AIDS briefs

Starting antiretrovirals reduces risk of death from all causes

MICHAEL CARTER

HIV-positive patients who take antiretroviral treatment reduce their mortality risk by 50%, an international team of investigators report in the January 2010 edition of *AIDS*. Particularly substantial reductions in mortality risk were seen among those who started taking HIV treatment when their CD4 cell count was below 100 cells/mm^3.

The study also showed the value of starting HIV treatment at higher CD4 cell counts. Patients with a CD4 cell count of 100 cells/mm^3 or below when they started HIV treatment were significantly more likely to die over 5 years than those who initiated antiretroviral therapy when their CD4 cell count was 500 cells/mm^3 or above.

Study background

The introduction of effective, combination antiretroviral treatment in 1996 transformed the outlook for HIV-positive individuals. There is currently a substantial corpus of research literature showing that therapy with anti-HIV drugs lowers viral load, increases CD4 cell count and extends AIDS-free survival.

However, non-HIV-related diseases are becoming an increasingly important cause of illness and death in patients with HIV. Therefore it is important to understand the impact of HIV treatment on overall survival among individuals with the virus.

Earlier studies that have attempted to examine this issue have been limited by a number of factors.

Importantly, they have often lacked sufficient numbers of antiretroviral-naïve patients to accurately determine the effect of starting HIV treatment on all-cause mortality. Moreover, earlier research often did not take into account possible confounding factors such as baseline CD4 cell count and viral load and HIV transmission group.

Investigators from the HIV-CASUAL Collaboration therefore wished to gain a better understanding of the initiation of HIV treatment on the overall mortality risk for patients with HIV.

They studied the records of 62 760 patients who, between 1996 and 1998, were enrolled in 12 different cohort studies in Europe and the USA. None of the patients had taken HIV treatment before their inclusion in these studies.

The investigators compared the mortality risk for patients who started treatment with those who did not. Mortality trends were also monitored over a 5-year period according to whether anti-HIV drugs were taken. The effect of baseline CD4 cell count and factors including HIV transmission group were also taken into account.

Results

Twenty-six per cent of patients started HIV treatment within 3 months of entering a cohort study and 55% of individuals by the end of follow-up (2003 - 2007). The average duration of follow-up was 3.3 years. A total of 2 039 patients died, providing an overall mortality rate of 10 per 1 000 person-years. Overall, the risk of death from any cause was reduced by 52% for patients who started antiretroviral therapy.

Starting HIV treatment was especially beneficial for patients with a very weak immune system, the risk of death being reduced by 71% for those who initiated antiretroviral therapy when their CD4 cell count was below 100 cells/mm^3.

Benefits were also apparent for individuals with CD4 cell counts that are considered 'normal'. Those who started HIV treatment when their CD4 cell count was 500 cells/mm^3 or more had their risk of death from any cause reduced by 23% compared with those with a similar CD4 count who remained treatment naïve.

Next, the researchers calculated the probability of surviving for 5 years for patients who initiated antiretroviral therapy and for those who did not.

The overall survival probability was 96% for those who took treatment compared with 92% for those who did not.

Once again, these results varied according to CD4 cell count, with the greatest benefits seen for those with the weakest immune systems.

The 5-year survival probability for those who started HIV treatment when their CD4 cell count was 100 cells/mm^3 or below was 89% compared with only 43% for those with a CD4 cell count of this level who did not initiate antiretrovirals.

Starting HIV treatment also increased survival probabilities at higher CD4 cell counts. Patients who initiated therapy when their CD4 cell count was 200 - 350 cells/mm^3 were 6% more likely to be alive than those who did not (97% v. 91%).

A slight survival benefit was also seen among patients who started taking antiretroviral drugs when their CD4 cell count was above 350 cells/mm^3 (97% v. 94%).

The HIV risk group also affected the chances of survival even when HIV treatment was taken. Individuals who acquired HIV as a consequence of heterosexual sex, or through sex with another man, were much more likely to be alive 5 years after starting antiretroviral therapy than those who acquired HIV through injecting drugs (97% v. 97% v. 83%).

'We estimated that combination antiretroviral therapy halved the mortality rate of HIV-infected individuals in developed countries, and that the absolute reduction in mortality was stronger for those with a worse prognosis at the start of follow-up,' write the investigators.

However, they emphasise that such a finding does not argue for delays in starting HIV treatment.

