Children on ART in Africa need to continue cotrimoxazole prophylaxis

To stop, or not to stop?
Children on antiretroviral therapy (ART) in Africa do very well. ART dramatically reduces mortality and illness. But children on ART still have higher levels of illness and hospitalisation than HIV-negative children.

Prophylaxis with cotrimoxazole (see definitions box) has been shown to reduce death and illness among both children and adults with HIV before they start ART. A trial carried out in HIV-infected children in Zambia over the age of one, not yet on ART, found that cotrimoxazole reduced deaths by 43% and hospitalisation by 23%.

ART strengthens the immune system, so may make cotrimoxazole less necessary for those on treatment. Stopping cotrimoxazole prophylaxis would also reduce the pill burden for children on ART. But does stopping cotrimoxazole leave children on ART more vulnerable to illness and death?

In adults the DART trial showed that cotrimoxazole prophylaxis is also beneficial for the first 72 weeks on ART, with no benefit after that. But there has been no evidence on whether children in Africa who are on ART should continue cotrimoxazole prophylaxis. The only evidence available for children comes from observational studies in Europe and the USA, where bacterial infections and malaria are much less common.

Current guidelines & practice
The World Health Organization (WHO) guidelines currently recommend daily cotrimoxazole prophylaxis for all children <2 years, and for those >2 years with symptomatic disease or CD4 counts below age-related thresholds. They recommend that cotrimoxazole is generally continued once children start ART, but say that those >5 years old, with good adherence, full clinical recovery and CD4>350 cells/mm³ may stop cotrimoxazole.

National guidelines for cotrimoxazole prophylaxis for children in Africa vary. For example, in Malawi the national guideline says that cotrimoxazole prophylaxis should be continued for life in all HIV positive patients (including children). In Uganda the guidelines state that patients started on ART should continue with cotrimoxazole prophylaxis until their immune system has been adequately restored, as evidenced by a high CD4 of 350-500 for over six months. Zimbabwe national guidelines say that cotrimoxazole prophylaxis should be continued indefinitely or until CD4 counts are greater that 200 cells/mm³ for longer than six months.

In practice, the use of cotrimoxazole prophylaxis for children on ART varies even within countries. A situation analysis conducted in Malawi, Uganda and Zimbabwe as part of the Lablite project (www.lablite.org) found that different health facilities used varying criteria to decide who to give cotrimoxazole prophylaxis to.

Key Points
- Cotrimoxazole prophylaxis reduces hospitalisation and illness among children who are stable on ART, regardless of their age or CD4 count
- Continuing cotrimoxazole prophylaxis in children on ART is cost-saving, because of the reduction in hospitalisations
- Children of all ages should continue to take cotrimoxazole even if they have high CD4 counts on ART
- Supply chains need to be strengthened to avoid stock-outs of cotrimoxazole

Cotrimoxazole prophylaxis
Cotrimoxazole (trimethoprim-sulfamethoxazole) is a widely available, low cost, broad-spectrum antimicrobial drug.

Prophylaxis is a measure taken to maintain health and prevent disease. Cotrimoxazole prophylaxis is given daily to prevent a range of infections in children with HIV.
Effectiveness of cotrimoxazole prophylaxis for children on ART

The ARROW trial is the first randomised controlled trial to look into whether children in Africa on ART can stop cotrimoxazole prophylaxis. 760 children aged 3 years or older, who had been on ART for more than 96 weeks, were randomised to either continue taking cotrimoxazole prophylaxis, or to stop it.

The median age of children taking part in this study at the time of randomisation was 8 years old, and 99% of them were still on first line ART. Only 5% had CD4<15% at randomisation, and the median CD4 count in those over 5 years old was 720 cells/mm³. These children were followed up for around 2 years from randomisation. Death rates were low in the ARROW trial, and similar in both groups. However, the combined measure of hospitalisation or death (the primary outcome for this trial) was 4% higher among children who stopped cotrimoxazole prophylaxis than those who continued. The proportion of children who were hospitalised or died was lower in those who received cotrimoxazole prophylaxis, regardless of age, and persisted throughout the follow-up. Cotrimoxazole prophylaxis was beneficial to all children, including those with CD4% >=30%.

