(involving 20,468 patients from 89 centres in 50 cities) also showed lower prescription of lipid-lowering drugs to patients following acute coronary syndrome (ACS) which was even lower among poorer patients. Some of the earlier statins are off-patent and can be made available in generic forms. Given the wider availability of generic forms of statins and with the current evidence of long-term safety, use of statins for secondary prevention should be pursued aggressively. Various economic evaluations, including those of Patel et al., and Gaziano et al., support the use of statins for secondary prevention as a cost-effective strategy for developing countries. Therefore, what is needed to ensure wider availability of statins at all levels of healthcare and a quality improvement programme similar to the ‘get with guidelines’ programme by the American Heart Association (AHA) to improve evidence-based care after ACS. While this requires support from the ministries of health, a larger need is on the part of the treating physicians in prescribing statins to those needing secondary prevention and for high-risk primary prevention as done in the HPS study.

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Does early initiation of antiretroviral therapy prevent HIV transmission in serodiscordant couples?

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SUMMARY

This multicentre, prospective, randomized, controlled trial was done at 13 sites in nine countries, including seven sites in Africa, two in Brazil, one in Thailand, one in the USA and two sites in India (Pune and Chennai). The investigators sought to answer two questions: Is early initiation of combination antiretroviral treatment (ART) effective in preventing the transmission of HIV-1 to the uninfected partner in a serodiscordant couple? What are the effects of early ART on clinical events in the infected partner?

Serodiscordant couples (couples of whom one partner was HIV-1-positive and the other was HIV-1-negative), were recruited from June 2007 till May 2010. Only couples who had been in a stable sexual relationship for at least 3 months and who reported ≥2 episodes of intercourse over this period were included. Recruited HIV-1-positive patients were ART-naïve and had a baseline CD4 count of 350–550 cells/cumm. Participating couples were randomly assigned, in a 1:1 ratio, to either an early or a delayed ART group. In the early therapy group, antiretroviral drugs were initiated in the HIV-1-positive partner at enrolment. In the delayed therapy group, ART was started once two consecutive CD4 counts were <250 cells/cumm or an AIDS-defining illness developed. HIV-1-infected patients with active tuberculosis were excluded and isoniazid (INH) prophylaxis for latent tuberculosis was provided as per local guidelines.

Follow-up consisted of three initial visits at 1 month intervals followed by quarterly visits. Both partners were encouraged to come for visits and counselling and risk reduction advice including condom use was provided. Uninfected partners were assessed for seroconversion every 3 months. Those who became infected were released from the study and referred to a local clinic.

Virological failure for treated HIV-1-infected participants was defined as a plasma HIV-1 RNA viral load of 1000 copies/ml or more on two occasions beyond 16 weeks from enrolment. Clinical and laboratory evaluation was provided for each HIV-1-positive participant at each study visit. Women who became pregnant during the study were treated according to standard guidelines. If the original uninfected partner had been released from the study, a new partner could be recruited if the inclusion and exclusion criteria were met.

A pre-specified combination of first-line antiretroviral drugs was used in the study. The commonest combination, given to 72% of HIV-1-positive participants, was lamivudine, zidovudine and efavirenz. In order to establish whether seroconversions were from HIV-1-positive patients with active tuberculosis were excluded and isoniazid (INH) prophylaxis for latent tuberculosis was provided as per local guidelines.

After screening 10 838 persons, 1763 HIV-1 serodiscordant couples were recruited; of these, 886 couples were randomly assigned to early and 877 to delayed ART. Most of the participants were 26–40 years old; 97% of couples were heterosexual and 94% were married. Half the HIV-1-infected participants were men. Rates of unprotected sex were 5% among HIV-1-infected and 6% among uninfected participants. The median baseline CD4 counts among HIV-1-infected partners were 442 cells/cumm in the early therapy group and 428/cumm in the delayed therapy group. Consistent (100%) condom use was reported by 96% of those in the early therapy group and 95% of those in the delayed therapy group. Having met pre-specified end-points, the study was stopped after 1.7 years with 90% of couples still remaining in follow-up.

Transmission of HIV-1 was documented in 39 instances with an incidence rate of 1.2 per 100 person-years (95% CI 0.9–1.7). Of these, four events occurred in the early therapy group with an incidence rate of 0.3 per 100 person-years (95% CI 0.1–0.6) and 35 events occurred in the delayed therapy group with an incidence rate of 2.2 per 100 person-years (95% CI 1.6–3.1). Of these transmissions, viral genetic analysis confirmed 28 linked transmissions—one in the early therapy group and 27 in the delayed therapy group. This represents a reduction in incidence rate per 100 person-years from 1.7 (95% CI 1.1–2.5) in the delayed therapy group to 0.1 (95% CI 0.0–0.4) in the early therapy group giving a hazard ratio in the early therapy group of 0.04 (95% CI 0.01–0.27, p<0.001). The remaining 11 transmissions included seven unlinked, three unclassified and one yet to be evaluated.

The single transmission in the early therapy group occurred 3 months after initiation of ART in the infected partner. All transmissions in the delayed therapy group occurred while the infected partner was not receiving ART. Of the 28 linked transmissions, 61% occurred while the CD4 count was <350 cells/cumm in the infected partner. Using Kaplan–Meier curves, for both overall and linked transmissions, there was an immediate and sustained reduction in transmission risk following the initiation of ART.

