Effect of HIV-1 low-level viraemia during antiretroviral therapy on treatment outcomes in WHO-guided South African treatment programmes: a multicentre cohort study

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Summary

Background Antiretroviral therapy (ART) that enables suppression of HIV replication has been successfully rolled out at large scale to HIV-positive patients in low-income and middle-income countries. WHO guidelines for these regions define failure of ART with a lenient threshold of viraemia (HIV RNA viral load ≥1000 copies per mL). We investigated the occurrence of detectable viraemia during ART below this threshold and its effect on treatment outcomes in a large South African cohort.

Methods In this observational cohort study, we included HIV-positive adults registered between Jan 1, 2007, and May 1, 2016, at 57 clinical sites in South Africa, who were receiving WHO-recommended ART regimens and viral load monitoring. Low-level viraemia was defined as the occurrence of at least one viral load measurement of 51–999 copies per mL during ART. Outcomes were WHO-defined virological failure (one or more viral load measurement of ≥1000 copies per mL) and switch to second-line ART. Risks were estimated with Cox proportional hazard models.

Findings 70930 patients were included in the analysis, of whom 67644 received first-line ART, 1476 received second-line ART, and 1810 received both. Median duration of follow-up was 124 weeks (IQR 56–221) for patients on first-line ART and 101 weeks (IQR 51–178) for patients on second-line ART. Low-level viraemia occurred in 16013 (23%) of 69454 patients, with an incidence of 11.5 per 100 person-years of follow-up (95% CI 11.4–11.7), during first-line ART. Virological failure during follow-up occurred in 14830 (22%) of 69454 patients on first-line ART. Low-level viraemia was associated with increased hazards of virological failure (hazard ratio [HR] 2.6, 95% CI 2.5–2.8; p<0.0001) and switch to second-line ART (HR 5.2, 4.4–6.1; p<0.0001) compared with virological suppression of less than 50 copies per mL. Risk of virological failure increased further with higher ranges and persistence of low-level viraemia.

Interpretation In this large cohort, low-level viraemia occurred frequently and increased the risk of virological failure and switch to second-line ART. Strategies for management of low-level viraemia need to be incorporated into WHO guidelines to meet UNAIDS-defined targets aimed at halting the global HIV epidemic.

Funding None.

Introduction In a global effort to halt the HIV epidemic, UNAIDS has set ambitious targets for expansion of access to HIV testing and antiretroviral therapy (ART), and for high treatment success rates in patients on ART. Access to ART has expanded substantially and is currently reaching approximately 18 million HIV-infected patients, of whom more than 14 million reside in low-income and middle-income countries. Although large-scale roll out of ART in these countries is accompanied by concerns about sustained adherence to treatment and retention in care, increasing rates of transmitted drug resistance to first-line ART, and growing uptake of second-line ART, treatment programmes in low-income and middle-income countries generally report durable success rates of ART and low on-treatment rates of virological failure.

The definition of virological failure differs around the world. Substantial differences exist between guidelines in high-income countries, which use HIV RNA load (viral load) thresholds of 50–200 copies per mL to define virological failure, and WHO guidelines for low-income and middle-income countries, which apply a more lenient threshold of 1000 copies per mL. Low-level viraemia refers to detectable viraemia during ART between these thresholds (50–999 copies per mL). In high-income countries, clinical interventions are initiated upon detection of viral loads higher than 50 copies per mL. This approach is based on associations in this setting between persistent low-level viraemia and suboptimal adherence to ART, selection of resistance to some ART regimens with a low genetic barrier to resistance, and subsequent virological failure.

Current WHO guidelines do not advise interventions in monitoring or treatment interventions even after repeated measurements of low-level viraemia, resulting in patients being kept on a failing first-line ART regimen with a low genetic barrier to resistance. The incidence of
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Research in context

Evidence before this study
We searched PubMed for studies published between Jan 1, 2000, and July 1, 2017, on the effect of HIV low-level viraemia, defined as a detectable viral load between 50 and 1000 copies per mL during antiretroviral therapy (ART), on subsequent failure of ART. We used the search terms “HIV”, “low-level viraemia”, and “antiretroviral therapy”, and common synonyms. We identified studies in adult patients that reported virological failure as an outcome. We did not review studies that exclusively reported on viral blips (ie, detectable viraemia immediately followed by suppression of <50 copies per mL), reports of cohorts treated with outdated ART regimens, or studies without a control group.

