

Quick Questions and Answers about Hormonal Contraception and HIV

I've heard that hormonal contraception – things like the Pill and Depo – can cause HIV infection. Is this true?

No, hormonal contraception (HC) does *not* cause HIV infection – the HIV virus does. If a woman is at risk of becoming infected with HIV, it is possible (though not yet proven) that using HC may increase her risk somewhat. But a woman at risk of contracting HIV who is using HC will still be at risk of contracting the virus even if she stops using HC. There are many factors that go into determining a woman's risk of contracting HIV. Even if hormonal contraceptive use turns out to be one of these factors, there will still be many others. And many of these other factors – number of sexual partners; use or non-use of condoms; use of injecting drugs – have a stronger impact on risk than hormonal contraception is likely to have, even in a worst-case scenario. So we should not focus on hormonal contraception and forget about everything else. Looking at the “big picture” is the best way to reduce HIV risk for everyone.

Even if hormonal contraception doesn't cause HIV infection, can it increase a woman's chances of contracting HIV?

The answer isn't clear, at present. Some studies have shown no association between hormonal contraceptive use and HIV transmission, while other studies (which were conducted among sex workers rather than among women in general) suggest that using HC results in a small increase in risk. The question is very difficult to study, however, in part because it involves sex and sexuality, which are difficult to research. So at this point, it is hard to be certain what is true and what isn't. However, World Health Organization guidelines continue to place no restrictions on the use of hormonal contraceptives for women at risk of acquiring HIV. There is yet no compelling reason to conclude that HC has an effect on HIV transmission among women in general.

But how could using hormonal contraception affect HIV transmission?

Any sort of hormonal treatment has the potential to affect many of the body's systems (think of how the Pill, for example, not only prevents pregnancy but can also cause breast tenderness, affect bone density, and protect against ovarian cancer). In the case of HIV and hormonal contraception, lab researchers have found at least seven plausible mechanisms through which use of HC might increase a woman's chances of contracting or spreading the virus. But just because a mechanism is plausible doesn't necessarily mean it is operating.

Has anyone looked at real people, outside the lab, to see if an effect of hormonal contraception on HIV transmission is really taking place?

Yes - but the results are mixed. Some studies have found no link, while others – conducted among sex workers, not among women in general – have found that using hormonal contraception increased a woman's chances of contracting HIV, increased the likelihood of an infected woman spreading the virus to her sexual partners, and increased the speed at which disease developed in HIV-positive women. But it isn't at all clear that the results of the studies among sex workers apply to women, in general –and there are additional problems. For one thing, many researchers have pointed out that women who use HC might be different from women who do not use HC in other ways, as well. For example, HC users might have more frequent sex, have more sexual partners, use condoms less frequently, and/or engage in more risky sexual practices. If any of these things are true, then the effect that HC seems to be having on HIV may, in reality, be an effect of these other behaviors on HIV instead. And since people are not always willing to talk openly about sex, it is hard to know whether these kinds of differences between HC users and non-HC users really exist or not.

I really rely on hormonal contraception. I would hate to stop using it unless there was a very good reason to do so.

This is the heart of the problem. HC provides huge benefits to women all over the world. It is a very effective form of contraception which a woman can use even without male cooperation, and one which she can stop using relatively quickly if she decides she wants to have a baby. Beyond this, HC actually saves lives every year,

since in many parts of the world an unwanted pregnancy means that a woman is at risk of dying or being injured in childbirth or due to an unsafe abortion. HC is very useful. Any risks it may turn out to pose need to be weighed against its benefits.

What should women do, then? Should they keep using hormonal contraception? Should they stop?

