JAMA Clinical Evidence Synopsis

Antiretroviral Therapy for Prevention of HIV Transmission in HIV-Discordant Couples

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CLINICAL QUESTION Does treating the HIV-infected partner in a serodiscordant couple reduce the risk of HIV transmission to the uninfected partner?

BOTTOM LINE Compared with serodiscordant couples without treatment, couples in which the infected partner is treated with antiretroviral therapy have a lower risk of HIV transmission.

Antiretroviral therapy prevents perinatal transmission of human immunodeficiency virus (HIV),[1] and several observational studies suggest that an HIV-infected patient's sexual partner is less likely to become infected if the patient is taking antiretroviral therapy.[2] A serodiscordant couple is one in which one member is HIV-infected and the other is not. Data from Africa suggest that up to half of new infections occur in stable serodiscordant couples.[3] Understanding serodiscordancy can help clinicians better counsel their patients with HIV about transmission risk to uninfected partners and, more broadly, about the importance of antiretroviral therapy and adherence.

Summary of Findings

We identified 9 observational studies and the HIV Prevention Trials Network Study 052 (HPTN 052), a randomized clinical trial (RCT), that compared treated and untreated serodiscordant couples. The HPTN 052 study included asymptomatic patients with HIV who had a CD4 cell count of 350 to 550/μL and compared those who received antiretroviral therapy with those in whom treatment was delayed until their CD4 cell counts were less than 350/μL.[4] The end point was HIV transmission to the uninfected partners. The trial showed that early antiretroviral therapy was associated with a decreased risk of HIV transmission (rate ratio [RR], 0.11 [95% CI, 0.04-0.32]) to uninfected partners (treated couples, 4 transmissions within 1585 person-years; untreated couples, 35 within 1567 person-years).[4] Cohen and coauthors[4] conducted phylogenetic analyses of the transmitted viruses and found only 1 instance of linked transmission among treated couples compared with 27 linked transmissions among untreated couples (RR, 0.04 [95% CI, 0.00-0.27]).

In each group, 14% of participants had 1 or more severe or life-threatening events (grade 3 or 4, defined by the National Institutes of Health),[4] suggesting no increased risk associated with antiretroviral therapy in this setting. The most frequent adverse events were infections and gastrointestinal, metabolic, nutritional, psychiatric, and nervous system disorders. In contrast, grade 3 or 4 laboratory abnormalities (most frequently neutropenia, hyperphosphatemia, and hyperbilirubinemia) were more common in participants receiving early antiretroviral therapy (27%) than among those receiving delayed treatment (18%).[4]

The 9 observational studies examined the association of antiretroviral therapy with HIV transmission in serodiscordant couples. In 8 studies, antiretroviral therapy was associated with decreased transmission from infected to uninfected partners (RR range, 0.08-0.91) (**Figure**). One study showed no association of antiretroviral therapy with reduced risk, though the authors did not provide person-time data needed to calculate an RR. The summary RR was 0.58 (95% CI, 0.35-0.96) for the 9 studies (treated couples, 1021 transmissions within 81 393 person-years; untreated couples, 1059 within 41 350 person-years).

We performed sensitivity analyses, removing the results of studies without adequate person-time data or in which only 1 antiretroviral drug was used. The resulting meta-analysis found an RR of 0.36 (95% CI, 0.17-0.75). Tests for interaction between subgroups of CD4 cell count strata, index case sex, and country income level showed no statistically significant differences among subgroups.

Evidence Profile

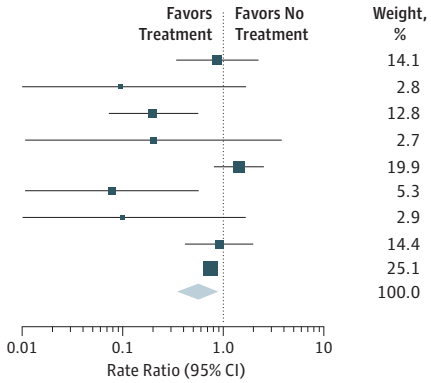
No. of studies: 9 observational studies, 1 randomized clinical trial (RCT)
Study years: Published 1994-2012
No. of Participants: Observational, 49 083 couples; RCT, 1763 couples
Men: Observational, 50%; RCT, 51%
Women: Observational, 50%; RCT, 49%
Race/ethnicity: Not stated
Age, mean: 26-44 years
Setting: Multicenter
Countries: Observational: Italy, Brazil, Spain, China, Zambia, Rwanda, Uganda, Botswana, Kenya, South Africa, and Tanzania; RCT: Botswana, Brazil, India, Malawi, Kenya, South Africa, Thailand, United States, and Zimbabwe
Comparison: Treated serodiscordant couples vs untreated serodiscordant couples
Primary Outcome: Incident HIV infection
Secondary Outcome: Adverse events

