Briefing Paper
March 2013
Issue 7

Induction-maintenance strategies for first-line ART for children

Introduction

Treating children with HIV is often perceived as more complex than treating adults. This is perhaps why children's access to ART has lagged behind that of adults, with only 28% of children in need of treatment receiving it by the end of 2011, compared to 58% of adults. There are certainly differences between HIV-infected children and adults. Untreated children tend to have higher viral loads than adults, and three-drug regimens have been less successful in achieving viral load suppression in children than adults, possibly because how drugs are absorbed and used by the body is more variable in children, and possibly because of challenges giving medicines to children. Less research has been done looking at how best to treat children with HIV than adults, and the results from adults may not necessarily apply for children. This brief looks at the evidence from the ARROW trial, which compared a standard WHO-recommended regimen for children with a strategy of starting with a potentially more potent 4-drug regimen (induction) and then dropping to 3 drugs (maintenance), to see if this can improve outcomes for children.

ART strategies

The WHO guidelines for treating children in low and middle-income countries currently recommend a 3-drug regimen consisting of 2 NRTIs and 1 NNRTI. NRTI/NNRTI-based regimens are recommended because they are efficacious and generally less expensive than other regimens. In addition, generic formulations are available as fixed dose combination (FDC) paediatric mini-pills, and a cold chain is not required.

Results from several small observational studies have suggested that regimens of 4 drugs (3NRTIs+1NNRTI) may have better viral load and immunological outcomes than 3 drug regimens.

Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs suppress replication of retroviruses by interfering with the reverse transcriptase enzyme. The main NRTI drugs used for treatment of children in low-income countries are Lamivudine (3TC), Emtricitabine (FTC), Zidovudine (AZT), Abacavir (ABC), Tenofovir (TDF) and Stavudine (d4T).

WHO recommend 3TC with ABC or with ZDV as the 2NRTIs to be used in first-line treatment. ABC+3TC has been shown to be more potent than ZDV+3TC and the ARROW trial also showed that it can be given once daily.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTIs also block the replication of HIV by interfering with reverse transcriptase. They are widely used, and effective at rapidly reducing viral load, but a single mutation can cause cross-class resistance. The most commonly used NNRTI drugs for the treatment of children in low-income countries are Efavirenz (EFV) and Nevirapine (NVP).

Key Points

- WHO guidelines currently recommend treating HIV-infected children with 3-drug regimens (including 2NRTIs +1 NNRTI)
- **Children responded very well to a standard treatment with an NNRTI regimen with ABC+3TC**; this was equally the case in children <3 years taking nevirapine compared with older children taking nevirapine or efavirenz. Overall, very few children died or needed to switch treatment because of first-line failure; and after nearly 4 years, 83% had suppressed viral load and only 1% had low CD4.
- **Children receiving an induction phase of 4 drugs had better early CD4 and viral load responses compared with those taking 3 drugs**, particularly in those with low CD4 when treatment started; however, these benefits were not sustained after the fourth drug was dropped during the 3 drug maintenance phase
- **After an induction phase with 4 drugs (including an NNRTI), children treated with triple NRTI long-term maintenance did well clinically and immunologically even though their viral load suppression was less good than those on a regimen of 3TC/ABC/NNRTI.** This suggests that 3NRTI can be used during short-term TB treatment in children who are already on ARVs, avoiding challenges of complex drug-drug interactions. In addition, young children who are on a 4 drug regimen can safely drop nevirapine if they need to start treatment for TB.

These regimens have been used mainly in very young children who have particularly high viral loads, as an alternative to using a protease inhibitor (PI) with 2NRTI drugs which is potent in young children but logistically difficult to give and costly. However, using 4-drugs long-term would also have substantial cost implications, as children need to be treated for life. There are also possibilities of increased side effects from using 4 drugs rather than 3 drugs, and adherence issues related to pill burden.

An induction-maintenance approach, where children are treated for an induction period with 4 drugs, followed by a maintenance period with 3 drugs, may offer several advantages, including reducing viral loads more quickly than 3-drug regimens, but also being less costly and with fewer side-effects than continued 4-drug regimens. If an NRTI drug can be dropped after the induction phase, and the benefits sustained long-term with maintenance on 2NRTI+NNRTI, this could be as good as using a PI+2NRTI regimen which is increasingly used for young children. In addition, if the NNRTI were dropped after induction and treatment safely continued with 3NRTIs, that would avoid the difficulties of managing interactions with anti-tuberculosis drugs, particularly for young children unable to take efavirenz.

The ARROW trial tested whether these approaches were safe and effective.

