AIDS briefs

Late treatment in Africa may disadvantage those with HIV for years

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Starting antiretroviral therapy earlier, before the development of symptoms, is the most likely way to reduce the high death rates after treatment initiation seen in people with HIV in resource-limited settings, two large cohort analyses show. The studies also show that the major disadvantage of starting treatment late – an increased risk of death – may persist for some years, burdening already overstretched health systems with illness that could be avoided by earlier treatment.

The findings, presented last week at the Sixteenth Conference on Retroviruses and Opportunistic Infections in Montreal, are likely to strengthen the case for a stronger global recommendation that people with HIV should start treatment when the CD4 cell count falls below 350 cells/mm^3, wherever resources permit.

Current World Health Organization guidelines endorse treatment for anyone with a CD4 count below 200, and advise clinicians to 'consider' treatment in anyone with a CD4 count between 200 and 350 cells/mm^3, with the aim that treatment should start before the CD4 count falls below 200 cells/ mm^3.

Current national guidelines in many countries in Asia and sub-Saharan Africa continue to emphasise treatment for those with CD4 counts below 200 cells/mm^3, due to concerns about the cost of treatment and the capacity to deliver it to larger numbers of patients.

However, there is accumulating evidence that, due to late diagnosis, many people are continuing to start HIV treatment very late – often at CD4 counts below 50 cells/mm^3. These individuals are much more likely to die or develop serious illnesses after starting treatment and, as Dr Stephen Lawn of the University of Cape Town pointed out to the conference, 'Our hospitals are chock-a-block and just can't cope' as a consequence of the failure to identify patients with HIV earlier and to begin treatment earlier. A systematic review of published studies by Stephen Lawn and colleagues shows death rates of between 8% and 26% among cohorts starting treatment late.

The two studies presented at CROI 2009 provide compelling evidence of the costs of late treatment initiation, for people with HIV in terms of lives lost, and for health systems in terms of the burden of avoidable disease occurring as a result of late identification and treatment of people with HIV infection.

The consequences of late treatment initiation in Gugulethu, South Africa

Stephen Lawn presented results from patients receiving antiretroviral treatment through a community-based programme in Gugulethu, a township near Cape Town. The study looked at the risk of death not only on the basis of the CD4 count at the time treatment was started, but on the basis of the updated CD4 count at specific time-points during the 4-year follow-up period.

Follow-up data were available for 2 423 people who had initiated antiretroviral therapy, observed for 3 155 person-years. The study population's median baseline cell count was 105 cells/mm^3; CD4 cell count levels were subsequently measured at 4-month intervals.

The cumulative mortality after 48 months of follow-up was 13.2%, lower than many cohorts in Africa, but among individuals who started treatment with a CD4 count below 100 and an AIDS-related illness, the 48-month cumulative mortality was 24.8%.

There were 197 deaths, with the following associations between updated CD4 cell count levels and mortality rate ratios: 0 - 49 cells/mm^3 11.6; 50 - 99 cells/mm^3 4.9; 100 - 199 cells/mm^3 2.6; 200 - 299 cells/mm^3 1.7; 300 - 399 cells/mm^3 1.5; 400 - 499 cells/mm^3 1.4; and 500 cells/mm^3 or more 1.0.

When the researchers calculated person-time within updated CD4 cell count strata, they found high mortality during the first year of treatment to be related to the large proportion of person-time spent at less than 200 CD4 cells/mm^3. People with less than 100 CD4 cells/mm^3 had higher cumulative mortality estimates at 1 and 4 years than those whose baseline CD4 cell counts were higher (1-year: 11.6% v. 5.2% mortality; 4-year: 16.7% v. 9.5% mortality).

The researchers attribute this to person-time spent at low CD4 cell counts, and conclude: 'National HIV programmes in resource-limited settings should be designed to minimise the time that patients spend with CD4 counts [below] 200 cells/mm3 both before and during [use of antiretroviral therapy].'

Dr Lawn said that health systems have two options: either continue in 'firefighting' mode, treating AIDS-related illnesses as they arise in people who start treatment late, or treat people earlier and reduce the burden of mortality and morbidity caused by HIV. But he warned: 'Firefighting is very difficult and time-consuming and takes up a huge amount of resources'.

Mortality in people with HIV compared with background population levels

The other study compared the mortality rates of antiretroviral-treated people in four sub-Saharan African countries with all-cause mortality in the corresponding populations. HIV-related mortality data were drawn from antiretroviral treatment programmes in Ivory Coast, Malawi, South Africa and Zimbabwe. The researchers used estimates from the World Health Organization (WHO) Global Burden of Disease project to calculate the expected numbers of non-HIV-related deaths in the relevant populations.

Data on clinical stage of HIV disease were available for 13 249 HIV-positive people with 14 695 person-years of follow-up; 85% had advanced disease when they began taking antiretroviral therapy. A total of 1 177 deaths occurred during 14 695 person-years of follow-up, a cumulative mortality of 11.7%.

They found that people with advanced HIV disease (<50 cells/mm^3) had a mortality rate 500 times higher than the background rate in the local population, and among those who started treatment with a CD4 count below 25 cells/mm^3 the mortality rate remained 47 times higher than the background rate in the local population after 2 years of follow-up. Among those who started treatment without symptoms and a CD4 count above 200 the mortality rate remained slightly elevated compared with the general population, but was substantially lower than that seen in those who started treatment much later (1.24 to 3.4-fold higher than the general population).

