Evidence For Action on HIV treatment and care systems

DART

Briefing Paper
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Reducing early mortality on ART

Early mortality on ART

Increasing access to antiretroviral therapy (ART) has helped to reduce mortality and morbidity massively for people living with HIV. However, early mortality rates of those who on ART in sub-Saharan Africa are very high. A substantial proportion of patients die within the first year of starting ART. This briefing paper explores the evidence on whether Cotrimoxazole (CTX) prophylaxis can reduce mortality for those on ART, and how long it is useful for. We also present new evidence supporting the use of CTX prophylaxis for at least the first 72 weeks after starting ART.

A nurse dispensing cotrimoxazole to a patient in Uganda

CTX prophylaxis to reduce morbidity and mortality

There is strong evidence that CTX prophylaxis reduces mortality, morbidity and hospital admissions among adults and children with HIV who are not on ART. This is even the case in areas of high background bacterial resistance.

WHO issued recommendations in 2006 that CTX prophylaxis should be given to all HIV-exposed infants from 6 weeks until shown not to be infected; all symptomatic HIV-infected adults and children; all HIV-infected adults and children who are asymptomatic but have mild to moderate immune suppression.

There is also good evidence that CTX prophylaxis is highly cost-effective, both for adults and children. It may even be cost saving in some settings (such as for children in Zambia), as it reduces hospital admission costs.

While there is good evidence of the effectiveness of CTX for HIV-infected people who are not on ART, less is known about

Key Points

- Cotrimoxazole prophylaxis can reduce mortality of people living with HIV, including those on ART
- New evidence suggests that it can be beneficial for at least 72 weeks after starting ART, regardless of CD4 count

Key terms

Cotrimoxazole (CTX) (trimethoprim-sulfamethoxazole) is a widely available, low cost antibiotic that can be used as prophylaxis against several important opportunistic infections, including Pneumocystis jirovecii pneumonia.

its use for people who are on treatment.

What do the guidelines say about when to stop CTX prophylaxis?

The 2006 WHO guidelines acknowledge that there is a lack of evidence for when to discontinue CTX prophylaxis for patients on ART in resource-limited settings. Because of this, "the general recommendation is to continue CTX prophylaxis among adults living with HIV indefinitely" (WHO 2006). However, the guidelines also suggest that some countries may consider discontinuing CTX prophylaxis for adults when patients CD4 cell counts reach more than 200 or 350 after at least 6 months of ART. For children the recommendation is to continue for the long-term.

When is CTX prophylaxis being stopped for people on ART?

In high-income countries CTX prophylaxis is usually stopped for people on ART when their CD4 count exceeds 200 cells per µL. Much less in known about when (and why) CTX prophylaxis is stopped for those on ART in low-income settings. In order to find out what is being done in relation to stopping CTX prophylaxis for patients on ART, Evidence for Action are carrying out a research project into current CTX prophylaxis practice on this in three sub-Saharan African countries. Early findings suggest that there are differences in the way data on CTX prophylaxis are recorded in clinics and in the way in which the provision of CTX prophylaxis is monitored and evaluated.

Cotrimoxazole prophylaxis can help reduce mortality of ART patients like Christine for the first 72 weeks of treatment.

Evidence on when to stop

Most of the evidence of when CTX prophylaxis should be stopped for patients on ART comes from high-income settings. This evidence suggests that CTX prophylaxis should be stopped for patients on ART when their CD4 cell count has increased to more than 200 cells per µL. However, there are considerable differences between high-income and low-income settings in terms of the prevalence of different opportunistic infections that CTX can help prevent, and levels of resistance to CTX. This means that evidence from low-income settings is needed to help inform policy and practice in this area.

To date the evidence from low-income settings comes from observational studies rather than randomised controlled trials (RCT).

A retrospective cohort study from Malawi, comparing ART clinic outcomes from clinics giving CTX as well as ART with clinics only providing ART, found that CTX prophylaxis was associated with a 6-month mortality risk reduction of over 40%. This indicates that for at least the first six months of ART, CTX prophylaxis is beneficial. A study in Uganda that compared clinical outcomes of patients on ART who discontinued CTX prophylaxis with those who continued it after their CD4 count exceeded 200 found that those who discontinued CTX prophylaxis had 28 times the risk of malaria than those who continued, and 1.8 times the risk of diarrhoea.

We present here new evidence on the use of CTX prophylaxis for patients on ART, from observational data from the DART trial in Uganda and Zimbabwe. Outcomes were compared between patients on ART who received CTX, and those on ART who did not. CTX prophylaxis reduced mortality by 35% overall. The reduction was similar for those with CD4 counts over and those under 200. In the first 4 weeks of initiating ART the reduction was even more marked, at 58%, but this effect declined to 5% in weeks 68-72, with no effect after 72 weeks. The research found that CTX prophylaxis continued to reduce mortality for up to 72 weeks in patients on ART, irrespective of CD4 count. The DART data also showed that in Uganda, where malaria incidence is high, CTX prophylaxis reduced the risk of a new malaria episode by 26%, even after 72 weeks.

This evidence is not as strong as ideally required for decision making. But until results from randomised trials are available this evidence does help to inform decisions about when CTX prophylaxis should be used for patients on ART. The ARROW trial is including a study of when CTX prophylaxis should be stopped for children. The results of this study are due in mid-2012. Research has also started on the COSTOP Trial, which is examining the safety of discontinuing CTX prophylaxis among adults in Uganda, and results are expected in 2012. However, until these results are available, management of CPT for patients on ART will continue to be based on limited evidence.

This new evidence from the DART trial suggests that CTX prophylaxis can reduce mortality for at least the first 72 weeks of ART, even for patients with CD4 counts above 200. It is safe, has good tolerability and is low-cost, and could have a substantial public health effect.

Policy recommendations

- Ensure that supplies of CTX prophylaxis are available for people living with HIV both before and after initiation of ART.
- Until further evidence from RCTs, CTX prophylaxis should be provided to patients on ART in Africa for at least the first 72 weeks of treatment, to reduce mortality and morbidity.
- National control programmes should improve the consistency of monitoring and evaluation of CTX prophylaxis provision, to allow assessment to be made of whether it is provided to those who could benefit from it.

Research priorities

- The ARROW and COSTOP trials of discontinuation of CTX prophylaxis will provide very useful evidence for formulating policy in this area.
- Little is known about when CTX prophylaxis is actually stopped in practice. The results of the current Evidence for Action study mapping CTX prophylaxis implementation will shed some light on this.

Credits

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Recommended Readings

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Evidence For Action on HIV treatment and care systems

About Evidence for Action

Evidence for Action is an international research consortium with partners in India, Malawi, Uganda, UK and Zambia, examining issues surrounding HIV treatment and care systems.

The research is organised in four key themes:

1. What "package" of HIV treatment and care services should be provided in different settings?
2. What delivery systems should be used in different contexts?
3. How best should HIV treatment and care be integrated into existing health and social systems?
4. How can new knowledge related to the first three questions be rapidly translated into improved policy and programming?

Partners:

International HIV/AIDS Alliance, UK

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London School of Hygiene and Tropical Medicine, UK

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