Briefing Paper
March 2013
Issue 6

Clinically-driven monitoring of children on ART is safe and may increase access to treatment

We need to improve children's access to HIV treatment

Major progress has been made in scaling-up access to HIV treatment for adults, but children's access to treatment has lagged behind. More than 2 million children were in need of treatment by the end of 2011, but only 28% of those in need were accessing it. Mortality is high among HIV-infected children who are not on antiretroviral therapy (ART). More than half of HIV-infected infants and young children die before their second birthday. We urgently need to increase ART coverage for children.

There are substantial barriers to treating children, including:

- difficulties in testing infants for HIV;
- poor linkage between different parts of the health service (e.g. between parts of the health service that test children, and ART treatment programmes);
- lack of health workers trained and confident to initiate and manage paediatric ART;
- stock-outs of paediatric ART medicines;
- the complexity of some paediatric ART formulations, which need to be given at different doses as the child grows.

This policy brief examines the issues around two related factors that may act as barriers to treatment for children: healthcare workers' nervousness about putting children onto ART because of worries about side effects to the medicines; and the perceived need for routine laboratory monitoring of children on ART (both for side-effects and effectiveness).

Children do very well on ART

Healthcare workers are often nervous about starting children on ART, because they are not used to treating children and may also have concerns about side effects. However, the evidence from ARROW (and other studies of paediatric ART) shows that children respond very well to treatment and have few side effects. At the start of the ARROW trial two-thirds of the children were sick and had WHO stage 3 or 4 disease, and their weight-for-age was well below normal. Despite this, after almost 4 years on treatment, 95% were still alive and 93% had not had a new WHO 4 event or died.

Key Points

- **Access to HIV treatment for children is lagging behind that of adults – by the end of 2011 only 28% of children who needed treatment were on it (compared with 58% of adults)**
- **The perception that routine laboratory monitoring is needed for children on antiretroviral therapy may be a barrier to increasing access to life-saving treatment**
- **Once children are stable on HIV treatment they do very well, with low death rates, little need for switching and excellent CD4 responses and viral load suppression several years after starting treatment**
- **HIV treatment can be delivered safely to children with good quality clinical care, without any need for routine laboratory tests for side effects of ARV medicines**
- **Routine CD4 monitoring provided only a very small and late benefit mainly in older children. There was no difference in viral load suppression with routine CD4 monitoring compared with clinically-driven monitoring alone**
  - **Monitoring weight-gain in children appeared to be useful in picking up failure of first-line treatment early**
- **Treatment programmes should focus on increasing children's access to HIV treatment, rather than spending resources on expensive laboratory tests that provide limited benefit**

Only 5% of children had to switch to second-line ART over an average follow-up of 4 years. At their last follow-up visit only 1% of children had CD4 percentage <5%, and after almost 4 years on treatment nearly 80% had viral loads below 400 copies/ml, which compares well to levels of viral load suppression seen in adult ART trials. In fact if we look at children who received standard treatment with NNRTI + 2NRTI (abacavir and lamivudine(3TC)), 84% had viral load suppression after nearly 4 years on treatment.

Only a small minority of children had side effects from their ART medicines. Of those who stayed on first-line ART, only 7% had to change one or more of their first-line drugs for any reason (of which side effects was just one). Treatment for tuberculosis was as common a reason for changes as side effects of ART (~3.5% children changed for side effects; ~3.5% because of needing to take TB drugs as well).

These results should encourage healthcare workers to get children who need it onto treatment, as its effectiveness far outweighs any concerns about side effects.

Laboratory versus clinically-driven monitoring for children

Laboratory monitoring for effectiveness and toxicity requires (working) machinery, electricity, reliable supplies of reagents and trained staff. These are often unavailable in many settings in Africa, particularly in lower-level health facilities. Point-of-care tests that can be used in low-level health facilities are not yet widely available (although a simple stick-based test that will show if CD4 counts are below a specific cut-off will soon be available). Requiring patients to travel to facilities where laboratory tests can be done is often not feasible due to transport costs and time. Laboratory tests are also expensive, and every dollar spent on them reduces the money available for treating more children.

Trials have been carried out in adults looking at the impact of routine laboratory monitoring in addition to good clinical care. These have found that routine toxicity monitoring does not provide any additional benefit (for all the recommended first-line treatments including tenofovir). Routine CD4 monitoring provides only a small additional benefit over clinical monitoring for individual patients, but is not the best way to improve population level health (compared to giving drugs to more people) because of its cost. No trial has so far found regular viral load monitoring (which is very expensive, at USD$26-92 per test) to have a significant benefit over and above routine CD4 monitoring.