Discussion

Antiretroviral therapy is a potent intervention for prevention of HIV in discordant couples. A recent trial confirms the suspected benefit seen in observational studies.[4] Questions remain about durability of protection, the balance of benefits and adverse events associ-

Figure. Risk of HIV Transmission in Serodiscordant Couples Treated vs Untreated With Antiretroviral Therapy in Observational Studies

Study	Untreated[a] HIV Cases	Untreated[a] Person-Years	Treated[a] HIV Cases	Treated[a] Person-Years	Rate Ratio (95% CI)	Weight, %
Musicco, 1994	21	481	6	157	0.88 (0.36-2.16)	14.1
Melo, 2008	6	1272	0	1085	0.10 (0.01-1.67)	2.8
Sullivan, 2009	171	5038	4	571	0.21 (0.08-0.56)	12.8
Del Romero, 2010	5	938	0	417	0.21 (0.01-3.75)	2.7
Lu, 2010[b]	18	1585	66	3888	1.44 (0.85-2.44)	19.9
Donnell, 2010	102	4558	1	273	0.08 (0.01-0.57)	5.3
Reynolds, 2011	32	372	0	25	0.10 (0.01-1.64)	2.9
Birungi, 2012	8	348	9	440	0.91 (0.38-2.20)	14.4
Jia, 2012[c]	696	26758	935	74537	0.74 (0.65-0.84)	25.1
Total					0.58 (0.35-0.96)	100.0



Source: Figure adapted with permission from Cochrane HIV/AIDS Group.[2]
[a]Effect estimates may not reflect raw counts due to confounder adjustment.
[b]Estimated from median follow-up time.
[c]Hazard ratio.

ated with earlier therapy, long-term adherence, and transmission of antiretroviral therapy–resistant strains to partners.

Counseling, support, and follow up, as well as mutual disclosure, may have a role in supporting adherence. Future programs should be designed with these components.

Limitations

Most observational studies did not report the risk of HIV transmission stratified by the index case's baseline CD4 cell count, obviating our ability to explore fully the association at different CD4 cell count levels. Although data from the HPTN 052 study clearly demonstrate the large, positive benefit among index partners with a CD4 cell count of 350 to 550 /μL,[4,5] participants in this study were long-term couples. Women in the study were somewhat older, and results may not be generalizable to all contexts in which transmission risk exists. Additionally, current research is almost exclusively among serodiscordant heterosexual couples and may not be generalizable to serodiscordant homosexual couples. While 1 RCT provides strong evidence of benefit from early treatment, unmeasured confounding potentially weakens evidence from the 9 observational studies.

Comparison of Findings With Current Practice Guidelines

In 2012, the World Health Organization (WHO) recommended that the partner living with HIV be offered antiretroviral therapy regardless of CD4 cell count.[6] Additionally, WHO recommended that individuals beginning antiretroviral therapy should be counseled that adherence to antiretroviral therapy can reduce their risk of transmitting HIV to their sexual partners. In the United States, the International Antiviral Society practice guidelines recommend initiating antiretroviral therapy regardless of CD4 cell count for patients' benefit.[7]

Areas in Need of Future Study

Additional data are needed on the durability of protection for uninfected partners, whether HIV infected partners will successfully adhere to long-term antiretroviral therapy, adverse events associated with earlier initiation of antiretroviral therapy, the potential for earlier development of antiretroviral resistance if antiretroviral therapy is started earlier, HIV-related morbidity and quality of life, and the potential for risk compensation (ie, engaging in high-risk behavior in response to a lower perceived risk). Outside of high-income countries, another concern is the financial cost of expanding indications of antiretroviral therapy.

ARTICLE INFORMATION

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Section Editor: Mary McGrae McDermott, MD, Senior Editor.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Submissions: We encourage authors to submit papers for consideration as a JAMA Clinical Evidence Synopsis. Please contact Dr McDermott at mdm608@northwestern.edu.

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