Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples – a Cochrane Systematic Review

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Antiretroviral drugs reduce the risk of human immunodeficiency virus (HIV) transmission from the mother to her child (1, 2), and are widely used for the prevention of transmission after exposure to the virus through sexual and non-sexual contact (e.g. occupational exposure) (3, 4). They can also prevent HIV infection when they are consumed before exposure to the virus (5). Observational studies suggest that sexual transmission may be lower in couples in which one partner is infected with HIV and the other is not (HIV-discordant couples) if the infected partner is on antiretroviral therapy (ART). If ART does confer a prevention benefit, in addition to its well established therapeutic efficacy, it may be an indication to initiate treatment earlier than currently recommended (2). The objectives of a recently conducted systematic review on the issue were as follows (6):

- To determine if ART in HIV-discordant couples is associated with lower risk of HIV transmission to an uninfected partner compared to untreated discordant couples.
- To assess if HIV transmission is lower in couples in which an infected partner has CD4 cells ≥ 350 cells/µL.

Lower risk of HIV transmission in treated couples

One randomised controlled trial (RCT) with 1750 HIV discordant couples (7) and seven observational cohort studies with 9791 couples were included in this review. The RCT was conducted in nine countries (Botswana, Brazil, India, Malawi, Kenya, South Africa, Thailand, United States of America and Zimbabwe). While this trial mostly included heterosexual partners, homosexual partners were also included. Most of the cohort studies were conducted in African countries and focussed on heterosexual partners.

The included studies identified 464 episodes of HIV transmission, 72 among treated couples and 392 among untreated couples. In the RCT, the risk of HIV transmission was reduced by 96%. All HIV infected partners in this study had CD4 cell counts of 350-550 cells/µL at baseline.

In the observational studies, the risk of HIV transmission was 66% lower in treated compared to untreated couples. There were major differences between these studies, as two had inadequate data corresponding to the time patients were followed up. After excluding these two from the analysis, the risk of transmission was 84% lower in untreated couples. Among couples in which the infected partner had a CD4 count greater than 350 CD4 cells/µL, the risk of transmission was 98% lower among treated couples. In this subgroup, there were 61 transmissions in untreated couples and none in treated couples. The safety data is extracted from the HPTN052 study which was stopped early. Fourteen per cent of participants who received ART, regardless of their CD4 count, had one or more severe or life-threatening events, which may or may not have been causally related to the antiretrovirals, suggesting no increased risk associated with starting ART at high CD4 count. In contrast, there was a relative increase in grade 3 or 4 laboratory abnormalities among participants receiving therapy with CD4 counts greater than 350 cells/µL (27%) when compared to participants receiving treatment at lower CD4 counts (18%). The study had been powered to evaluate HIV incidence, and was stopped before all safety data was collected, therefore we cannot draw conclusions from the safety results provided.

Implications for practice

Based on the evidence provided by one randomised controlled trial and seven observational cohort studies, ART has been shown to be a potent intervention for prevention of HIV in discordant couples. An important question from a clinical standpoint is whether being in a serodiscordant relationship and having a CD4 count greater than 350 cells/µL should be an additional indication for ART under WHO guidelines. European and U.S. guidelines already allow for starting at a CD4 count of up to 500 cells/µL routinely and even higher for certain subgroups and based on clinician judgment. The included RCT provides definitive data demonstrating a large positive benefit. Therefore, patients beginning ART may also be informed that adherence to ART can also reduce their risk of transmitting HIV to their uninfected partners. A related policy question is how much effort should be
focused on treating individuals with CD4 counts greater than 350cells/μL, when access to ART for persons with less than 350 CD4 cells/μL is far from universal. Significant questions remain about the durability of protection, cumulative antiretroviral toxicity, when to start treating an infected partner (for instance, at diagnosis or at a specific CD4 or plasma viral load level) and transmission of ART-resistant strains to partners. The success of this intervention likely relies on good adherence, especially in stable couples. Programmes should be designed that include counselling, support, follow up and mutual disclosure, as these components may have a role in supporting adherence. In addition to ART provision, limitations in resources needed to implement such expanded ART indications must be addressed.

Implications for research

Additional data are needed on durability of protection for uninfected partners, adverse events associated with initiation of ART on individuals with CD4 counts greater than 350cells/μL, including effects of longer-term ART, the potential for earlier development of antiretroviral resistance (resulting in a need to change regimens prematurely) and HIV morbidity, quality of life and the potential for risk compensation. There are multiple opportunities to examine these issues in existing cohorts.

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