Antiretrovirals and prevention of sexual transmission of HIV - A TAC Briefing

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A TAC Briefing

Exciting new evidence has demonstrated the potential of antiretroviral medicines (ARVs) to prevent HIV from being sexually transmitted. This TAC briefing explains the evidence and then discusses policy implications.

Our recommendations

- The WHO must release its guidelines on serodiscordant couples.
- People living with HIV should be offered highly active antiretroviral treatment (ART) when their CD4 counts fall below 350 cell/mm3, or if they have an AIDS illness or TB.
- HIV-positive people in serodiscordant couples should be offered ART irrespective of their CD4 count.
- For serodiscordant couples trying to conceive, both partners should be offered ARVs until conception is confirmed, after which the HIV-positive partner should continue on ART.
- Pre-exposure prophylaxis (PrEP) should be made available to sex workers.
- In other cases, pre-exposure prophylaxis should be made available to HIV-negative people who request it or who will --in the opinion of their nurse or doctor-- likely benefit from it.
- The rollout of ARVs for prevention must not divert funding away from treatment programmes. Achieving universal access for people with HIV must remain the priority for governments, policy makers and funders.
- Effective prevention interventions such as voluntary medical male circumcision and ensuring availability of male and female condoms continue to be critically important.

Evidence that ARVs will reduce new infections

A number of trials have demonstrated, with varying success, that ARVs given either to HIV-positive or HIV-negative people reduce new HIV infections. Most of the successful trials have tested ARVs in the form of tablets. One has tested an ARV-based microbicide gel.

HPTN 052

The most dramatic reduction in new infections was seen in the HPTN 052 trial, where ARV treatment (ART) was provided to the HIV-positive partner in serodiscordant couples. 1,763 couples in nine countries took part in the trial and were randomised into two groups. In the first group the HIV-positive partner received ART immediately, while in the second group the HIV-positive partner was only given ART once his or her CD4 cell count dropped below 250 cells/mm3 or he or she developed an AIDS-related illness. The HIV-positive partner had to have a CD4 count between 350 and 550 cells/mm3 when he or she enrolled in the trial.

Providing ART to the HIV-positive partner reduced new infections by 96%. Twenty seven genetically linked HIV infections occurred in the delayed treatment group, while only one occurred in the group receiving treatment.[i] Furthermore the single infection that occurred in the group receiving ART was detected three months after the HIV-positive partner initiated treatment and therefore the newly infected partner was likely already in the window period when the HIV-positive partner initiated treatment.[ii]

Pre-Exposure Prophylaxis (PREP)

Studies also show that ARVs can offer significant preventative benefit when given to HIV-negative people in the form of tablets or microbicide gel.

- The iPrEX trial investigated the use of daily tenofovir (TDF)/emtricitabine (FTC) tablets to reduce the risk of men who have sex with men contracting HIV. 2,499 men who have sex with men from six countries participated in the trial. The trial compared men receiving daily TDF/FTC tablets with men receiving placebo tablets. The results showed that daily TDF/FTC reduced the risk of contracting HIV by 44% for men who have sex with men.[iii] [iv]
- The PARTNERS PrEP study investigated the use of daily TDF/FTC and daily TDF to reduce the risk of the HIV-negative partner in serodiscordant couples contracting HIV. The study enrolled 4,758 serodiscordant couples in Kenya and Uganda. Participants received daily TDF/FTC or daily TDF or daily placebo tablets. Early results showed that the protection rates were 62% for the TDF arm[v] and 73% for the TDF/FTC arm.[vi] [vii]
- The TDF2 trial investigated the use of TDF/FTC to reduce the risk of contracting HIV. The trial randomised 1,219 men and women in Botswana to receive either TDF/FTC or placebo tablets. Twenty four participants receiving placebo tablets contracted HIV during the trial compared to nine receiving TDF/FTC. The protective benefit was therefore 62.6%.[viii] Looking only at participants known to have a supply of drugs when infected, the protective benefit goes up to 77.9%.[ix] [x]
- The FEM-PrEP trial investigated the use of daily TDF/FTC tablets to reduce a woman?s risk of contracting HIV. The trial enrolled 1,951 women in Kenya, Tanzania and South Africa. The trial was stopped early because analysis of the data revealed that the same number of infections were occurring in women receiving TDF/FTC as in women receiving a placebo. Twenty eight infections occurred in each arm. Scientists do not yet understand why the intervention arm of this trial failed to show efficacy when three other pill-based pre-exposure prophylaxis regimens showed benefit.[xi]
- The CAPRISA 004 trial investigated the use of microbicide gel to reduce a woman?s risk of contracting HIV. 889 women from South Africa and Tanzania participated in the trial. The trial compared gel containing 1% TDF versus placebo gel. The results showed that gel containing TDF reduced a woman?s risk of contracting HIV by 39%.[xii] [xiii]

What does this mean for policy?

Early ART for prevention

The HPTN 052 trial showed the greatest efficacy of all these trials. Following the results of this trial, we have an opportunity to significantly reduce new HIV infections.

Eventually nearly all people with HIV will need ART for their own health. Furthermore, nearly all people with HIV do not want to transmit the virus to their sexual partners. It therefore makes sense for the new National Strategic Plan

(NSP) to recommend offering ART to HIV-positive partners in all serodiscordant relationships, heterosexual or homosexual, irrespective of the CD4 count of the HIV-positive partner. In doing so, it must be policy that the HIV-positive partner is informed that we currently do not know the optimal time to start ART from the perspective of the HIV-positive partner's health.[xiv] We do however know that initiating treatment when a person's CD4 count falls below 350 cells/mm3 is better than a CD4 threshold of 200 cells/mm3 or lower.