We identified three multicentre observational cohort studies. In a combined European and North American cohort, a significantly increased risk for virological failure was seen in HIV-infected patients with repeated measurements of low-level viraemia of 200–499 copies per mL during ART (hazard ratio [HR] 3·97, 95% CI 3·05–5·17), but not in those with low-level viraemia of 51–199 copies per mL (HR 1·38, 0·96–2·00). By contrast, in a French cohort, low-level viraemia of 51–199 copies per mL was associated with significantly increased risk for virological failure (HR 2·30, 1·65–3·20), but this study did not assess low-level viraemia of more than 200 copies per mL. A British–German cohort showed a significantly increased risk for virological failure after unstratified low-level viraemia between 50 and 400 copies per mL (risk ratio [RR] 2·18, 95% CI 1·15–4·10).

Taken together, the effect of low-range low-level viraemia (51–199 copies per mL) remains unclear, although both studies that assessed middle-range low-level viraemia (200–500 copies per mL) showed increased rates of virological failure in patients with viral loads within this range. However, these two studies set thresholds for virological failure at 400 copies per mL and 500 copies per mL, respectively, precluding the study of high-range low-level viraemia (400–1000 copies per mL). We identified two single-centre studies that used a threshold for virological failure of 1000 copies per mL. Of these, one study from the USA reported that patients with low-level viraemia of 50–999 copies per mL had a significantly increased risk for virological failure (HR 3·8, 2·2–6·4), whereas in a Canadian cohort, a significant risk for virological failure was seen in 165 patients with repeated measurements of low-level viraemia of 51–199 copies per mL (HR 2·22, 1·60–3·09), 200–499 copies per mL (HR 2·15, 1·46–3·17), or 500–999 copies per mL (HR 4·85, 3·16–7·45). Identifed studies reported prevalence figures of low-level viraemia ranging between 6·2% and 25·5%.

All studies were done in high-income countries where frequent viral load monitoring is performed. In these settings, upon detection of raised viral loads higher than 50 copies per mL, interventions such as adherence counselling, intensified monitoring, resistance testing, pharmacokinetic measurement, and switch of ART regimen might already be initiated. Therefore, the available evidence might not apply to treatment programmes in low-income and middle-income countries, where WHO guidelines recommend that annual viral load testing and interventions are only advised if viraemia exceeds the threshold of 1000 copies per mL. Furthermore, available studies included patients on a range of ART regimens from the earliest phase of combination therapy onwards, and do not reflect the situation in low-income and middle-income countries, where first-line ART with a low genetic barrier to resistance is provided to all patients.

On the basis of the available evidence from high-income countries, no conclusions can be drawn regarding the prevalence of low-level viraemia or its effect on virological failure in low-income and middle-income countries.

Considering that this evidence was collected in settings where strict monitoring is applied, the threat of low-level viraemia to treatment success might be even more pronounced in low-income and middle-income countries, where the majority of the global population of HIV-positive patients on ART reside.

Added value of this study
To our knowledge, our study is the first to analyse the occurrence of low-level viraemia and its effect on treatment failure in low-income and middle-income countries. It is also the largest analysis on this topic to date, including nearly 71 000 patients from 57 South African clinics. Our results support available evidence of an increased risk of virological failure even after a single occurrence of low-level viraemia of the lowest range. Our study is also the first to show clinical consequences of low-level viraemia—namely, the increased risk of switching to second-line ART. Compared with previous studies from high-income settings, the observed rates of low-level viraemia and virological failure in this setting were higher and the risk of virological failure after low-level viraemia was equal to or more pronounced, indicating that low-level viraemia is a serious threat to treatment programmes in low-income and middle-income countries.

Implications of all the available evidence
Active clinical follow-up of raised viral loads should be prioritised and strategies for specific management of low-level viraemia should be included in WHO guidelines to mitigate the risk of subsequent virological failure. The high threshold for virological failure currently used in low-income and middle-income countries should be reconsidered.

low-level viraemia during ART and its effect on outcomes of ART in treatment programmes in low-income and middle-income countries have not been studied. We aimed to describe the effect of low-level viraemia on outcomes of ART in a large multicentre rural-urban South African cohort of HIV-positive adults undergoing treatment and monitoring according to WHO guidelines.
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