JOURNAL REVIEW

Prevention of HIV-1 infection with early antiretroviral therapy

Cohen MS, Chen YQ, McCauley M, *et al*. *N Engl J Med* 2011 **365**:493–505.

The exciting evidence generated by this paper – that antiretroviral treatment of HIV-1 infection definitively reduces the risk of onward transmission of the virus by 96% – was rightly dubbed *Science* magazine's 'Breakthrough of the Year' in 2011.[1 2]

It has long been known that the probability of sexual transmission of HIV is strongly correlated with concentrations of HIV in blood and genital fluids.[3 4] Effective antiretroviral therapy (ART) produces prolonged and sustained suppression of HIV replication in these compartments, reducing the amount of free virus.[5 6] Thus, there has long been a tantalising hypothesis that ART may reduce transmission. This has been supported by observational studies suggesting a reduction in rates of HIV transmission to the partners of people on therapy, and by ecological studies showing a reduction in incident HIV infections in studied communities after the introduction of ART.[7–9]

The HPTN 052 Study, from Cohen *et al.*, provides the first Level 1 evidence that supports this hypothesis. They enrolled 1763 sero-discordant couples – where one partner was HIV-1 positive and the other HIV-1 negative – across nine countries. Nearly all couples were heterosexual. HIV-infected participants, all of whom had a CD4 count between 350 and 550 cells/μl at baseline, were randomised 1:1 to receive ART immediately after enrolment (early therapy) or after a decline in CD4 to below 250 cells/μl (delayed therapy). The primary endpoint was linked HIV-1 transmission to susceptible partners.

The study reported earlier than planned, after a median patient follow-up of 1.7 years, and after a total of 39 HIV-1 transmissions had occurred, of which 28 were virologically linked to the infected partner. Of the linked transmissions, only one occurred in the early therapy arm, representing a 96% reduction in transmission events ($p<0.001$). Behavioural indicators were similar between the two arms. Condom use at baseline was also protective against infection (hazard ratio 0.33, 95% CI 0.12–0.91).

Sixty-four per cent of transmissions occurred from the female to the male partner, and 82% of transmissions took place at African trial sites. Importantly, the majority of ransmission events in the delayed arm occurred when the index partner had a CD4>350 cells/μl, indicating the prevention benefit of treatment might only be fully realised if ART is given above the CD4 threshold currently recommended by the World Health Organization.

ART can now definitively be lauded as a powerful HIV prevention tool, and further prospective work is ongoing to investigate the extent of its effect. But ART can only be afforded to those who are aware of their HIV status, and to only a proportion of those who need it. 'Treatment as prevention' can join one of many proven bio-behavioural prevention tools now available to us (HIV testing, safer sex education, condom use, male circumcision). These tools need to be employed in combination: only through 'combination prevention' will the epidemic be curtailed.

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