**High mortality among people starting ART with low CD4 counts**

Recent changes in guidelines and the scale-up of ART in sub-Saharan Africa have seen a move towards recommending people start ART at higher CD4 counts. But a substantial proportion of people still do not get diagnosed or started on ART until their CD4 counts are very low. Between one in four and one in five people initiating ART in many low and middle income countries have CD4<100 cells/mm$^3$. These people are at a high risk of dying during the first weeks of treatment. Data from South Africa showed that people starting ART with CD4<50 cells/mm$^3$ were six times more likely to die in the first year on treatment compared to those starting ART with CD4>200 cells/mm$^3$. In the DART (adult) and ARROW (paediatric) trials, around one in every 10 people with CD4<50 cells/mm$^3$ died within the first 24 weeks of starting ART, most often within the first month. We need to identify ways to reduce this early mortality and severe HIV-related illness.

There are a combination of factors that may account for this high early mortality, including:

- high rates of co-infections (including tuberculosis, bacterial infections (such as pneumonia), fungal/protozoal infections (such as cryptococcal meningitis) and parasites (such as gut worms))
- immune reconstitution inflammatory syndrome (IRIS)
- malnutrition
- advanced HIV infection (ie. anti-HIV drugs cannot work fast enough)

This means there are a number of interventions addressing these different factors that may help to reduce early mortality on ART among people with severe immune-suppression.

**Key points**

- Many people in Africa are still not starting ART until their CD4 counts are very low (<100 cells/mm$^3$), placing them at high risk of death in the early stages of treatment
- CD4 testing is essential to identify who needs additional support while initiating ART as many have few or no symptoms
- REALITY tested an enhanced prophylaxis package (adding isoniazid, fluconazole, azithromycin and albendazole, to standard cotrimoxazole prophylaxis) for the first 12 weeks of treatment, to reduce this early mortality
- Enhanced prophylaxis led to a decrease in deaths and HIV-related illness and hospitalisation
- Enhanced prophylaxis for the first 12 weeks of ART can prevent more than 3 deaths for every 100 people starting ART with CD4 <100/mm$^3$
- Enhanced prophylaxis is a low-cost, acceptable intervention that could help countries in sub-Saharan Africa to reduce HIV deaths and illness
- It could be that this package would also be valuable for patients switching to secondline ART with low CD4 counts
Does enhanced prophylaxis reduce early mortality?

Why investigate enhanced prophylaxis?
Bacterial infections, TB, oesophageal candidiasis and cryptococcal meningitis are key causes of deaths and illness in the first few months on ART for people in sub-Saharan Africa. Prophylaxis to prevent these infections could have a significant impact on mortality and morbidity.

Current WHO guidelines recommend cotrimoxazole prophylaxis for all adults and children initiating ART. They also recommend that people who are unlikely to have TB should be offered Isoniazid Preventive Therapy (IPT).

The REALITY trial
The REALITY trial aimed to identify ways to reduce early mortality among those initiating ART with advanced disease. It was investigating three different approaches for the first three months of treatment, in addition to standard triple ART and cotrimoxazole prophylaxis:

1. Enhanced prophylaxis (including isoniazid, fluconazole, azithromycin and albendazole, all started at the time of starting ART) to prevent infections
2. Increasing the potency and speed of action of ART by adding raltegravir to reduce the viral load faster
3. Ready-to-Use Supplementary Food to improve nutritional status

1,805 people (1733 adults and 72 children/adolescents) from Kenya, Malawi, Uganda and Zimbabwe took part in the REALITY trial. The REALITY trial was open to HIV infected adults, adolescents and children aged 5 years or older who:

• Had not taken ART before (including drugs for prevention of mother to child transmission)
• Had a CD4 cell count <100 cells/mm³
• Had no major contraindications to any study drugs
• Were not pregnant or intending to become pregnant during the next 12 weeks

The median age of participants was 36 years, and 53% of people taking part were male. Median baseline CD4 cell count was 36 cells/mm³ (IQR 16-62) but 47.3% were WHO stage 1/2 (ie. had at most mild/moderate illnesses associated with HIV).

The REALITY trial started in 2013, and the last patient visit was in March 2016. Participants were followed up for 48 weeks.

However, they do not say when IPT should be started in relation to ART initiation for those with severe immune-suppression. In addition, national guidelines have varied (eg Malawi guidelines did not recommend IPT for patients after starting ART at the time of the trial) and while cotrimoxazole prophylaxis is routinely given to people starting ART, IPT implementation is very low, with few patients being given it.

What bundle of enhanced prophylaxis did REALITY investigate?
• Continuous daily cotrimoxazole
• At least 12 weeks of daily isoniazid and pyridoxine (with duration of treatment depending on local guidelines)
• 12 weeks of daily fluconazole (100mg)
• 5 days of azithromycin
• A single dose of albendazole

The enhanced prophylaxis bundle did increase the number of pills patients had to take, although this was helped by providing cotrimoxazole, isoniazid and vitamin B6 (pyridoxine) in a single fixed dose combination tablet. In effect, this meant that people taking part only had to take one extra tablet a day for the full 12 weeks (fluconazole), plus 5 days of azithromycin and a single dose of albendazole.

This bundle of enhanced prophylaxis was compared against the standard of care, which was continuous cotrimoxazole prophylaxis (plus IPT started at 12 weeks, where local guidelines recommend IPT).