Testing the induction-maintenance strategy in the ARROW trial

ARROW was a large randomised controlled trial carried out in Uganda and Zimbabwe. It compared the WHO-recommended 2NRTI+NNRTI ART strategy with two induction-maintenance approaches

- 397 children were treated with lamivudine+abacavir+NNRTI (2NRTI+NNRTI) continuously
- 404 children were treated with an induction phase of lamivudine + abacavir + NNRTI + zidovudine (3NRTI+NNRTI) for 36 weeks, followed by maintenance of lamivudine+abacavir+NNRTI (2NRTI+NNRTI)
- 405 children were treated with an induction phase of lamivudine + abacavir + NNRTI + zidovudine (3NRTI+NNRTI) for 36 weeks, followed by maintenance of lamivudine+abacavir+zidovudine (triple NRTI)

During the induction phase, children on 4 drugs could drop a drug due to side effects or potential drug interactions if needed (for example, if they needed to start anti-tuberculosis treatment). The children were followed-up for up to 5 years (average 4 years).

Induction-maintenance or three drugs throughout?

ARROW looked at clinical, immunological and viral load outcomes from the three arms.

Regimens by the end of the trial

Children in all three arms of the trial did well on their treatment. Nearly all children stayed on first line treatment, with no significant differences between the arms:

- 93% in the continuous 2NRTI+NNRTI regimen
- 96% in the 4 drug induction followed by 2NRTI+NNRTI maintenance regimen
- 95% in the 4 drug induction followed by 3NRTI maintenance regimen

At their last clinic visit, after around 4 years of follow-up, nearly all children were alive and still on their exact randomised regimen:

- 83% in the continuous 2NRTI+NNRTI regimen
- 88% in the 4 drug induction followed by 2NRTI+NNRTI maintenance regimen
- 91% in the 4 drug induction followed by 3NRTI maintenance regimen

Immunological (CD4) and virological (VL) responses

Children who received 4-drug induction when starting ART had greater early CD4% increases than those in the 2NRTI+NNRTI arm (at week 36, the end of the induction phase). However, once the fourth drug had been dropped in the two induction-maintenance arms, this difference was not sustained long-term. By weeks 72 and 144 there was no significant difference between the arms in change in CD4 . The same was true for viral load: initial suppression at 24 weeks was better in the 4-drug than the 3-drug arms (88% vs 77% <400copies/ml) but this was not sustained long-term.

There was a suggestion that children starting treatment with very low CD4 percentages (<5%) who received a four-drug induction phase had better CD4 responses even through to week 72 than those who had 3 drugs throughout, and that fewer children remained at high risk of getting sick with CD4% <5% in the induction arms compared to the standard arm. However this group of children was small, so the evidence on this is not very strong.

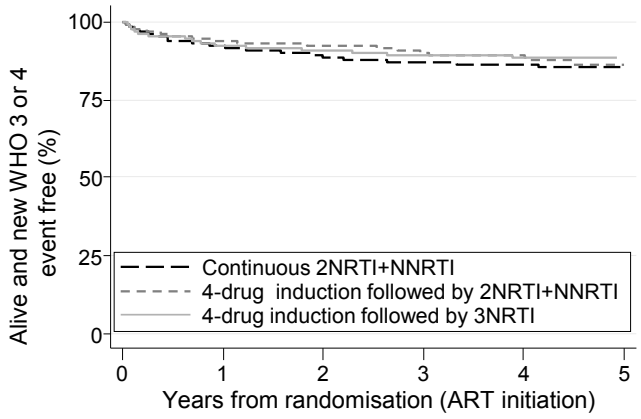
At the end of the trial children who were receiving 2NRTI+NNRTI as either a maintenance regimen or from the start of the trial had better viral load suppression than those who were receiving 3NRTI maintenance (84% vs 65% <400copies/ml, 79% vs 57% <80copies/ml).

Clinical outcomes

There was no difference in mortality, progression to new WHO 4 events or deaths, or progression to new WHO 3/4 events and death between the three strategies. Deaths and clinical progression were rare in all arms of the trial. Only 40 children in the continuous 2NRTI+NNRTI arm, 32 children in the 4 drug induction followed by 2NRTI+NNRTI maintenance arm, and 32 children in the 4 drug induction followed by 3NRTI maintenance regimen died or had a new WHO 4 event.

There was also no evidence of differences in weight-for-age or height-for-age across the ART strategies. The

Time to new WHO 3 or 4 event or death



greater initial CD4 increases in children taking 4-drug inductions did not significantly reduce disease progression in the first year. Despite having lower long-term viral load suppression, children on the 3NRTI maintenance regimen did not have higher rates of clinical events (WHO3/4 or deaths) – if anything they had fewer events after one year than children in the other two arms, but this was not statistically significant.