The short answer to this question is that, given the current uncertainty about an HC/HIV link, there is no reason for women to change what they are already doing with regard to hormonal contraception. The longer answer is: If it turns out that HC does increase the chances of contracting and spreading HIV, different women may choose to do different things in response. For example: If you are only having sex with one partner, and you are pretty sure he is only having sex with you, and both of you are uninfected – then there would be no reason for you to change what you do at all. If you happen to live in a community with very high rates of HIV, and/or you cannot be sure of the HIV status or sexual behavior of your partner or partners – well, then continuing to use HC might not be a risk you want to take. If you live in a country with high maternal mortality and modest HIV rates, then the benefits you get from hormonal contraception might outweigh any risks it might bring. And so on – there are lots of other possibilities in between. What is clear is that there will never be a “one-size-fits-all” solution. What we all need to do is to pay attention to the results of future studies and, if the HC/HIV link turns out to be real, make our decisions about hormonal contraceptive use based on the specifics of our particular lives and circumstances.

For now, however, there is no reason for women, in general, to change their current choices and behavior with regard to HC.

If you want to know more about hormonal contraception and HIV, please turn to the next pages, where we talk about the subject in more detail.

Detailed Questions and Answers about Hormonal Contraception and HIV

1. **There has been talk that using hormonal contraception may increase a woman's chances of contracting or spreading HIV. Is this true?**

At this point, it is difficult to say whether it is true or not. Over the past decade, a variety of studies have produced evidence suggesting that hormonal contraceptive use *may* result in a small increase in a woman's chances of contracting or spreading HIV. On the other hand, other studies have found no such effect. And even if the effect turns out to be real, it is by no means obvious what should be done in response, since hormonal contraceptives bring great benefits to women, as well. This "Questions and Answers" sheet attempts to summarize what we do and don't know on this subject to date, and to discuss possible ways we might respond to this knowledge.

2. **When did scientists become concerned that hormonal contraception might affect HIV transmission?**

It has long been known that hormonal treatments are capable of affecting many of the body's systems. For example, oral contraceptive pills have effects not only on whether or not a woman gets pregnant, but also on things like her bone density and risks of cardiovascular disease and cancer. Thus, the question whether or not hormonal contraceptive use might affect how, and how easily, a woman can contract or transmit the HIV virus is, in theory, a reasonable one to ask.

Serious practical concern about the potential effects of hormonal contraception on HIV transmission arose in the middle of the 1990s, when experiments with monkeys suggested that hormonal contraception might very significantly thin the epithelium – or lining – of the vagina. This, in turn, could weaken the epithelium's ability to function as a barrier to infection. Since this time, researchers have been investigating whether this, or any other effect relevant to HIV transmission, might occur in women using hormonal contraception, as well.

3. **Is all hormonal contraception the same? Is all hormonal contraception implicated in possible effects on HIV transmission?**

All hormonal contraception is *not* the same. There are many varieties, each with its particular formulation. All contain one of a class of hormones called "progestins," while some also contain different hormones known as "estrogens." This is important, because evidence to date suggests that – if there *is* an effect of hormonal contraception on HIV transmission – it is likely that it is progestins that have the most serious negative effect. Estrogens, on the other hand, may actually be somewhat protective.

Even in those hormonal contraceptives that contain estrogens, however, the progestin portion of the formulation is more active, or "dominant." Not surprisingly, then, such evidence as we have to date suggests that "progestin-only" contraceptives (such as Depo-provera) may have a more serious effect on HIV transmission than "combined" contraceptives (such as the most common oral contraceptive pills), but that even "combined" hormonal contraceptives may have a net detrimental effect.

4. **What have we learned since the mid-90s about the effects of hormonal contraceptives on HIV in human beings?**

A great deal of research on this topic has taken place since the mid-1990s. Some of it has been "lab-based" – that is, it has examined in detail the effects of hormonal contraceptives on particular bodily systems in women in an attempt to establish possible mechanisms through which hormonal contraceptives might affect acquisition and transmission of HIV. Less often, research has been "epidemiological" or "population-based" – that is, it has looked at groups of real people in an attempt to determine if hormonal contraceptive use actually seems to have an effect on HIV transmission in the real world. Although these two types of research often overlap, it can be helpful to discuss them separately, since the first type addresses itself to the question of how hormonal contraceptive use *might plausibly* affect HIV transmission, while the latter asks whether or not hormonal contraceptive use *is actually having* such an effect.

