The Cost and Impact of Alternative Strategies for Monitoring Child Patients on ART

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Executive Summary

- Very little modelling work has been done to examine the costs and impact of alternative strategies for monitoring children on ART. Therefore, this report cannot provide firm recommendations. In this brief report, we summarise our interpretation of the available evidence and draw comparisons with the few modelling results that do exist.

- In general, monitoring HIV-infected children taking antiretroviral therapy (ART) may provide similar clinical and health benefits as adult patient monitoring. However, different monitoring strategies may have different comparative advantages and disadvantages because young children have a less developed immune system, progress faster to AIDS, are not at risk of transmitting HIV and have fewer licensed regimen options.

Available Evidence

There is little evidence to inform monitoring guidelines specifically for children. The only available evidence comes from one completed trial [1], the preliminary results from another trial [2] and one published modelling study [3].
The PENPACT trial compared the effectiveness of protease-inhibitor containing regimens versus regimens containing non-nucleoside reverse transcriptase inhibitors (NNRTIs). For each regimen, the trial also evaluated the impact of switching to second-line ART at a viral load of 1,000 copies/mL or 30,000 copies/mL (thus, the trial had a two-by-two factorial design). The study was conducted among 266 previously untreated children (median age 6-5 years, median follow-up 5 years) from Europe and North and South America [1]. HIV-infected children achieved good long-term outcomes with all treatment strategies. For children taking protease-inhibitor-based ART, the higher switching threshold did not increase the risk of NRTI and protease-inhibitor resistance, while children on the NNRTI-combination therapy switching at the higher threshold accumulated more NRTI resistance mutations. The trial results suggest a higher viral load threshold for switching to second line therapies is reasonable for children with limited access to second line therapies.

The ARROW trial investigated the impact of routine laboratory and clinical monitoring (LCM) compared to clinically driven monitoring (CDM) in children on ART [2]. In this randomised trial, 1206 ART-naïve children (median age 6 years, median follow-up 4 years) from Uganda and Zimbabwe visited a clinician every 12 weeks after initiating ART. Those in the CDM arm underwent tests for toxicity (haematology, biochemistry liver and renal function tests) if requested by their clinician, while those in the LCM arm had routine 12-weekly tests for toxicity and CD4. Children switched to second-line ART after new WHO Stage 3/4 events or if they satisfied age-dependent CD4 criteria for those undergoing LCM (WHO 2006/10). Preliminary data suggest that routine CD4 monitoring added substantial costs but provided only small clinical and health gains over clinically driven monitoring. Differently from adults, most switching in the CDM arm was for failure to thrive, which in growing children maybe a more sensitive indicator of failure than in adults, and a reason why switching occurred at similar CD4 values irrespective of the monitoring strategy used. The results suggest wider ART rollout would have a greater population level impact on children than routine CD4 monitoring.

A stochastic agent-based model studied the cost-effectiveness of monitoring viral load in a small cohort of HIV-infected children starting ART in Thailand [3]. This cohort had 304 patients with a median age of seven and a low CD4 percentage (percentage of total lymphocytes in a blood sample that are CD4 positive) at ART initiation. The authors found a single test six months after ART initiation followed by annual testing was the optimal strategy, but this was very costly for the incremental health benefits: ~US$68,000 per QALY gained, approximately six times the Thailand GDP per capita. The vast majority of costs incurred, however, were for the provision of second line therapies, so this strategy may become more affordable if costs of second-line drugs decrease. The authors made no comparisons to clinical or immunological monitoring strategies. The cheapest strategy -- performing only one viral load test, at six months after treatment initiation -- provided large clinical and health gains but was still costly. In terms of viral load monitoring, the results for children were similar to modelling results for adult patients (see adult monitoring report) with increased frequency of testing giving greater health gains but at increased cost.
Differences between children and adults potentially affecting monitoring

If children were also monitored according to adult guidelines, it would unlikely adversely affect the children but a number of differences between adult and child patients should be considered:

- Immunologic monitoring in children is a poorer indicator of treatment failure than in adults and requires the measurement of CD4 percentage in children 4 years or younger; in older children, CD4 cell counts can be used as in adults.
- Unsuppressed virus in children leads to faster infection progression and there are fewer licensed second-line treatment options available. However, as children generally do not transmit HIV, a higher threshold may be acceptable.
- Child patients may require different drug formulations (such as syrups), which are more expensive or less feasible to use.
- Adherence is another potential issue as it is dependent on caregivers and there can be psychosocial issues among adolescents.
- There is potential for first-line failure because of inherited resistance from mothers taking treatment to prevent mother-to-child transmission.

Another important difference is that child patient guidelines only temporarily apply to HIV-infected children because children will transition to adult guidelines as they age.

Future modelling directions to inform policy recommendations

Further modelling studies are required to build the evidence-base for child patient monitoring recommendations. Mechanistic models should investigate:

- The relative cost-effectiveness of clinical, immunological, and viral-load monitoring strategies for child patients (as done for adult patients) and determine the impact of future cost reductions in second-line regimens and diagnostic technologies (such as point-of-care tests).
- The optimal viral load threshold for transitioning to second-line therapy (building on available trial data).
- The transition to adult guidelines as children age and begin sexual activity. This is particularly important because the time horizons required for viral load monitoring to demonstrate benefit may be sufficiently long that many children may become monitored according to the adult monitoring guidelines before the effect is realised.
- The potential for inherited resistance due to prevention of mother-to-child transmission and its impact on treatment pathways
- Sensitivity and specificity for different criteria in detecting drug resistance
Conclusions

The HIV Modelling Consortium Patient Monitoring group cannot make clear recommendations for child patient monitoring distinct from the recommendations for adults due to the limited evidence available. However, epidemiologists and modellers in the group agree that:

- Laboratory monitoring is beneficial for child patients and it is unlikely that following adult guidelines will adversely affect child patients.
- It is important to maximize ART coverage in children in resources limited settings.
- The cost of second-line therapy is the primary factor affecting the cost-effectiveness of monitoring strategies—performing laboratory tests only makes a small contribution to the overall cost. New model analyses are necessary to determine the potential impact of future cost reductions and the trade-off between increasing first-line coverage versus a more

References