Presenting the results, Martin Brinkhof of the University of Berne, concluded

that while there is greater mortality among HIV-positive people taking antiretroviral therapy than in the general population, 'for some patients the excess is moderate and mortality reaches that of the general population in the second year of [antiretroviral therapy]'. They add that more timely initiation of antiretroviral therapy might prevent much of the excess mortality.

Brinkhof M, *et al. Mortality of HIV-infected patients starting ART: comparisons with the general population in Southern Africa.* Sixteenth Conference on Retroviruses and Opportunistic Infections, Montreal, abstract 141, 2009.

Lawn S, *et al. Changing mortality risk associated with CD4 cell response to long-term ART: Sub-Saharan Africa.* Sixteenth Conference on Retroviruses and Opportunistic Infections, Montreal, abstract 140, 2009.

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Tanzanians still suffer stigma of HIV, even with universal access to antiretrovirals

John Owur

The roll-out of antiretroviral therapy may paradoxically increase stigma, reduce uptake of counselling and testing, and increase sexual risk-taking, according to the findings of a Tanzania-based study published in the online edition of the journal *Sexually Transmitted Infections*.

Campaigns for universal access to antiretroviral therapy have enabled wider access to treatment in resource-limited settings. Advocates hoped that this would reduce stigma by making HIV a long-term, manageable condition resulting into more HIV testing and changes in sexual behaviour.

Although HIV has become a long-term condition, available evidence suggests that the link between antiretroviral therapy roll-out, stigma and uptake of voluntary counselling and testing (VCT) is not as clear-cut as initially anticipated. Whereas some studies from southern Africa indicate that treatment availability has not encouraged widespread testing because HIV-related stigma still persists, others suggest that treatment access has reduced stigma (Wolfe *et al*., 2008).

The current study (led by Maria Roura of the London School of Hygiene and Tropical Medicine) was done to investigate the impact of treatment availability on various forms of stigma and VCT, because the researchers noted that less research has been done to find out why stigma and low VCT uptake still persists despite increased access to treatment. It was conducted in Northern Tanzania in a locality with access to free antiretroviral therapy and VCT services.

The investigators used snowballing and purposive sampling (for geographic and demographic balance) to recruit participants. They used semi-structured interviews and group activities to elicit participants' views. The findings show that the antiretroviral therapy roll-out has had a mixed impact on HIV-related stigma and VCT uptake.

The investigators found a reduction in 'burdens' stigma. People living with HIV/AIDS (PLWHA) are no longer a burden to the community because they are less dependent on help with daily living activities. Treatment availability has made HIV a normal disease 'just like malaria' and PLWHA feel 'like normal people', the respondents said. This has increased VCT uptake and some PLWHA have gone public about their status and are involved in testing campaigns, with remarkable success.

However, the researchers also found that treatment availability has not reduced 'blame stigma' because HIV infection is blamed on personal lifestyle choices and behaviours such as alcoholism and sexual recklessness, which are viewed as 'avoidable' and 'shameful'. PLWHA are accused of 'negligence' and 'irresponsibility', especially if they are known to be alcohol users. They are thought to be 'deserving' punishment (HIV).

Some community leaders equated antiretroviral roll-out to increased HIV prevalence. They said PLWHA looked 'attractive' and 'difficult to identify physically' because they got healthier as a result of treatment and were engaging in sexual relationships, thus 'spreading the disease'. Where such participants thought PLWHA had reduced sexual activities, they believed it was only because they are being 'avoided by others'. Some of the community leaders even suggested that PLWHA should be locked away in 'isolation camps' or be made 'impotent'.

The study further found that the drug side-effects were blamed for 'aggressiveness' (mental health problems), 'gluttony' and 'greed' among PLWHA, and economic and nutritional support offered to PLWHA was questioned by some members of the community – leading to further stigma.

This evidence of widespread persistence of blame stigma is a huge barrier to VCT, noted the researchers.

Lastly, the investigators found that the availability of therapy has not removed collective stigma, where the whole community is in denial of HIV and believed in other causes of the AIDS epidemic such as witchcraft. These explanations of causality have sanctioned risky sexual behaviours and limited VCT uptake.

The researchers acknowledged that these findings may have been limited by the recruitment methods and reliance on self-reporting by PLWHA.

The investigators concluded that the potential of making HIV 'normal' through antiretroviral therapy roll-out provides an opportunity to use treatment as a prevention tool that could be lost if local communities were not mobilised to accept antiretroviral therapy. They recommended information, education and communication to engage with local communities to overcome context-specific barriers.

Implications for practice

These findings demonstrate the potential to use treatment as a prevention tool in resource-limited settings because people get to see the benefits of testing and treatment and to live 'normal lives' once again, providing a basis for positive prevention.

They also demonstrate the need for further HIV awareness education in similar settings to reduce the various myths and misconceptions about HIV, particularly targeting community leaders who have huge influence on their followers.

Lastly, communal denial due to cultural explanations for ill health calls for context-specific approaches to challenge cultural beliefs about illness because otherwise availability of treatment will not make a difference to HIV incidence in such settings.

Roura M, *et al.* Scaling up stigma? The effects of antiretroviral roll-out on stigma and HIV testing. Early evidence from rural Tanzania. *Sex Transm Infect* (Online edition), 2008.

Wolfe WR, *et al.* The impact of universal access to antiretroviral therapy on HIV stigma in Botswana. *American Journal of Public Health* 2008; 98(10):1865-1871.

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