagues carried out an analysis of the medical records of 6956 individuals treated with ART in Sweden between 1996 (when potent combination ART first became available) and 2017.

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These individuals were placed into one of three categories according to their viral load:

- persistent viral suppression below 50;
- low-level viral load (50-999) in two or more consecutive tests;
- persistent detectable viral load of 1000 or above.

In some analyses, individuals with low-level viral load were sub-divided according to whether their viral load was between 50 and 199 or between 200 and 999. This was because guidelines for ART in some richer countries now set a viral load of 200 as a benchmark for virological failure of ART, whereas World Health Organization guidelines for resource-limited countries use a threshold of 1000.

The main aims of the study was to compare the risk of death from any cause (all-cause mortality) between individuals with an undetectable viral load and those with a low-level viral load, and also to determine if a low viral load was associated with the development of AIDS or another serious such as cardiovascular disease, stroke, cancer, liver disease or kidney failure. The results were adjusted to take into account factors such as age, sex and CD4 cell count and viral load before starting ART.

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Most of the study sample was male (63%) and born outside Sweden (60%), while the median age when starting ART was 37 years.

During follow-up, 14% had two consecutive low-level viral load results at some point (evenly distributed between the 50-199 and 200-999 groups). At the end of follow-up, 60% had viral suppression, 9% had low-level viral load (5% in the 50-199 group; 4% 200-999 category) and 31% were not virally suppressed.

The median duration of follow-up was 5.7 years (maximum 21 years). During this time, 459 deaths were recorded. The most common causes of death were HIV-related illnesses, cardiovascular disease and non-AIDS-defining cancers.

The first set of results showed that, when compared to people who were virally suppressed, those with a low-level viral load had a more than twofold increase in mortality risk (HR = 2.6; 95% CI, 1.8-3.7). The mortality risk associated with low-level viral load was still doubled when the researchers took account of potential confounders (HR = 2.2; 95% CI, 1.3-3.8).

Interestingly, the increased risk of death associated with low-level viral load met the test for statistical significance for the 50-199 category, but not for the 200 and 999 group. Analysis according to the year ART was started or the type of medication used did not affect the headline findings.

Only individuals with a persistent viral load above 999 were at risk of developing an AIDS-defining illness.

A viral load above this level was also associated with an almost threefold increase in the risk of a serious non-AIDS event (aHR = 2.8; 95% CI, 1.6-5.2), while a viral load between 200-999 was associated with a doubling of the risk (aHR = 2.0; 95% CI, 1.2-3.6), with no association seen for viral loads between 500-199.

The table summarises the statistically significant hazard ratios for these outcomes:

| | Mortality | AIDS-defining illness | Serious non-AIDS event |
|---|---|---|---|
| 50-199 | 2.2 | - | - |
| 200-999 | - | - | 2.0 |
| Over 1000 | 7.7 | 23.9 | 2.8 |

The investigators suggest that the poorer outcomes seen in individuals with low-level viral loads were linked to immune activation and inflammation.

The results will need to be validated in more rigorous research – the retrospective design was a potential limitation of the reliability of the study's findings. However, if supported by other studies, the findings show the importance of suppressing viral load to undetectable levels and that the thresholds used for virological failure in treatment guidelines could expose people to the risk of adverse outcomes.

"In conclusion, we observed increased mortality for participants with low level viraemia 50-999 copies/ml during cART, which was also found in the subset of persons with low level viraemia 50-199 copies. In addition, individuals with low level viraemia 200-999 copies/ml had an elevated risk of serious non-AIDS events compared with those with virologic suppression," conclude the authors. "The findings add to mounting evidence that low level viraemia is associated with worse clinical outcomes."