The results from these trials in adults may not apply to children. There are differences in how good CD4 levels are at predicting disease progression during childhood, how HIV manifests in children, and the presence of other illnesses and conditions which are common in African children (eg malaria, severe malnutrition). This may affect the relative advantages of routine laboratory monitoring versus clinical monitoring. Because of this, scientists in Uganda and Zimbabwe carried out the ARROW trial, which compared clinically driven monitoring with laboratory and clinical monitoring for children. This brief draws on their findings.

Efficacy of routine laboratory monitoring versus clinically-driven monitoring

In ARROW, 1,206 children were split randomly into two groups. Both groups were tested every 3 months to check for both drug side effects (haematology and biochemistry tests) and how well the anti-HIV drugs were working (CD4 tests). In one group the results of all routine 3-monthly laboratory tests were sent back to the clinic, while in the other group CD4 tests were never returned, but doctors and healthcare staff could request biochemistry, haematology or other tests at any time to diagnose illnesses or to detect side effects. They could never order CD4 tests.

Clinical outcomes

Outcomes were very good for children in both groups. Overall, there was no significant difference in the proportion of children who had a new WHO 4 event (like AIDS) or death (the primary endpoint) over the whole course of the trial. Most deaths and WHO 4 events happened during the first year (65 in total) and only 39 occurred altogether over the rest of follow-up (~3 years), ie. 13 per year. After the first year a small but statistically significant difference was found between the groups, with the clinical monitoring group having a slightly higher proportion (1% per year extra) of new WHO 4 events or death. A similar pattern was found for mortality alone, with no difference overall, but slightly higher mortality (a difference of 0.6% per year) in the clinically-driven monitoring group after the first year.

Immunological and virological outcomes

There was no difference in CD4 counts / percentages between the two groups. Viral load testing was subsequently carried out at the end of the trial on samples that had been stored throughout the course of the trial. There was no difference in viral load suppression between the two groups, which was also very similar across all ages.

Safety

There was no difference in the proportion of children who had one or more side effects (adverse events) over the course of the trial (47% in both groups). 69% of these adverse events were only abnormal laboratory results (commonly low numbers of one kind of white cell in the blood) with no clinical symptoms and their

> “Routine laboratory tests are expensive and provide very little benefit for children”

importance was felt to be low as very few children needed to change drugs because of this. There was no difference in severe adverse events, but a higher proportion of children in the clinically-driven monitoring group were hospitalised for malaria. This appeared to be due to doctors being more likely to admit children if they did not know their CD4 count, rather than an actual difference in severity of malaria between the two groups.

In the clinically-driven monitoring group, laboratory tests were carried out, but were not returned to the clinician unless they had requested the test result, or if the result was severely abnormal. The only other routine test results that were returned to doctors for children in the clinically-driven monitoring arm were the haemoglobin after 8 weeks on treatment for children receiving zidovudine, to check it was not causing severe anaemia. Only 126 (0.1%) of 125,302 tests carried out in the clinically-driven group were severely abnormal and had not already been requested by a doctor, showing that doctors were missing very little. More importantly, only 1.4% of all the toxicity tests done were requested by doctors to help them manage the children. The rest were all done routinely, and had no impact on management. If anything, the doctors asked for more extra tests in the arm with laboratory monitoring, showing that clinical monitoring alone did not make doctors ask for more tests when children were sick.

Switching to second-line treatment

The main concerns about using clinically-driven monitoring without routine testing for effectiveness is that patients with low CD4 counts who should be switched to second-line ART will be missed (and then be at risk of getting very sick) or that patients with high CD4 counts will be switched unnecessarily. ARROW found that the proportion of children with a very low CD4 percentage when they switched to second-line was similar, whether or not they had been monitored with routine CD4 testing. 39% of children in the clinically-driven monitoring arm and 40% of children in the laboratory monitoring arm had CD4% less than 5% when they switched to second-line treatment. Very few children in the clinically-driven monitoring group stayed on first-line ART with low CD4 percentages without being switched: only 2% had a CD4% of less than 5% at their last visit. This indicates that doctors were not missing children who should have been switched.

> **“Resources should be focused on getting as many children onto treatment as possible, rather than providing routine laboratory monitoring that has little impact”**

Switching to second-line treatment was mainly triggered by falling CD4 in the laboratory group, and failure-to-thrive (growth faltering) in the clinically-driven group. One of the reasons that doctors were not missing many children who should have been switched may be that failure to thrive is a particularly good clinical monitoring tool in children. This is plausible because children should be gaining weight all the time; if they start to fail first-line therapy, this weight gain may stop which is easily apparent on standard growth charts. Thus failure-to-thrive may be a sensitive indicator of when to switch, where CD4 tests are unavailable. In contrast, adults need to actually lose weight to show first-line failure, which may take longer.

