AIDS briefs

Half a million deaths from cryptococcal meningitis a year in people with HIV

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Researchers have estimated that there were about 1 million infections and half a million deaths from HIV-related cryptococcal meningitis worldwide in 2006. The findings, published in the 20 February edition of the journal *AIDS*, also show that sub-Saharan Africa had the highest global burden of cryptococcal meningitis among people living with HIV (PLHIV).

In regions with higher HIV burdens, particularly sub-Saharan Africa, cryptococcal meningitis has been reported to be on the increase (more than any other type of meningitis).

Studies from Zimbabwe, Rwanda, Central African Republic, Kenya and Tanzania have all shown an increased incidence of cryptococcal meningitis as an AIDS-defining illness and a leading cause of AIDS mortality. Away from Africa, similar reports have emerged from India, Thailand and Asia-Pacific.

The investigators carried out a systematic review of all available literature published in English after 1996. Articles were selected if they used a prospective or retrospective cohort study design, reported incidence among PLHIV or reported results which could allow calculation of incidence among PLHIV. The researchers found 19 studies that met eligibility criteria.

The scientists used the 2007 United Nations Programme on HIV/AIDS (UNAIDS) estimates for adult and child prevalence as the global HIV estimates. They used median incidence rates from available studies to estimate region-specific cryptococcal incidence. For regions where data were not available, the investigators imputed the rates using medians from regions of geographical proximity and similar economic development level.

The researchers estimated the regional cryptococcal burdens by multiplying the median incidence rate by the 2007 UNAIDS population prevalence estimate for each region. They then got the sum of all regional estimates to get the global burden of cryptococcal meningitis.

Due to variations in regional mortalities, the investigators estimated deaths using case-fatality rates from clinical trials conducted in high- and middle-income countries. They also reviewed case series, surveillance reports, reports on outcomes of cryptococcal meningitis and consulted with clinical experts. The scientists assumed a 10-week case fatality rate of 9% among infected people in high-income countries and 55% for middle- and low-income countries, except sub-Saharan Africa where the estimate was 70%.

The investigators found that the cryptococcal incidence ranged from 4% to 12% per year in the reports. They had at least one eligible report per region except for Eastern Europe and Central Asia, North Africa and the Middle East, and the Caribbean. The incidence for Eastern Europe and Central Asia, and North Africa and the Middle East was estimated at 1.7% per year (same as East Asia). For the Caribbean, the researchers assumed an incidence of 3.4% per year (same as Latin America).

The scientists estimated 957 900 (range 371 700 - 1.54 million) cases of cryptococcal meningitis in 2006. Sub-Saharan Africa had the highest number of infections (720 000; range 144 000 - 1.3 million), followed by South and South-East Asia (120 000; range 24 000 - 216 000). Oceania had the fewest estimates (100 cases), followed by western and central Europe (500 cases). The researchers said these estimates of both infections and deaths will be useful for public health efforts to prevent, diagnose and treat the disease.

The researchers further estimated about 624 725 (range 124 956 - 1.2 million) cryptococcal meningitis deaths in 2006. Again sub-Saharan Africa had the highest (504 000; range 100 800 - 907 200) and Oceania the fewest (9) death estimates.

When the scientists compared the death estimates for sub-Saharan Africa with diseases other than HIV, they found that cryptococcal deaths were higher than tuberculosis (350 000) which has received greater public health attention, and were closely comparable to childhood cluster diseases combined (530 000), diarrhoeal diseases (708 000) and malaria (1.1million).

The researchers acknowledged that their estimates were restricted by limited available studies and the limitations of the available studies. They also noted that provider-based cohort studies may be limited by incomplete follow-ups.

However, they felt the estimates are fairly accurate (particularly for sub-Saharan Africa) because their estimates are consistent with possible calculations from HIV cohort and natural history studies which have reported that about 13 - 44% of AIDS deaths in the region result from cryptococcal meningitis.

Although most of the estimates in their study were determined before antiretroviral roll-out efforts, the researchers said the expansion of treatment is not likely to impact on the global burden soon because access to treatment is not yet universal and in some cases (such as South Africa) the rates of cryptococcal meningitis have actually increased despite increased access to treatment.

Acknowledging that access to treatment can substantially reduce the disease among PLHIV, the scientists noted that the introduction of antiretroviral therapy has led to a drop in incidence of cryptococcal meningitis mainly in North America and western Europe.

The researchers said their findings emphasise the growing and future need for attention to the problem in regions with a higher HIV burden. They suggest the expansion of accurate and simple-to-implement diagnostic technologies, further research into the disease and expansion of treatment options.

In his commentary, Thomas S Harrison of St George's University, London, acknowledged that, despite study biases, there is little doubt that HIV-related cryptococcal mortality in Africa has been underestimated over the years.

He further said that the current study is important in stressing the need to address the problem of cryptococcal disease. Apart from fluconazole prophylaxis, he suggested pre-emptive fluconazole therapy for those who screen positive for cryptococcal antigen before starting antiretroviral treatment, suggesting that such strategy would prevent one-third of cases that present after starting antiretroviral therapy.

He concluded that many patients in Africa simply present too late for current antifungal therapy to be effective. He also called for efforts to facilitate earlier diagnosis and treatment and trials to compare amphotericin B-based and oral antifungal

regimens as well as to determine the best time to start anti-HIV treatment for those diagnosed with cryptococcal infection.

