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QUESTIONS AND ANSWERS

Secondary Analysis of VOICE: Injectable Contraception and HIV Risk

Results of VOICE Secondary Analysis / Use of contraception in VOICE

1. **What exactly are injectable contraceptives, specifically DMPA and NET-EN?**
   DMPA, or depot medroxyprogesterone acetate, and NET-EN, short for norethisterone enanthate, are contraceptives that contain a kind of hormone called progestin. Both are given by injection. DMPA (widely known by its marketed name Depo-Provera®) is administered every three months, while NET-EN (or Noristerat®) is given every two months. Both types of injectable contraception are highly effective for the prevention of pregnancy and typically more effective than oral contraceptive pills. DMPA is widely used throughout the world; NET-EN is available in fewer countries so its overall use is less common. There are other types of injectable contraceptives as well.

2. **Why did you conduct this study?**
   Researchers from the Microbicide Trials Network (MTN) wanted to conduct an observational study as part of the larger HIV prevention trial VOICE to understand whether there is a relationship between the use of injectable contraceptives and the risk of acquiring HIV. While some studies have suggested women who use the injectable contraceptive DMPA had an increased risk of HIV compared to those not using a hormonal method, a number of other studies have shown no association, and few studies have separately examined the impact of NET-EN on HIV risk. The MTN study, which involved conducting an analysis of data collected during VOICE, was the first head-to-head observational study that directly compared differences in HIV risk between users of DMPA and NET-EN.

3. **How was it conducted?**
   The type of study MTN researchers conducted was a secondary analysis, a type of observational study. With secondary analyses, researchers ask a different question than the main one the trial was designed to ask. VOICE – Vaginal and Oral Interventions to Control the Epidemic – was designed to determine whether different antiretroviral (ARV) approaches were safe and effective for preventing HIV in women. For this particular secondary analysis, researchers wanted to know whether there were differences in HIV risk among women using different injectable contraceptives. As with any HIV prevention trial testing an unproven biomedical intervention, VOICE enrolled only women willing to use effective contraception. Women made their own choices about what to use, together with clinic health providers. The majority of women in VOICE chose to use injectable contraceptives.

   While VOICE involved 5,029 women from 15 sites in South Africa, Uganda and Zimbabwe, the observational study focused only on the women enrolled at VOICE's 11 sites in South Africa, where both DMPA and NET-EN injectable contraceptives are popular methods of birth control. There were 4,077 women enrolled in VOICE in South Africa, 3,163 (78 percent) of whom used an injectable method and were therefore included in the analysis. Of these, 2,055 women (65 percent) used DMPA and 1,363 women (43 percent) used NET-EN (a small percentage used both methods at different times). At the end of VOICE, researchers looked to see how many women in each of these two groups acquired HIV during the trial. Because the analysis was planned in advance, researchers were able to capture a lot of relevant information at every monthly visit throughout the trial, including the dates when contraception injections actually took place, the type of injectable used, and any changes women made in their methods of contraception.

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4. What did the analysis find?

The MTN study found that women who used the injectable contraceptive DMPA were more likely to acquire HIV than women using NET-EN. The researchers looked at the number of HIV infections that occurred within each group during VOICE and then calculated HIV incidence rates. For women using DMPA, the HIV incidence was about 8 percent, meaning that for every 100 women who used DMPA in VOICE in South Africa, about eight became infected each year of the study. For NET-EN users, HIV incidence was about 5 percent. Combined, the HIV incidence for women using either injectable contraception was about 7 percent. (There were 204 women who acquired HIV across both groups; 150 HIV infections in women using DMPA and 54 in women using NET-EN.) Overall in VOICE, the HIV incidence was 5.7 percent.

Compared to NET-EN users, DMPA users tended to be slightly older, more likely to be married or living with a partner, and HSV-2 positive.