Lessons learned from lab-based research. Lab-based human research has established at least seven mechanisms or pathways through which hormonal contraceptive use might plausibly affect HIV transmission. Some of these mechanisms affect how susceptible a woman is to *contracting* the HIV virus, some affect how likely she is to *pass it on* to someone else, some affect *how HIV disease develops in a woman who has been infected*, and some affect two or more of these categories. These mechanisms are as follows:

- i) Although the thinning of the vaginal epithelium that has been seen in human women is not nearly as dramatic as that seen in monkeys, it does appear possible that hormonal contraception – by thinning the epithelium, by decreasing its number of cell layers and changing the characteristics of certain of its cells, and/or by affecting its ratio of mature to immature cells – may reduce the barrier that a woman’s vaginal epithelium presents to HIV. This could, in turn, make her more susceptible to infection and/or more capable of transmitting the virus.
- ii) Hormonal contraceptive use may make women more susceptible to contracting certain infections or irritations of the reproductive tract, such as Chlamydia and cervicitis (inflammation of the cervix). It may also “re-activate” a pre-existing *Herpes simplex* infection. Since active reproductive-tract infections compromise the body’s barrier against HIV, it is possible that these hypothesized effects of hormonal contraception might increase women’s chances both of contracting and of passing on the virus.
- iii) One way that HIV invades the human body is by attacking certain types of cells in the reproductive tract, as well as cells that exhibit certain types of receptors on their outer membranes. Thus, any increase of these types of cells, or of cells “expressing” these receptor types, in a woman’s vagina might make her more susceptible to infection. There is some evidence that hormonal contraception may produce such an increase in susceptible cells in women.
- iv) Organisms such as lactobacilli living in a woman’s vagina provide her with protection against certain infections. If hormonal contraception use leads to changes in the number or nature of these organisms, it may reduce a woman’s resistance to infection.
- v) It is possible that the nature of the HIV virus as well as the way it behaves is different in women using hormonal contraception than in other women. Thus, women using hormonal contraception may be infected by a wider *variety* of HIV virus types, they may have a higher viral *set point* (the level of virus characteristic of the period after acute infection and before full-blown AIDS), and the virus may *reproduce* more readily in them. If some or all of these are true, HIV disease may progress faster in women using hormonal contraception, and they might be more liable than other women to pass the virus on to their sexual partners.
- vi) It is possible that HIV-infected women who are using hormonal contraception *shed* more HIV virus into their vaginas than do other HIV+ women. This is another mechanism that could make these women more liable to pass on the virus.
- vii) Some hormonal contraceptives may increase cervical “ectopy” – that is, the number of cells from the lining of the cervical canal that are exposed to the vagina. This, in turn, might possibly increase a woman’s susceptibility to HIV infection.

Lessons learned from population-based research. Even if lab-based research establishes plausible mechanisms by which hormonal contraceptive use might affect HIV transmission, this does not necessarily mean that such an effect actually takes place in the real world. To determine whether or not this is happening, researchers must conduct studies in actual human populations.

This sort of research faces many obstacles: Keeping track of a defined group of people over a lengthy period of time (often years) is difficult and expensive. Furthermore, measuring every factor relevant to HIV acquisition in real-life situations (rather than in the controlled conditions of the laboratory) is not a simple matter. Not surprisingly, then, relatively little population-based research has been completed, and that which has is imperfect.

Some population-based study found no statistically significant association between hormonal contraceptive use and increased HIV incidence. Other studies, however – which generally looked at sex workers, as opposed to women in the population at large – did find hormonal contraceptive use to be significantly associated with an increased risk of HIV acquisition, as well as with faster disease progression and a greater likelihood of HIV+ women spreading the disease to others.

Evidently, then, the matter is not settled – we must wait for more evidence from other well-designed studies. But both lab-based and population-based studies suggest that a hormonal contraception/HIV transmission interaction is at least a possibility; neither type of research, however, has yet proven that such an interaction actually taking place – especially among the general population of women.

