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Viral load versus CD4 monitoring of ART in HIV-positive children

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In sub-Saharan Africa, by 2012, only about 30% of children eligible for antiretroviral therapy (ART) were under treatment. ART coverage is less than half of that in adults (1). As coverage of paediatric ART increases and guidelines for ART initiation change, it will be necessary to determine how best to monitor ART. Routine monitoring of HIV viral load (VL) is common practice in ART programmes in high-income countries, but, in sub-Saharan Africa, most ART programmes rely on CD4 cell measurements or clinical monitoring to detect treatment failure (2). These are poor predictors of virological failure (3), and without routine VL monitoring patients may suffer delayed and unnecessary switches to second-line therapy. This, in turn, increases the chances that patients will develop drug resistance, and limits treatment options. Previous studies in adults (4-6) showed that routine VL monitoring, which substantially increases costs, may reduce mortality only slightly, but these results cannot be generalised to children because HIV progression and ART regimens for children and adults are different (2, 7). A randomised trial found that routine CD4 and toxicity monitoring, and monitoring based on clinical progression and toxicity alone, had similar treatment outcomes (8), but we know of no empirical study that directly compares routine VL and CD4 monitoring in children.

Computer simulation of HIV-positive children to predict the effect of ART monitoring strategies

We developed an individual-based model that simulates synthetic cohorts of HIV-positive children on ART. We simulated cohorts with different monitoring strategies and compared the resulting outcomes. We based disease progression and characteristics at treatment initiation of the simulated children on data from a cohort of 11,903 real children enrolled in seven South African cohorts that participate in the International epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) collaboration. In the model, the simulated children progress independently of each other through states that include various levels of VL and CD4 cell percentage or count (depending of the age of the child), subsequent treatment failure, switching to second-line ART and death. Children were assigned to start with a first-line ART regimen that contains either a non-nucleoside transcriptase protease inhibitor (NNRTI) or a protease inhibitor (PI) in addition to two nucleoside reverse transcriptase inhibitors (NRTI). The WHO currently recommends PI based first-line ART for all children younger than 3 years when they start ART, but NNRTI-based regimens are still much more common in sub-Saharan Africa.

In order to compare the effect of CD4 cell and VL routine monitoring, we simulated independent cohorts of children followed for 5 years from ART start and monitored with three different strategies:

- CD4 cell count or percentage monitoring every 6 months
- VL monitoring every year
- VL monitoring at 6 and 12 months after treatment initiation, and once every year thereafter (WHO recommendation (2))

Children who failed ART, according to the WHO guidelines (2), either immunologically or virologically, depending on the monitoring strategy, were switched to second-line ART. Children on PI-based regimens, aged <3 years at time of failure, were not switched (3).
We parameterised the model with data from South Africa, which differs from most other sub-Saharan African countries. In South Africa, new effective ART regimens and frequent laboratory measurements including VL are widely available. We therefore explored different scenarios of treatment efficacy by covering a wide range of rates of virological failure.

Replacing CD4 cell monitoring with VL monitoring is unlikely to reduce mortality but leads to improved treatment outcomes

We found that routine VL monitoring does not reduce mortality in children during their first 5 years on ART. The 5-year mortality remained around 7% across monitoring strategies and treatment efficacy scenarios. However, our model revealed other benefits of routine VL monitoring over routine CD4 cell monitoring such as preventing immunodeficiency by identifying virological failure earlier: the percentage of children with immunological failure was 1.6% with CD4 monitoring, and only 1.0% with routine VL monitoring. Routine VL monitoring increased the demand for second-line ART from 1.1% to 12.0%, but it also prevented many unnecessary switches; with CD4 monitoring, 44% of children who switched to second-line ART did so without virological failure.

Routine VL monitoring also reduced the average time children spent on failing ART, from 6.6 to 3.3 months. The time spent on failing NNRTI-based regimens was reduced by 73%. NNRTI-based treatment is associated with higher risk of resistant mutations than the more expensive PI-based regimens (9). Currently, PI-based ART is considerably more expensive than NNRTI-based ART, and therefore only rarely available in sub-Saharan African countries other than South Africa. Our study supports the claim that VL monitoring reduces the risk of drug resistance, but other interventions, like better adherence counselling or improved sequencing of regimens, may offer a more realistic approach to preventing drug resistance than VL monitoring (10).

VL monitoring helps to detect poor adherence and identifies children and caretakers who need counselling. This, in turn, may reduce the risk of virological failure. We tested this hypothesis with various assumptions of treatment efficacy, and still found that mortality was not reduced. However, beneficial effect on immunological outcomes and reduction in time spent on failing treatments was more pronounced when we assumed treatments were less efficacious, or that virological failure was more frequent with CD4 than with VL monitoring. Increasing the frequency of viral load monitoring from every year to every 6 months did not improve outcomes, which suggests that the WHO recommendation for annual viral load tests is appropriate (2).

Our study had several limitations. Guidelines and clinical practice in South Africa changed over the study period, and the data used to parameterise the model may not reflect current practice. There is a trend to earlier ART initiation, so children are now healthier at ART start than they had been previously. The efficacy of drugs and the effectiveness of ART programmes have improved. We did not explicitly model these trends, but incorporated them implicitly by varying treatment efficacy. We also did not explicitly model adherence, resistance, or differences in the efficacy of NNRTI- and PI-based regimens. Further research will increase our understanding of the causal relationships between adherence, virological failure and drug resistance.

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