As an observational study, the data cannot explain *why* these results occurred. The study cannot say that one thing caused another. Because women were not randomly assigned to contraceptive methods – they chose the methods they wanted together with study staff – it's possible that the results are related to factors other than what kind of injectable contraception the women used.

5. What did the study find about herpes simplex virus type 2 (HSV-2)?

Herpes simplex virus type 2, or HSV-2, is the most common form of genital herpes and prevalent among sexually active adults worldwide but particularly widespread in sub-Saharan Africa. It's also thought to play a role in this region's high rates of HIV. Nearly half of all women in VOICE tested positive for HSV-2 at enrollment.

When the analysis took into account whether or not women were HSV-2 positive, the difference in HIV risk between DMPA and NET-EN users was two-fold. Among 1,032 HSV-2 positive women having ever used DMPA during the study, 95 acquired HIV, an incidence rate of 10 percent. In contrast, the HIV incidence was 5 percent among the 537 HSV-2 positive NET-EN users, in whom 20 acquired HIV during VOICE. Among those women who were HSV-2 negative, DMPA and NET-EN users did not differ significantly in their risk of acquiring HIV during the study.

6. Were there any geographical differences among the South African sites? What about the prevalence in areas around the sites?

Most participants in VOICE were enrolled from the Durban area, where HIV prevalence and incidence in young women are both generally high. Recent survey data from South Africa suggest that women in the same age group as VOICE participants have an HIV prevalence ranging from 17 to 37 percent, depending on their specific age group.

While the effect we observed (higher HIV incidence among DMPA users compared to NET-EN users) could also be seen when just examining data from the Durban area, the effect was less clear and not statistically significant when examining just the sites with lower HIV incidence outside the Durban area. However, drawing conclusions based on analyses restricted to sub-groups within any study is not reliable. Looking at smaller and smaller sub-groups runs the risk of getting a result that is related more to particular characteristics of that smaller group rather than the variable the study intended to examine, in this case, the kind of contraceptive method used. The results are even more unreliable if the study was not designed to look at those smaller groups in the first place.

7. Did the analysis look at whether or not women actually used the study products in VOICE? In other words, for women using injectable contraception, was HIV risk less among those who were high adherers?

Although the plan is to look at stored blood samples for the presence of active drug – a measure of product use – it will not be possible to have a complete picture of the impact of study product adherence on HIV risk among women using DMPA and NET-EN because this data is only available for a subset of women and for limited time-points during VOICE.

8. **We know in the VOICE trial that many women were not honest about product use. Could they also not have been honest about the number of sexual partners, or other risk behaviors that might factor in to why the incidence of HIV was different between the two groups of injectable users?**
   Self-reporting is not the most reliable measure of any behavior, and this is true in many settings – not just in VOICE. Moreover, many people don't feel comfortable talking about sexual behavior, condom use, etc. However, if reporting of risk behavior differed between the two groups, this could have impacted the results of the analysis. This is exactly why this kind of study (an observational study) has limitations. Randomization can "even out" different tendencies to report or not report sensitive behaviors, by spreading out people among study arms randomly. However, in VOICE, participants were not randomized to contraceptive method, so it is possible that people with different tendencies in reporting ended up clustering within particular contraceptive methods.

9. **Why wasn't data from Uganda and Zimbabwe included in the analysis?**
   VOICE participants in those countries didn't use the injectable contraceptive NET-EN, and it was important to be able to compare DMPA to NET-EN use in the same population of women.

10. **Why was it necessary that women use contraception in VOICE?**
    As with any HIV prevention trial of an unproven biomedical intervention, great attention is paid to the safety and well-being of participants. Potential volunteers are carefully screened by study staff to ensure that only women for whom it would be safe to participate are enrolled. Because it was not known how the study drugs might affect a woman's pregnancy or the development of her fetus, only women who were willing to use an effective contraceptive throughout the study were enrolled.