Harrison TS. The burden of HIV-associated cryptococcal disease (Editorial comment). *AIDS* 2009; 23: 531-532.

Park BJ, *et al*. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS* 2009; 23: 525-530.

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Factors influencing heterosexual transmission of HIV in Africa

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Researchers conducting a meta-analysis of studies of the risk of HIV transmission during heterosexual sex have found that, in high-income countries before the introduction of combination therapy, the risk per sexual act was 0.04% if the female partner was HIV positive, and 0.08% when the male partner was HIV positive. However, these rates were considerably higher in lower-income countries if the source partner was in either the very early or the late stage of HIV infection, or if one partner had genital ulcer disease.

Marie-Claude Boily and colleagues attempted to identify all relevant observational studies of sufficient methodological quality that provided empirical estimates of the transmission risk per sexual act (rather than the cumulative risk during an ongoing relationship with an HIV-positive person).

Looking for material on HIV-1 only, they found 43 relevant publications covering 25 different study populations. More than half were conducted in the USA or western Europe, with most of the others carried out in Africa, and a handful conducted in Thailand and Haiti. Although the researchers looked for studies published up to September 2008, almost all the reports used data collected in the 1980s or early 1990s, which means that the findings do not reflect combination therapy's impact on transmission.

High-income and low-income countries

Pooling the data from studies in high-income countries, the researchers calculated that the risk of transmission from an HIV-positive man to his female partner was 0.08% per sexual act, i.e. it was likely to occur once every 1 250 sexual acts. When it was the female partner who was HIV positive, the male partner's risk of acquiring HIV was 0.04% per sexual act, i.e. once every 2 500 sexual acts.

The findings from each of these studies were broadly consistent, with the result that the 95% confidence intervals for the above figures were not too wide (e.g. for transmission from men to women: 0.04 - 0.16%). This was not the case for the pooled data from studies in Africa, Thailand and Haiti.

In these countries, the researchers calculated a transmission risk of 0.19% when the male partner was HIV positive, and 0.87% when the female partner had HIV. However, the wider confidence intervals (e.g. from men to women: 0.28 - 2.6%) could, the authors suggest, reflect poorer study quality, a wide variation in risk factors between study populations or some under-reporting of high-risk behaviour. They speculate that the overall higher apparent risk could be driven by higher rates of sexually transmitted infections or higher viral load levels.

Nonetheless, they point out that the figures from low-income settings suggest that there is a greater risk of transmission from women to men than the other way round, which is the inverse of the high-income country findings and is generally considered less biologically plausible.

One possibility could be that men in these settings might be more likely to have sex outside their primary relationship than women, and so what appear to be transmissions from the primary female partner are in fact infections acquired elsewhere.

Moreover, when the researchers excluded studies which involved sexual acts as part of commercial sex work (either as a client or a sex worker), the risk of female-to-male transmission decreased.

Co-factors

Comparing populations involved in commercial sex work with those that were not (in any part of the world), the transmission risk was 11 times higher. The authors judge that this increased risk may be primarily driven by high rates of sexually transmitted infections in these populations.

Moreover, the per-act transmission risk when one of the partners had genital ulcer disease was 2.8%, or once every 36 sexual acts. Compared with situations when it was known that there were no sexually transmitted infections, the transmission risk was 5 times higher.

Two studies provided data on the circumcision status of male partners who were at risk of HIV infection. In both cases, the transmission risk was higher for men who were not circumcised, especially if they also had genital ulcer disease.

A few studies incorporated information on the source partner's disease stage, focusing on early infection and late-stage disease, both periods when viral load is likely to be high. With an asymptomatic partner, the per-act risk was 0.07% compared with 0.66% at early stage (9 times higher), and 0.55% at late stage (7 times higher).

However, because few studies have been conducted in the past decade, no estimates of the transmission risk were specifically provided for a partner taking antiretroviral treatment.

Just 2 studies provided data on the risk of transmission from anal sex, and the pooled estimate was 1.7% per act (i.e. about once every 60 sexual acts). However, the 95% confidence interval was wide: 0.32 - 8.9%.

Having conducted a similar meta-analysis a few months ago in the same journal, Kimberley Powers and colleagues argued that focusing on a single figure, as the per-act risk of transmission is misleading, frequently leads to the risk of transmission being underestimated. In the context of sexually transmitted infections, lack of circumcision, anal sex, acute infection or late-stage infection, she argued that 'The heterosexual infectivity of HIV-1 might exceed the commonly cited value of 0.001 [0.1%, 1 in 1 000] by more than an order of magnitude. The vast extent of the current epidemic is more easily understood in the context of these biological cofactors, which create a more favourable environment for HIV transmission.'

For her part, Marie-Claude Boily suggests that a figure of 0.07% or 0.08% may 'represent the average per-vaginal-sex-act transmission in the absence of cofactors, during the asymptomatic stage.'

She also notes the methodological challenges of these studies, and suggests that better quantification of per-act infectivity could help epidemiologists predict future patterns of the HIV epidemic as well as contributing to the development of more effective prevention strategies.

Boily MC, *et al*. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infectious Diseases* 2009; 9: 118-129.

Powers KA, *et al*. Rethinking the heterosexual infectivity of HIV-1: systematic review and meta-analysis. *Lancet Infectious Diseases* 2008; 8: 553-563.

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