Adverse events & drug substitutions

There were 151 first-line drug changes (ie changing or stopping one drug in the regimen), 59(39%) of which were due to adverse events, and 59(39%) due to starting anti-tuberculosis treatment (the rest for a number of different reasons, many because of carer preference). 59 children stopped nevirapine because of starting anti-tuberculosis treatment within the first 36 weeks. In the continuous 2NRTI+NNRTI arm children swapped nevirapine for zidovudine if they were less than 3 years old, or efavirenz if they were over 3 years old. In the 4-drug induction-maintenance arms about a third of children who needed to start anti-tuberculosis treatment were able to simply drop nevirapine and continue on 3NRTIs.

Children in the induction-maintenance arms (which included zidovudine) were more likely to experience at least one grade 3/4 adverse event However, this difference is almost exclusively due to more low neutrophils (neutropenia) without any clinical symptoms, and only 6 had to change treatment because of this. The most common drug change made by doctors was for children on the 4-drug induction phases to stop or change zidovudine for anaemia (27 children). However, there was no evidence that anaemia was more common in children taking zidovudine than those who did not take zidovudine. This suggests that anaemia in children on ART is more likely due to their underlying HIV disease, than the drugs they take to treat it.

Adherence

Self-reported early adherence was slightly better in children on the continuous 2NRTI+NNRTI arm than in the 4-drug induction-maintenance arms.

Conclusions

One of the key findings from the ARROW trial is that children respond very well to treatment with 2NRTIs + NNRTI, with good CD4, viral load and clinical outcomes, regardless of ART strategy or monitoring approach. Responses to treatment were just as good in those under the age of 3 and those older than 3 years. Treatment failure was rare, with more than 95% of children still on first-line ART after nearly four years of treatment. For most outcomes there was little or no difference between the three ART strategies overall.

The induction-NNRTI-maintenance approach may offer some advantages over continuous 2NRTI+NNRTI treatment. During the induction phase, children had better CD4 responses and viral loads. However these differences were not sustained once the children moved onto the maintenance phase. For children starting treatment with very low CD4%, the benefit of the induction phase may last longer, at least to 72 weeks, although further evidence is needed to confirm this. As children starting treatment with very low CD4% have greater risks of long-term failure, this approach might still be worth considering.

ARROW provides reassurance about the use of zidovudine for children. Anaemia was no more common in those taking zidovudine than in those not taking it. Children taking zidovudine were more likely to have neutropenia, but this was asymptomatic, and did not require changes to their drug regimen.

The arm with the 3NRTI maintenance regimen was less good at suppressing viral loads over the long-term than the continuous 2NRTI+NNRTI and the 2NRTI+NNRTI maintenance arms, which suggests that this should not be used as a long-term approach. However, children in the 3NRTI maintenance arm did as well in terms of CD4 and clinical responses compared to those on 2NRTI+NNRTI, suggesting this strategy is safe for a short time for children who develop TB while on ARVs and need to start taking anti-TB drugs. This indicates that children already on ART who need anti-tuberculosis treatment can safely switch to a 3NRTI for the length of their TB treatment.

RECOMMENDATIONS

- Health workers should not delay putting eligible children on to ART: children respond very well to treatment and side-effects are unusual and less common than in adults.
- A regimen of ABC+3TC+NNRTI is as good as an induction-maintenance approach for most children over the long-term, leading to excellent long-term clinical, immunological and viral load outcomes
- Children starting ART with very low CD4% (<5%) may benefit from a 3NRTI+NNRTI induction phase for 36 weeks, although more research is needed to confirm this.
- The good clinical and immunological effects of 3NRTI maintenance long-term suggest that for children already on ART, 3NRTIs can safely be used if a child gets tuberculosis and needs to go onto anti-tuberculosis drugs

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**.

World Health Organisation, **Antiretroviral therapy for HIV infection in infants and children: towards universal access: Recommendations for a public health approach. 2010 Revision.** 2010, World Health Organisation: Geneva. http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf

Credits

This policy brief was written by Annabelle South, Mutsa Bwakura-Dangarembizi, Adrian Cook, Jane Crawley, Adeodata Kekitiinwa, Paula Munderi, Andrew Prendergast, Sarah Walker and Di Gibb on behalf of the ARROW trial team.

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.

UKaid
from the British people

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. It also examined whether children stable on ART could safely stop cotrimoxazole prophylaxis.

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