11. **What kinds of contraception were offered to women in VOICE?**
    The types of contraception offered to participants depended on the contraceptive methods available within the particular country, and what could be offered at the research site and/or at referring clinics. At the very minimum, women in VOICE had the choice between receiving oral contraceptives and injectable contraceptives. Women wishing to use contraceptive implants, copper intrauterine devices (IUDs), or sterilization were referred to facilities offering those services, if they were not offered on-site.

12. **Were women in VOICE counseled on the potential risks of the injectable contraceptives?**
    All women who received contraception at VOICE sites were informed of the benefits and risks for all options available to them, including injectable contraceptives.

13. **Why, when there were already questions about a possible increased HIV risk with DMPA, did VOICE sites continue providing DMPA to participants? Were women put at higher HIV risk than they already were?**
    First, it's important to understand that VOICE site staff worked actively to decrease all participants' risk of HIV infection by providing free condoms, regular counseling about preventing HIV and other STIs, and STI testing and treatment, throughout the trial. Women in VOICE were also counseled on a range of contraceptive methods available in the countries where they lived, using the most up-to-date World Health Organization (WHO) guidance. Women made their own choices of what to use, together with clinic staff and other providers. In South Africa, as in many other African countries, many women opt to use injectable contraceptives such as DMPA. The fact is that evidence across studies regarding DMPA use and HIV risk remains unclear.

<u>Implications – Body of evidence and WHO guidelines</u>

14. **What are the implications of the results of the secondary analysis of VOICE data?**
    While these are important findings, they need to be considered within the context of the limitations of this kind of study and the larger body of evidence on DMPA. Moreover, the results, which were only just reported at a scientific meeting, have yet to be published in in a peer-reviewed journal. It will then be up to policy makers, scientists and groups such as the WHO to decide the implications of this study and other emerging data in relation to what previous studies have found. However, if there is one thing the results of the new analysis make very clear, it is the need for more safe and effective contraceptive and HIV prevention options for women.

15. What kind of information was available about HIV risk and DMPA prior to this study?
There have been at least 25 different studies, all of these observational in nature. Some concluded that DMPA may pose an increased risk of HIV, while others did not. This is why WHO sought the advice of an expert panel, which it convened in 2012.

16. What did the WHO recommend from that meeting in 2012?
WHO routinely reviews new research on contraception to see if new clinical guidance is needed. In 2012, WHO convened a panel of experts to review the body of evidence available at that time. Because of the conflicting information related to HIV risk, WHO recommended that women using injectable progestin-only contraception be strongly advised to always use condoms and other means to prevent HIV. WHO also recommended that women have more choices for family planning and that more research be done on the relationship between hormonal contraception and HIV.

17. Are WHO recommendations expected to change, based on these or other recent results?
For many years, WHO has used an established strategy for changing clinical guidance based on emerging evidence. As part of this process, WHO determines when it's prudent to reconvene panels of experts to weigh new study results. Just recently (in early March 2014), WHO reconvened an advisory panel to discuss new information reported since its 2012 meeting. The results of the VOICE secondary analysis were not available in time to be considered in this discussion. Nonetheless, it's more likely that WHO will want to wait until the team has published a more comprehensive report of the findings before evaluating their implications in the context of the full body of research.

WHO has already expressed the need to expand the contraceptive method mix for women. That's not likely to change. Meeting the health needs of women means ensuring that a variety of safe and effective methods are available for both pregnancy and HIV prevention.

18. Does the secondary analysis of VOICE only provide more of the same kind of observational data that offers little in the way of definitive information?
The results of the secondary analysis of VOICE have provided very valuable information – when taken in the context of the limitations inherent in this kind of study. The VOICE trial was a large, well-conducted trial, and this analysis was pre-planned so that researchers could be very precise about the data to be collected. The study involved more than 3,000 women using injectable contraception, and it was the first to compare HIV risk directly between DMPA and NET-EN. But it's important that these findings be viewed within a much larger context of evidence on DMPA and the risk of HIV.