Women were the infected partners in 18 of 27 (67%) linked transmissions in the delayed therapy group and a man was the source of transmission in the single-linked transmission in the early therapy group. Risk of transmission increased with higher viral load in infected partners. Consistent (100%) use of condoms at baseline was found to be associated with a lower risk.

To assess the effect of ART on individuals who were HIV-1-positive at enrolment, a composite of serious HIV-1-related clinical events and death in these patients was measured. A total of 105 such events were observed, 40 in the early and 65 in the delayed therapy group. The adjusted hazard ratio for clinical events in the early therapy group was 0.59 (95% CI 0.40–0.89). The difference in the rate of clinical events was largely due to a difference in the incidence of extrapulmonary tuberculosis which occurred in 3 patients in the early and 17 in the delayed therapy group (p=0.002). The two Indian sites contributed 55% of cases of extrapulmonary tuberculosis. Only 4% of participants in each group were given INH prophylaxis. Pulmonary tuberculosis occurred in 13 patients in the early therapy group and in 15 in the delayed therapy group. Twenty-three participants died during the course of the study—10 in the early and 13 in the delayed therapy group. The calculated hazard ratio for death in the early therapy group was 0.77 (95% CI 0.34–1.76, p=0.27).

Using a composite end-point of death or serious HIV-1-related clinical events and transmission of HIV-1 to the uninfected partner, a total of 102 such composite events were observed. Of these, 23 occurred in the early and 79 in the delayed therapy group; hazard ratio 0.28 (95% CI 0.18–0.45, p<0.001).

Severe or life-threatening adverse effects occurred in 246 HIV-1-infected participants: 14% in each of the therapy groups (p=0.64). Virological failure occurred in 5% of those treated in the early and 3% of those treated in the delayed therapy group (p=0.23).

COMMENT

Checking the spread of HIV infection is an important public health priority. One aspect of this effort is the prevention of HIV transmission to sexual partners of HIV-infected individuals. The use of barrier contraceptives such as condoms has been shown to reduce transmission in this setting.1
Viral RNA levels strongly predict sexual transmission risk. Quinn et al. assessed transmission of HIV to the uninfected partner of 415 serodiscordant couples in Uganda. Ninety seroconversions occurred over 30 months. The rate of transmission was 2.2 per 100 person-years with RNA levels of 3500 copies/ml and rose to 23.0 per 100 person-years as the level increased to ≥50 000 copies/ml.²

Observational studies showed that the risk of HIV transmission is lower if the HIV-positive partner is receiving ART. Reynolds et al. retrospectively identified 250 HIV-1 serodiscordant couples in Uganda between 2004 and 2009. Infected participants with a CD4 count <250 cells/cmm or WHO stage IV disease were offered free ART. Uninfected partners were screened annually for HIV-1. Transmission rates for HIV-1 decreased from 42 transmissions over 459.4 person-years of follow-up before ART initiation to zero transmission in 32 couples in which the HIV-1 index partners started ART during 53.6 person-years.³

In observational studies, HIV-infected partners were started on ART only once they met the current guidelines—low (<350 cells/cmm) CD4 counts or stage IV HIV disease, which often meant delaying ART and exposing the uninfected partner to risk of transmission.

This study was undertaken by the HIV Prevention Trials Network 052 (HPTN 052), to address some of the lacunae in previous studies. The trial enrolled 1763 HIV-1 serodiscordant couples prospectively. The follow-up rate was 90%. One of the strengths of the study was the use of pol gene analysis to confirm that transmission was linked. A 96% reduction in HIV-1 transmission was found in the early therapy group at the end of 1.7 years. There was a 41% reduction in clinical events in infected individuals in the early therapy group, showing that it was beneficial for the infected partner, besides reducing HIV transmission.

A Cochrane meta-analysis evaluated one randomized controlled trial (the present study) and seven observational studies assessing the effect of ART on HIV transmission.⁴ The summary rate ratio for transmission among treated couples for the seven observational studies was 0.34 (95% CI 0.13–0.92).

The findings of this meta-analysis and those of the present study make it clear that ART is highly effective in preventing HIV-1 transmission between serodiscordant partners.

Should ART be initiated in patients with CD4 counts >350 cells/cmm and/or who stage I or II disease? In this study the mean baseline CD4 counts in the infected partners were 442 cells/cmm and 428 cells/cmm in the early and delayed therapy groups.

The WHO recommends initiation of ART for all HIV-positive patients with a CD4 count ≤350 cells/cmm and for those with WHO clinical stage III or IV if CD4 testing is not available.⁵ However, recent trials have shown improved outcomes when ART is started at a CD4 count <500 cells/cmm.⁶ This study provides some data to show that early initiation of ART at CD4 counts higher than those recommended by the WHO would cut down transmission and is also beneficial for the infected partner. The development of resistance to ART has not been formally addressed by this study but second-line antiretroviral drugs were given to 66% of patients. The details of second-line therapy have not been provided.

What would be the impact of this study in India? Using data from the National Family Health Survey-3, Arora et al. found that in 0.8% of all couples one or both were HIV-1 infected.⁶ Serodiscordance was observed in 73% of couples. Given India’s large population, these figures would translate into a large number of uninfected partners in serodiscordant couples who would need to be protected from HIV transmission. Early initiation of ART in the infected partner could translate to a significant protection for such partners.

On a larger scale, the findings of this study provide a boost for the ‘test and treat’ strategy. Proponents of this advocate universal, population-based testing for HIV infection with treatment of all those detected to be HIV-positive. This would limit transmission and bring us closer to containing the infection.⁷

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