Indeed, they conclude that the 5-year mortality risk of treated individuals with less than 100 cells/mm^3 at baseline (11%) was almost 4 times greater than that of treated individuals with more than 500 cells/mm^3 (3%).

The HIV-CASUAL Collaboration. The effect of combined antiretroviral therapy on overall mortality in HIV-infected individuals. *AIDS* 2010; 24: 123-137.

Article courtesy of www.aidsmap.com

Concurrency and the spread of HIV – the jury is still out

ROGER PEBODY

The theory that multiple, overlapping sexual partnerships are a key driver of generalised HIV epidemics in Africa has been attacked as being based on insubstantial evidence. The critics, writing in the journals *AIDS and Behavior* and *The Lancet,* argue that researchers lack a precise definition of concurrency or a standard way to measure it, and that the data do not show a significant association between concurrency and either HIV incidence or prevalence.

However, this critique has stimulated a fierce debate in the USA. Proponents of the concurrency thesis argue that the critics' analysis of the data is selective, that evidence from a wide range of sources supports the thesis, and that it would be irresponsible for prevention programmes in Africa to ignore this issue.

Concurrency

Concurrent sexual partnerships describe situations in which an individual has overlapping sexual relationships with more than one person. They can be contrasted with serial monogamy, when an individual has a sexual relationship with only one partner, with no overlap in time with subsequent partners.

A number of researchers, including Daniel Halperin, Timothy Mah and Martina Morris, have suggested that concurrent relationships can increase the size of an HIV epidemic, the speed at which it infects a population and its persistence within a population.

The explanation for this is that in situations where a significant proportion of both men and women have concurrent relationships, even if they only have two partners each, as soon as one person in the network of concurrent relationship contracts HIV, then other people in the network are at risk (unless condoms are used). More people are more often exposed to the virus, including during the acute infection period, when people are extremely infectious.

In contrast, in situations of serial monogamy, even if men and women have a relatively high number of sexual partners during their lifetime, one relationship is over before another is started. This means that if HIV is passed on within a relationship, it cannot be further transmitted as long as that relationship lasts.

Critique

Mark Lurie and Samantha Rosenthal, however, argue that even if this theory is persuasive, empirical evidence for it is lacking. They call for better designed studies to clarify the contribution concurrency may make to generalised epidemics in southern and eastern Africa. Moreover, they believe that delivering prevention interventions around concurrency could be counter-productive and may divert resources away from other prevention methods that have proven efficacy.

Lurie and Rosenthal argue that concurrency is often vaguely and inconsistently defined. Some studies in fact collect data on total numbers of partners, and not concurrent relationships. Moreover, some include very brief or one-off liaisons (e.g. with a sex worker), but most do not.

Mah and Halperin, proponents of the concurrency thesis, accept that the lack of a consensus definition of concurrency or of a universally accepted method of measurement hampers comparison between studies.

They report a proposed standard definition from a UNAIDS working group: overlapping sexual partnerships where sexual intercourse with one partner occurs between two acts of intercourse with another partner.

The debate between Lurie and the other researchers focuses on the different type of research studies that may or may not demonstrate the contribution that concurrency makes.

Prevalence of concurrency in a population

A number of studies have taken a representative sample of a population to quantify the proportion of people who are participating in concurrent sexual relationships. These surveys show wide variation between different countries, with populations in sub-Saharan Africa tending to report much more concurrency than populations in other parts of the world.

Lurie and Rosenthal's main criticism is that these studies simply cannot tell us anything about a link between concurrency and HIV.

In addition, they question the validity of comparisons between countries, given the variety of definitions used by researchers. They believe that there is no substantial evidence that levels of concurrency are significantly higher in Africa than elsewhere.

Lurie and the other authors tussle over the same studies. Referring to a review of sexual behaviour in 59 countries, Lurie insists that it found that concurrency rates could not be compared and that African adults are less sexually active than adults in other regions. In contrast, Mah and Halperin provide the following quote from the same study: 'Evidence is available that, although lifetime numbers of partners might be lower, concurrent relationships in men in some African countries might have been more common and of longer duration than in other regions'.

Qualitative data

Whereas Mah and Halperin believe that qualitative research can demonstrate that concurrency is a highly normalised behaviour in many parts of southern and eastern Africa and can help us understand its socio-cultural underpinnings, Lurie and Rosenthal dismiss qualitative research as inherently unrepresentative and prone to bias.