19. Is a randomized controlled trial needed to get definitive answers about DMPA and HIV risk?
Other research groups have been discussing the possible merits and challenges of a randomized control trial and how such a trial might be designed. As researchers, policy makers and funders are considering next steps, it's important that they consider what the women and communities most affected want. What do they want funders to invest in? In a clinical trial? Or in efforts focused on expanding the number of method choices available to women? Or in something else entirely different?

20. What is the ECHO trial?
ECHO – Evidence for Contraceptive Options and HIV Outcomes – is a trial being proposed by a consortium of researchers. The trial would randomly assign women, who provide informed consent, to use a particular contraceptive method, DMPA, for example, and then determine at the end of the study if women who used one method were more likely to acquire HIV than women who had been randomized to use another method.

21. Now what? What studies are needed moving forward? What do we still need to understand? Or is there any sense in continuing to study this?
There are a number of unanswered questions that only additional research can address. Some groups are looking at immunological factors; others are looking at women's perceptions of risk. It is important that HIV prevention studies in women continue to collect high quality data on contraceptive use.

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Implications – DMPA and choices in contraception

22. Do these results mean all injectable contraceptives aren't safe?
No. These results suggest NET-EN users may have fewer HIV infections than DMPA users among women in South Africa, where there are already very high HIV rates. DMPA is safely used by many women in many parts of the world, and other injectable contraceptives exist as well.

23. Do these results implicate all hormonal contraceptives?
No. The study involved only two injectable hormonal contraceptives containing the hormone progestin. Moreover, these results suggest that the risk of HIV may be higher with use of the injectable contraceptive DMPA compared to NET-EN.

24. Should DMPA (Depo-Provera) be taken off the market?
The results of the VOICE analysis must be considered in the context of the limitations of an observational study and the larger body of evidence on DMPA and the risk of HIV. It's up to policy makers and WHO to weigh the evidence, and the risks and benefits of different approaches in different populations of women. Questions about DMPA and HIV risk apply almost exclusively to women living in parts of Africa where injectable contraception use is very common and the risk of acquiring HIV is perhaps the highest of anywhere in the world. But for these same women, the use of effective contraception, such as DMPA, is a life-saving choice. Ultimately, the results of the VOICE secondary analysis support the need to provide women everywhere with more choices of and access to a variety of contraception options.

25. Why is DMPA use so high in Africa and in the developing world compared to in the U.S. and Europe? Some have even suggested that its use in Africa is why HIV rates are so high there.
Reasons that DMPA use is higher in Africa vary. Giving medicine by injection is seen as a trusted and potent form of medication delivery in many cultures in sub-Saharan Africa. Because DMPA is long-acting and does not require daily action by a woman, it's both an easy- to- use and discreet method. Some African countries have rolled out use of injectable methods in the public sector because of these reasons, and, importantly, because DMPA is an effective method of contraception. Although the incidence of HIV is higher in parts of Africa than in anywhere else in the world, no one factor – contraceptive use included – can be singled out to explain why this is so.

26. What about women who receive contraception at family planning clinics, i.e., outside the trial site setting – are they counseled on the potential risks of DMPA?
WHO and in-country guidance advise that all women are fully counseled on all available family planning options.

27. Will the results of this analysis affect clinical practice?
Contraceptive choice is a matter for healthcare providers to decide in consultation with their patients, and those decisions should be informed by the most current guidance available from WHO.

Implications – HSV-2

28. What have other studies found concerning HSV-2 and DMPA?
Two other studies involving DMPA use and HIV risk had results that differed from those of the VOICE secondary analysis. One study compared the use of DMPA to no contraception (except possibly condoms) and found the risk of HIV was higher among women who were HSV-2 negative and using DMPA. Another study did a similar comparison but did not see higher HIV risk for DMPA users in the HSV-2 negative or positive groups. Meanwhile, research is ongoing in a laboratory setting looking at possible interactions between HSV-2 and hormones.