Although a few more children in the clinically-driven monitoring group did switch with CD4 percentages over 25%, the actual number of children switching with high CD4 percentages was very small: only 6 out of 606 children in the clinically-driven monitoring group (compared with none in the laboratory monitoring group). Nevertheless it highlights that one way to use CD4 counts sparingly would be to check the CD4 count in children who appear to be failing according to clinical criteria, rather than doing regular CD4 tests on all children.

The potential impact of a clinically-driven monitoring strategy

As clinically-driven monitoring has now been shown to be a safe and effective way of delivering ART to children, it has the potential to increase access to treatment for children. Clinically-driven monitoring on ART does not depend on the routine use of laboratory tests, and so it increases the ability of lower-level health facilities to deliver ART. This has the advantage for families that there is a shorter distance to travel (which can often be a major barrier to accessing treatment). It could also relieve the pressure on bigger hospitals and treatment centres and prevent them being too overcrowded. Laboratory resources could then be focused on carrying out tests when they are most needed, such as for deciding when to start ART.

Routine laboratory tests are expensive and provide very little additional benefit for children (or none, in the case of routine toxicity tests). Cost-effectiveness analysis from ARROW shows that routine laboratory monitoring is not cost-effective. In the context of 72% of children in need of ART not having access to it, and limited financial resources, it is clear that more lives can be saved through a clinically-driven monitoring approach for healthcare workers to manage children clinically (including monitoring weight gain) with good mentoring and support, rather than routine laboratory monitoring. A paper examining the cost-effectiveness of monitoring approaches used in the ARROW trial is being written.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

We urgently need to increase access to ART for children. Once on treatment, children respond very well, with low mortality, good immunological and virological outcomes and little need for switching. The ARROW trial of over 1,200 children in Uganda and Zimbabwe has shown that ART can be delivered safely and effectively to children using a clinically-driven monitoring approach. Routine laboratory testing for toxicity provides no additional benefit, and routine CD4 tests have very little benefit over good quality clinical monitoring. Clinically-driven monitoring strategies can help to increase access to ART by facilitating increased decentralisation of HIV treatment, and reducing the costs of treatment. In the context of poor access to treatment for children, and stagnant financial resources for HIV, what resources there are should be focused on getting as many children onto treatment as possible, rather than providing routine laboratory monitoring that has little impact.

Recommendations

- Health workers should not delay putting eligible children on to ART because of fears of toxicity – children respond well to treatment and toxicity is not a major problem
- Paediatric HIV treatment resources should be focused on expanding access to ART and providing prophylaxis against opportunistic infections
- Prioritise training and mentoring healthcare workers about:
  - putting children on treatment and following them clinically.
  - ensuring continuous access to medicines, including, in the event of shortages of paediatrics ARVs, use of (parts of) adult ARVs where appropriate
- A clinically-driven approach should be used for monitoring children on ART, until all children in need of ART have access to it
- Laboratory resources should be focused on carrying out tests that are clinically indicated

Recommended reading

ARROW trial team, **ARROW: A 5-year randomised factorial trial of routine vs clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in HIV-infected African children.** Lancet, 2013. **381**.

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Medina Lara, A., et al., **Cost Effectiveness Analysis of Clinically Driven versus Routine Laboratory Monitoring of Antiretroviral Therapy in Uganda and Zimbabwe.** PLoS One, 2012. **7**(4): p. e33672.

World Health Organisation, UNAIDS, and UNICEF, **Global HIV/AIDS Response Epidemic update and health sector progress towards Universal Access: Progress Report 2011.** 2011, World Health Organisation: Geneva.

Credits

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This brief is an output from a research project funded by the UK Department for International Development (DFID) for the benefit of developing countries. The views expressed are not necessarily those of DFID.

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ARROW was a randomised controlled clinical trial designed to assess two different management strategies for giving first line anti-HIV medicines.

ARROW had two main aims: to find out whether anti-HIV drugs can be given safely and effectively without doing regular blood tests to monitor how children are doing on HIV treatment; and whether starting children on 4 anti-HIV drugs for a short period of time before continuing with 3 drugs is better over the long term than starting on the standard 3 drugs.

ARROW took place in Uganda and Zimbabwe. More than 1,200 children took part in the trial, and were followed-up for around four years.

The organisations involved ARROW were:

- University of Zimbabwe, Harare, Zimbabwe.
- Joint Clinical Research Centre, Kampala, Uganda
- The Paediatric Infectious Diseases Clinic (PIDC), Kampala, Uganda.
- MRC/Uganda Virus Research Institute Programme on AIDS, Entebbe, Uganda
- MRC Clinical Trials Unit, London, UK.

ARROW was funded by the Medical Research Council (MRC, UK) and the Department for International Development (UK). The MRC was the Sponsor of ARROW, which was coordinated by the MRC Clinical Trials Unit. GlaxoSmithKline Ltd supplied the drugs for the trial and paid for viral load assays..

For more information visit www.arrowtrial.org