Individual studies

Only a few studies have compared individuals' participation in concurrent relationships and their HIV status, and Lurie and Rosenthal note that a consistent relationship has not been found.

However Martina Morris, a leading researcher of concurrency, argues that such studies are 'theoretically misguided and empirically irrelevant'. She says that concurrency is not a risk for the person who has more than one partner, but a risk for that person's partners. A monogamous partner may be exposed to HIV, not by his or her own behaviour, but by the partner's concurrency. Because of this, future studies will need to enrol partners.

Mah and Halperin also believe that concurrency increases an individual's risk of transmitting HIV, not their risk of acquiring it. They point to studies from Uganda and Zimbabwe, where HIV infection was associated with the belief that one's partner was having concurrent relationships.

Population studies

In 2001, Lagarde and colleagues reported a study that used a standardised questionnaire to assess concurrency rates and HIV prevalence in five sub-Saharan cities. The study did not find that the two factors were correlated. For example, some lower prevalence cities had high rates of concurrency.

Lurie and Rosenthal cite this as a key study, but Martina Morris rejects the

study design entirely. This is because HIV prevalence represents infections that have accumulated over many years, whereas the survey measured concurrency only in the previous year.

Mathematical modelling

Lurie and the proponents of concurrency all agree that the most powerful demonstrations of the influence of concurrency have come from simulation models. For example, Martina Morris and Mirjam Kretzschmar worked on Ugandan data and concluded that increasing the level of concurrency would have a more significant impact on epidemic spread than increasing the number of partnerships.

Lurie and Rosenthal say that even if these models show that concurrency can drive an epidemic, such theoretical work cannot demonstrate whether concurrency is actually doing so in Africa.

They also comment that other modelling studies, which found that the total number of partners or mixing between different social groups were more important than concurrency, tend not to be cited by the other authors.

In addition, in the articles published by Lurie and Helen Epstein, there is much claim and counter-claim as to the definitions used and the validity of the assumptions that were fed into the various modelling studies.

Conclusions

Mark Lurie and Samantha Rosenthal believe that the evidence base for the role of concurrency is weak and contradictory, and that better research with more refined definitions needs to take place before interventions to reduce concurrency can be delivered.

Morris counters that the studies Lurie and Rosenthal have looked at cannot prove or disprove the hypothesis. More sophisticated studies are being worked on and will give a more precise picture of concurrency's role, 'but no one argues that concurrency is irrelevant to transmission', she says.

As such, she says it would be a 'real tragedy' if methodological limitations were used to justify a do-nothing policy.

Mah and Halperin also argue that if HIV prevention interventions were never implemented until the most reliable evidence had been gathered, the only ones in use today would be male circumcision and interventions to prevent mother-to-child transmission. They believe that prevention messages which encourage people to have only one partner at a time are needed as one component of a prevention response.

Further reading

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BRIDGET FARHAM

World Kidney Day

Diabetic kidney disease: act now or pay later

World Kidney Day 11 March 2010: we must act on diabetic kidney disease

In 2003, the International Society of Nephrology and the International Diabetes Federation launched a booklet called *Diabetes and Kidney Disease: Time to Act*[1] to highlight the global pandemic of type 2 diabetes and diabetic kidney disease. It aimed to alert governments, health organisations, providers, doctors and patients to the increasing health and socio-economic problems due to diabetic kidney disease and its sequelae, end-stage kidney disease requiring dialysis and death from cardiovascular causes. Seven years later, the same message has become even more urgent. World Kidney Day 2010, under the auspices of the International Society of Nephrology (ISN) and the International Federation of Kidney Foundations IFKF), together with the International Diabetes Federation (IDF), provides yet another chance to underline the importance of diabetic kidney disease, stress its lack of awareness at both public and government levels and emphasise that its management involves prevention, recognition and treatment of its complications. Primary prevention of type 2 diabetes will require massive lifestyle changes in the developing and developed world supported by strong governmental commitment to promote lifestyle and societal change.

The global threat of type 2 diabetes

The 21st century has the most diabetogenic environment in human history.[2,3] Over the past 25 years or so, the prevalence of type 2 diabetes in the USA has almost doubled, with 3 - 5-fold increases in India, Indonesia, China, Korea and Thailand.[4] In