29. Should there be routine screening for HSV-2 so that women who are positive are counseled against using DMPA?
The evidence from this study and others do not suggest there would be clinical benefit to screening women in the general population for HSV-2. There is evidence, however, that abruptly taking women off contraception is not a good idea. Using contraception can be a lifesaving choice for women.

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30. Could vaccinating young women against HSV-2 in sub-Saharan Africa help in reducing risk of HIV for women with HSV-2 using hormonal contraceptives?

While the significance of HSV-2 infection for contraceptive users is a critical area for more study, it is important to understand that HSV-2 is extremely common in sub-Saharan Africa, and so far, there is no proven effective vaccine for preventing HSV-2. Moreover, while the analysis of VOICE data found a higher risk of HIV in the sub-group of DMPA users with HSV-2 compared to NET-EN users with HSV-2, it's not known whether the combination of DMPA and HSV-2 truly put women at risk. There have been other studies that did not see an increased risk of HIV among DMPA users with HSV-2 compared to women with HSV-2 who were not using any hormonal contraception.

Implications – ASPIRE

31. How will these results change what contraceptives you provide in ASPIRE?

The MTN follows WHO guidance and national policies that impact the availability of methods within each country. Current WHO guidelines on contraception acknowledge the data is mixed on the potential risk of HIV with DMPA. The new study does not change the fact that conclusions from studies differ. So, until WHO makes changes to its guidelines, the ASPIRE team will continue to counsel women on the risks and benefits of the methods that are available locally, in accordance with current guidance. Importantly, the study team will also continue efforts focused on giving women a range of options to choose from. Even prior to these results, the ASPIRE study team and site staff, through the MTN Contraception Action Team, made it a goal to ensure that participants have access to a variety of methods. So, a woman may choose to use (or to continue using) DMPA, if that's what she prefers, or she may opt to use another form of effective contraception, such as the IUD or implants, which are now being offered to participants directly at many of the ASPIRE trial sites.

32. What about for women who are HSV-2 positive? Will they be advised to continue their current method of contraception or advised to change (if they are using DMPA?)

The significance of HSV-2 infection for contraceptive users is a critical area needing more study – the VOICE results provide one piece of information, but must be replicated in other studies or refuted by further research. The ASPIRE team will continue to counsel women on the risks and benefits of the contraceptive methods that are available locally, in accordance with current guidance. Importantly, the study team will also continue efforts focused on giving women a range of options to choose from. A woman may choose to use (or to continue using) DMPA, if that's what she prefers, or another form of effective contraception, such as the IUD and the contraceptive implant, which are now being offered to participants directly at all of the ASPIRE trial sites.

33. What is being done overall to expand the method mix?

In recent years, the MTN has taken to diversifying the range of effective contraceptive methods available to study participants. In May 2012, it formed the Contraception Action Team to help site staff gain the necessary training for providing a variety of methods, including the IUD and implants, directly at the clinic. Women have had access to more methods than ever before. Through this initiative, and the choices made by the participants themselves, the use of IUDs and implantable contraceptives have increased dramatically and fewer women have been choosing to use DMPA.

34. Should information about the findings of the VOICE secondary analysis be included in the ASPIRE informed consent form?

In the context of a clinical trial, the informed consent process (and informed consent form) concerns the study itself, and the risks and benefits of the procedures specified in the protocol for collecting information to answer the study's questions about safety and effectiveness of the dapivirine ring. While the informed consent form does stipulate that women must be willing to use an effective form of contraception, the decision about what methods are offered and women chose to use are outside the purview of the informed consent process for the trial. Site staff will continue to counsel participants on the risks and benefits of the methods that are available locally, in accordance with current WHO guidance, and women will also continue to receive guidance on the risks and benefits of different contraceptive methods from other providers in their communities. Importantly, the study team will also continue efforts focused on giving women a range of options to choose from.