While it is true that the trial only examined HIV-positive people with CD4 counts below 550 cells/mm3, relatively few people present to the public health system with a CD4 count higher than this. From a practical perspective, it therefore does not make sense to differentiate this intervention on the basis of CD4 count.

This intervention is by no means a panacea. For one thing, it only targets HIV-positive people in serodiscordant relationships. For another, it will not help with preventing the relatively large number of infections that take place during the primary infection stage when the vast majority of people, who have recently seroconverted, have no idea they have HIV. Nevertheless, this intervention in combination with other prevention interventions, such as voluntary medical male circumcision, condom distribution and, hopefully soon, microbicides, can help reduce HIV incidence.

On 10 August 2011, several organisations including TAC sent an open letter to the World Health Organisation (WHO) regarding its guidelines on serodiscordant couples. These guidelines were due to be released at the International AIDS Society Conference in Rome in July 2011.[xv] The guidelines recommended ART for all HIV-positive people in serodiscordant relationships. Publication of these guidelines was stopped at the last moment following pressure from a donor to the WHO. This was unprecedented and unacceptable. These guidelines need to be released.

ARVs for prevention in HIV-negative people

HIV-negative people with the following characteristics could benefit from taking ARVs to reduce the risk of becoming infected:

- People in relationships where they suspect their partner is HIV-positive or likely to become HIV-positive, and where it is not always possible to use condoms.
- Sex workers.
- Very sexually active people who have sex, sometimes unprotected, with multiple partners.
- People in serodiscordant relationships that are trying to conceive.

Clinicians should be able to prescribe ARVs to people with these characteristics. However, with the exception of sex workers and couples in serodiscordant relationships trying to conceive, it is difficult to see how the above situations could be written into HIV prevention guidelines.

There are several concerns with pre-exposure prophylaxis including the FEM-PrEP results and the health risks of ART. These need further discussion.

FEM-PREP trial

There has been much euphoria following the successful PrEP trials. However, the FEM-PrEP trial took place in extremely high incidence and prevalence areas. Only women participated in the trial. In other words, in the most vulnerable group of people in some of the highest prevalence HIV areas in the world, PrEP failed to show any benefit. The results of this trial cannot simply be ignored or wished away. Any PrEP policy must be cognisant of the fact that in a very large and important trial, this intervention failed. This does not mean that PrEP does not work; the other trials show that it does. But it does indicate that we have to be cautious.

Health risks

For people with HIV, the side-effects of ARVs are usually minor compared to the alternative of dying of AIDS. However, for HIV-negative people these risks are not negligible since they are not at risk of dying of AIDS so long as they stay HIV-negative. We know of no precedent for healthy people taking medicines daily their entire sexually active

lives in order to reduce the risk of contracting a disease.

Nausea and diarrhoea are common side effects of antiretroviral therapy. During pre exposure prophylaxis (PrEP) trials these side effects were reported by patients receiving TDF and TDF/FTC, although they were generally in the first month.[xvi]

TDF has also been associated with loss of bone mineral density and kidney problems in some HIV-positive people receiving these medicines. The safety of TDF/FTC has not yet been well established in HIV-negative people.

Microbicides
Further research is being conducted on the tenofovir gel microbicide. It is not yet ready for wide-scale implementation. However, the draft of the new HIV/AIDS and TB National Strategic Plan 2011-2016 (NSP) wisely provides for the possibility that in the next few years, the gel will be ready.

Affordability
There are constraints on financial resources. At present we are far short of treating everybody with HIV who needs to be treated. This is an enormous challenge, especially in sub-Saharan Africa. But it is far less of a challenge than making ARVs available to the general population. ARVs for HIV-negative people will only be manageable if targeted at specific people with high-risk characteristics.

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Footnotes

[i] 95% CI, 0.01 to 0.27; P<0.001
[ii] MS Cohen et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. 2011 Aug 11;365(6):493-505. Epub 2011 Jul 18.
[iii] RM Grant et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. 2010 Dec 30;363(27):2587-99. Epub 2010 Nov 23.
[iv]95% CI: 15 to 63%; p=0.005
[v] 95% CI: 34 to 78%; p=0.0003
[vi] 95% CI: 49 to 85%; p<0.0001
[vii] J Baeten. Antiretroviral Pre-Exposure Prophylaxis for HIV-1 prevention among heterosexual African men and women: the Partners PrEP Study. IAS 2011 Webcast. Available at http://pag.ias2011.org/flash.aspx?pid=886
[viii] 95% CI: 21.5 to 83.4%; p=0.0133
[ix] 95% CI: 41.2 to 93.6; p=0.0053
[x] MC Thigpen et al. Daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the TDF2 study. IAS 2011 Abstract. Available at http://pag.ias2011.org/abstracts.aspx?aid=4631
[xi] FHI presentation on the closure of the FEM-PrEP trial. FEM-PrEP Update June 2011. Available at http://www.fhi.org/NR/rdonlyres/e7eqslera65wohq74f5qmeurr4ohgbrofzuxlu3ulos6my24emn6qseom7eysom3cxrvmbeso
[xii]QA Karim et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science* 3 September 2010: Vol. 329 no. 5996 pp. 1168-1174
[xiii] 95% CI: 6 to 61%, p=0.017
[xiv] The Strategic Timing of Antiretroviral Therapy (START) is currently underway to assess the optimal time to start and results are expected in 2015.

xv TAC et al. Open letter to the WHO on Delayed Testing and Treatment Guidelines for Discordant Couples. 9 August 2011. Available at http://www.tac.org.za/community/node/3110

xvi Simon Collins, HIV i-Base. Tenofovir/FTC vs tenofovir as daily oral PrEP: preliminary results from Partners PrEP. August 2011. Available at http://i-base.info/htb/15468