Did the enhanced prophylaxis bundle work?
Enhanced prophylaxis significantly reduced mortality and morbidity:

• There was a significant absolute reduction in mortality at 24 weeks of 3.3%, from 12.2% to 8.9%. This is a 27% relative reduction.
• It also significantly reduced WHO 3/4 events and deaths, by about a quarter.
• TB incidence significantly dropped from 10.0% to 7.1%.
• Cryptococcal disease incidence fell significantly, from 2.6% to 1.0%, and cryptococcal deaths fell by over 70%.
• Oral/oesophageal candidiasis incidence fell significantly, from 2.6% to 1.1%.
• There was a reduction in the number of hospitalisations from 20.7% to 17.0%.
Diagnosing severe bacterial infections in settings like those where REALITY was carried out is difficult. Enhanced prophylaxis did not appear to significantly reduce diagnosed severe bacterial infections. However, it may be that it did have an impact on undiagnosed severe infections. A large proportion of deaths were from unknown causes and occurred soon after starting ART in the trial; these could be partly due to undiagnosed severe bacterial infections – these deaths from unknown causes were significantly fewer in the enhanced prophylaxis arm.

There was no difference in side-effects between the enhanced and standard prophylaxis groups, and few people had to discontinue prophylaxis drugs because of side effects. There was no difference in HIV viral load between the enhanced and standard prophylaxis groups, suggesting the extra pills in the enhanced group did not affect how people took their ART pills.

Implementing the enhanced prophylaxis bundle

Identifying people who need enhanced prophylaxis

CD4 tests at baseline are vital to identifying those who need the enhanced prophylaxis bundle. Almost half of participants who took part in REALITY (all with CD4 counts of <100 cells/mm$^3$; the average CD4 count was only 36 cells) were WHO stage 1 or 2, and would therefore be unlikely to be picked up through clinical screening as in need of enhanced prophylaxis. So while lack of availability of CD4 test results should not be a barrier to ART initiation, they still have a role to play in the era of immediate ART initiation.

Pill burden and acceptability of enhanced prophylaxis

The enhanced prophylaxis bundle does mean that patients are required to take more tablets for the first 12 weeks of treatment than they would under the current standard practice. Social science work and questionnaire surveys carried out as part of the REALITY trial found that people were not concerned about this. Similar numbers found taking the enhanced prophylaxis easy or very easy as those taking cotrimoxazole alone. The impact of enhanced prophylaxis on the pill burden was reduced by the use of the fixed dose combination tablet of cotrimoxazole, isoniazid and pyridoxine, meaning patients only needed to take one extra tablet a day for most of the 12 weeks.

This fixed dose combination tablet is on the WHO Model List of Essential Medicines. Using this fixed dose combination will ease the logistical burden on pharmacies and supply chains as well as the pill burden for patients, and may help to increase the availability of IPT, which is currently unavailable in many settings.

Cost-effectiveness of the enhanced prophylaxis package

The drugs that make up the bundle are all low-cost. The cost of the drugs used in the enhanced prophylaxis bundle ranged from $7.16 per adult in Kenya to $32.99 in Zimbabwe. Taking the minimum
drug costs across the countries involved in the trial, the drugs package was only $5 more expensive per patient than the standard cotrimoxazole drug costs ($5.61 vs $0.76). Health economists did an analysis which showed that the package was highly cost-effective in all the countries where the trial was carried out.

The remaining questions

What about children?

There were few children in REALITY, so we cannot be absolutely sure that the overall results apply to them. However, there was no evidence of a difference in results between adults and children in the trial and we have no reason to believe that the enhanced prophylaxis bundle would not be beneficial for them. Older children are vulnerable to TB, cryptococcal meningitis, other infections and worms, so we recommend that children aged 5 years and over are given enhanced prophylaxis if they have low CD4 counts.

Do we need all the components of the bundle?

REALITY tested the bundle of enhanced prophylaxis as a whole, and it is hard to unpick the effects of the individual drugs. While there was no difference in diagnosed severe bacterial infections between the groups, azithromycin may have contributed to the reduction in deaths from unknown causes (diagnosing severe bacterial infections is difficult in settings like those where REALITY took part). We cannot be sure that leaving out either azithromycin or albendazole would not reduce the benefit seen from the enhanced prophylaxis bundle. We are planning more research on samples collected in the trial to try and answer this question.

Recommendations

1. A bundle of enhanced prophylaxis, including:
   - Continuous cotrimoxazole
   - At least 12 weeks of isoniazid and pyridoxine
   - 12 weeks of fluconazole
   - 5 days of azithromycin
   - A single dose of albendazole
   should be given to all people over the age of five initiating ART with CD4 cell counts <100 cells/mm³.

2. While lack of availability of CD4 test results should not be a barrier to ART initiation, CD4 tests still have a role to play in the era of immediate ART initiation; to identify people with low CD4 counts who will require additional support.

Conclusions

One in five people starting ART in low and middle-income countries have CD4 counts of less than 100 cells/mm³. In sub-Saharan Africa, assuming 1.5m people initiate treatment each year, this translates to around 300,000 people a year. It would be hard to identify these people without a baseline CD4 test, as almost half of REALITY trial participants (median CD4 of 36 cells/mm³) were WHO stage 1 or 2 and had few symptoms. People with CD4 counts of <100 cells/mm³ are at a high risk of dying during their first 6 months on treatment – around one in eight people on standard cotrimoxazole prophylaxis died within 6 months of starting ART in the REALITY trial.

Providing an enhanced bundle of prophylaxis, including isoniazid, vitamin B6, fluconazole, azithromycin and albendazole in addition to cotrimoxazole, reduces mortality among those starting ART at low CD4 counts. For every 100 people who receive this bundle, more than three deaths are prevented. It could prevent around 10,000 deaths each year if given to everyone initiating ART with low CD4 counts in sub-Saharan Africa. The bundle also reduces illnesses including TB, cryptococcal disease and candida disease. This bundle should become part of the standard of care to be given immediately with initiation of ART in adults and children with CD4 counts of <100 cells/mm³ in sub-Saharan Africa.

Further information

- Film about the REALITY results

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