PrEP iPrEx Trial Reports

November 25, 2010 By Joseph Sonnabend, MD

I may as well jump in immediately: The iPrEx trial of pre-exposure prophylaxis is a failure. Maybe a shocking statement in view of the universally jubilant press reports:

“a breakthrough that will accelerate the prevention revolution.”

“This discovery alters the HIV prevention landscape forever”

“Daily Pill Greatly Lowers AIDS Risk, Study Finds”

“The results are in--pre-exposure prophylaxis (PrEP) works”

But do the results of iPrEx warrant such over the top praise? Let’s take a look at them.

Firstly does daily Truvada work as PrEP

Yes, but nowhere near well enough to be of any use at a population level (an intervention that may work for a particular individual has to be thought of in a different way to one that can be effective for populations - I’ll come back to this).

Daily Truvada reduced new HIV infections by only 44%. This is useless so how on earth can this be construed as a triumph?

We are told that this poor performance was seen because few people took their pills as prescribed. Unfortunately this is not a reassurance. Confining the analysis to a sub group of trial participants can lead to misleading interpretations of clinical trial results. I know this sounds counterintuitive, but subgroup analysis is less politely called data dredging.

Intention to treat analysis is widely accepted as the most reliable way to analyze clinical trials. Essentially, participants should be analysed in the group to which they were randomized, irrespective of whether they dropped out, or didn’t adhere to the treatment or strayed from the protocol in other ways. Again, this may sound counterintuitive, but intention to treat is now recognized as the most reliable way to analyze trial data. It also provides a better picture of real world conditions. Take a look at this: Making sense of intention to treat

So the most reliable estimate of Truvada’s efficacy, ***when administered in conjunction with an intensive HIV prevention education effort, condom distribution, counselling, rapid HIV tests and risk analysis every single month***, in reducing new infections is 44%.

This is unacceptable for an HIV prevention intervention. Even 73% is not good enough.

What about the danger of the development of resistant virus?
Many of the reports claimed this was not a problem. When it was acknowledged that resistant HIV was detected in two individuals, some reports, including one in POZ, dismissed this because the infections were acquired before randomization. This is a completely inappropriate argument. If this happened in the trial it will of course happen in real life.

The New England Journal of Medicine Editorial accompanying the iPrEx study report explains the issue:

" ...and most worrisome, viral resistance to FTC was documented in both of the subjects who were found to have had acute HIV infection at enrollment. Secondary FTC resistance after exposure to the drug clearly developed in one of these subjects, and the second subject had indeterminate resistance on baseline testing but showed FTC resistance 4 weeks after enrollment. This raises very serious concern about the deployment of oral FTC-TDF in populations of men who have sex with men...."

The danger of resistance developing is unfortunately quite realistic.

What about safety?

The claim in many reports that Truvada is without toxicity is also misleading.

Maybe poor adherence has some bearing on the lack of significant toxicity. A median of 1.2 years exposure can tell us little about cumulative and long term effects. Experience with long term use of Truvada in HIV infected people makes concern about toxicity realistic.

All of the above does not mean that PrEP has no place as a prevention strategy. It does seem on the showing of this trial, that it is not viable at a population level. However, as mentioned, there is a difference between an intervention at a population level and one involving particular individuals.

For certain individuals,in very limited settings, PrEP with daily Truvada may prove to be significant in protecting them from HIV infection, including some receptive partners in sexual intercourse who are unable to ensure condom use by their partners.

Also this trial does give some hope that intermittent PrEP might be effective.

It has been puzzling why this trial report provoked such hype about efficacy data and downplayed the problems, rather than present a more realistic picture of what this trial tells us.

Hopefully these glowing accounts of the trial will not prompt people to abandon the use of condoms or begin to use PrEP with unrealistic expectations.

The trial has also been trumpeted as "a proof of concept", the concept presumably being that daily Truvada can reduce new infections. This is pretty meaningless if the reduction achieved is too low to be useful.

Not working at all and not working well enough to be useful is the same thing.

The concept that was proved is that daily Truvada has no place as a prevention strategy on a widespread population level.

Gilead, who manufacture Truvada have made a public statement about iPrEx that includes the following.

Truvada is not indicated for the prevention of HIV. Based on the results of this study, known as the iPrEx or Pre-Exposure Prophylaxis Initiative trial, Gilead will be working with the appropriate regulatory agencies to determine if data from this study warrant inclusion in the prescribing information for Truvada.

Regardless of any action taken by the FDA or other public health agencies, Gilead believes that condoms, clean needles and behavioral interventions should remain the first line of defence for preventing HIV transmission.

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