Higher levels of hospitalisation for both malaria and non-malaria infections (particularly pneumonia, sepsis and meningitis) were seen in children who had stopped cotrimoxazole. Children who stopped cotrimoxazole were more likely to get malaria, and were also more likely to have anaemia. This is similar to what was seen in the CHAP study of Zambian children who had not started ART.

Other trials are currently looking at whether cotrimoxazole prophylaxis may also be beneficial to other groups, including HIV-negative malnourished children and children with anaemia.

Implementing continued cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis is routinely used for adults and children with HIV. Continuing cotrimoxazole prophylaxis for children on ART is therefore feasible. Cost is a major factor in the implementation of health interventions. Cotrimoxazole is a very inexpensive drug (a few cents per day). Cost-effectiveness analyses linked to the ARROW study found that continuing cotrimoxazole prophylaxis in children on ART is actually cost-saving. The reduction in hospitalisation more than outweighs the cost of the drug.

Acceptability and adherence are both important factors that affect implementation. Continuing cotrimoxazole prophylaxis once children are on ART does add to the pill burden faced by children and their carers, and there were concerns that this may reduce adherence to ART. However, ARROW found that there was no difference in adherence to ART between those who continued or stopped cotrimoxazole. Continuing cotrimoxazole prophylaxis does seem to be acceptable to carers and children, as less that 6% of carers/children reported missing doses of cotrimoxazole in the previous 4 weeks. In fact, a quarter of those approached to take part in the trial refused, mainly because carers had a strong belief that cotrimoxazole was beneficial, so did not want to stop.

The main barrier to children continuing on cotrimoxazole prophylaxis is problems with the supply chain and stockouts. The situation analysis conducted as part of the Lablite project found that 12 out of 37 health facilities in Uganda, 11 out of

**Box 1: Implementing continued cotrimoxazole prophylaxis for children who are stable on ART**

1. Ministries of Health should issue ‘rapid advice’ to health facilities advising them to continue cotrimoxazole prophylaxis in children who are stable on ART, while awaiting formal amendments to existing guidelines on ART and cotrimoxazole prophylaxis

2. National and international policies and guidelines need to be updated to recommend that children continue cotrimoxazole prophylaxis when they are on ART, irrespective of CD4 count and age

3. The updated guidelines and evidence on cotrimoxazole prophylaxis should be incorporated into training and teaching for existing and new healthcare workers

4. If necessary, ART treatment cards and registers for children should be updated to incorporate data on the use of cotrimoxazole prophylaxis

5. Ensure cotrimoxazole prophylaxis is available free-of-charge to HIV-positive children on ART

6. If necessary, order cotrimoxazole in appropriate formulations (eg. scored pills) for children, packaged in quantities that allow easy dispensing to save pharmacy time

7. Ensure cotrimoxazole drug forecasting, procurement and supply to all ART centres is done well to avoid stockouts

Based on Harries et al. 2011: Operational research in Malawi: making a difference with cotrimoxazole preventive therapy in patients with tuberculosis and HIV. BMC Public Health 11:593

"Cotrimoxazole prophylaxis reduced hospitalisations and deaths in all children, including those with CD4%>=30%"
CONCLUSIONS AND RECOMMENDATIONS

Conclusions

It has been known for years that cotrimoxazole prophylaxis for HIV-infected children and adults before they start ART saves lives and is highly cost-effective. The new findings from ARROW show that children should stay on cotrimoxazole prophylaxis long-term, even after they are stable on ART, regardless of CD4 count. Cotrimoxazole reduces hospitalisations for infections, and because of its low cost, continuing prophylaxis is actually cost-saving. In order to reap the benefits of cotrimoxazole prophylaxis countries should invest in their supply chain systems to make sure it is available to all who need it.

Recommendations

National and international policies should recommend that children continue cotrimoxazole prophylaxis when they are on ART, irrespective of CD4 count and age. Ensure that staff at all health care facilities involved in providing care to children with HIV are aware of which children should receive cotrimoxazole prophylaxis, and the need to continue it regardless of CD4 count. Improve supply chains to ensure uninterrupted supply of cotrimoxazole to health facilities of all levels.

Recommended reading


Credits

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