5. What are the difficulties and problems with population-based research on a possible hormonal contraceptive/HIV link? Are they important enough to undermine the conclusions of this type of research?

When researchers examine population-based studies, one of the main things they are alert to is the possibility of “confounding.” In brief, this means the possibility that an effect which *appears* to be the result of a factor that the study is measuring is, *in fact*, the result of another, different factor that the study is *not* measuring – or at least not measuring accurately enough. To take a fictional example: If we assume that cigarette smokers tend to get less exercise than non-smokers, then a study which looked only at the relationship between exercise and lung cancer (without measuring cigarette smoking!) might conclude that less exercise leads to greater risk of lung cancer. In fact, of course, it is unlikely that this is true. What is more likely is that cigarette smoking (which was not measured in the study) is the real cause of increased lung cancer risk, and that lower exercise (which was measured in the study) is merely a behavior associated with cigarette smoking but not itself linked to greater risk of cancer. In this example, cigarette smoking is an unmeasured *confounder* which negates the exercise/lung cancer link that the study appeared to establish.

How does this relate to population-based research into a possible hormonal contraceptive/ HIV link? The danger, simply put, is that women who use hormonal contraception in the real world may differ in other ways, as well, from women who do not. If this is true, then any perceived greater incidence of HIV infection in these women might be the result not of their contraceptive use, but of some other factor contributing to their difference from other women. To take a hypothetical example – if it were true that women who use hormonal contraception tended to have more frequent sexual intercourse than other women, or more sexual partners, or sexual partners who were more likely to be infected with HIV, or more risky sexual practices, then any measured increase in HIV incidence in these women might be the result not of hormonal contraceptive use, but of these other factors.

One very good way to guard against confounding is to conduct a “randomized controlled trial” (RCT). In this type of study, a large group of study participants is randomly assigned to “treatment” or “control” groups – in the present case, this would be the group using hormonal contraception versus the group not doing so. Since the group of participants is large and their exposure to the “treatment” of interest is randomly determined, there is a very good chance that any potential confounders will be evenly distributed between the two groups and thus will not be able to affect results.

Conducting an RCT of hormonal contraception, however, is not easy. For one thing, it is not clear that it is ethical – certain contraceptives really are more appropriate for certain women than are others; assigning a study participant to use a contraceptive that is not appropriate to her needs probably would violate medical ethics. Beyond this, however, it may not be practicable: a woman who prefers Depo-provera, for example, may not be very likely to continue using a diaphragm, even if she has been assigned to this method. Since such a woman may very well go and obtain Depo-provera no matter what her assigned contraceptive is, it would be very hard to assure that the original, randomized groups of contraceptive users actually continued throughout the duration of the study.

Short of an RCT, the best way to guard against confounding is to measure any and all aspects of study subjects that may have an effect on the outcome of interest. In the hypothetical example above, if we had clear and accurate measurements of frequency of sexual activity, number of partners, infection status of partners, and type of sexual activity, we could correct for any differences in these factors, and thus better determine if a perceived difference in HIV incidence was due to hormonal contraception or to something else. The problem, however, is that these sorts of confounders are very difficult to measure accurately – and even more difficult to be confident of measuring accurately! We are talking, after all, about sex – a subject which most people consider private. Knowing that we are getting honest, correct answers on such topics, and answers which actually shed light on the topics' most important aspects, is not easy. Furthermore, questions of this kind are probably subject to a more or less substantial “courtesy bias” from study participants. In other words, participants asked about condom use, for example, or number of sexual partners may feel some pressure to respond with the “right” answers – that is, the answers they believe the researchers wish to hear. In such cases, participants may respond that they use condoms regularly, or only have one sexual partner, even when this is not the case. This sort of bias presents yet another obstacle to accurately researching a possible HIV/hormonal contraception link.

Finally, there may be confounders affecting study results which researchers simply haven't thought of at all. Needless to say, if researchers haven't even realized that a given confounder might affect their results, they are not likely to measure the confounder accurately – or, indeed, to measure it at all. In this way, an unrecognized confounder could seriously undermine study results.

The upshot of all this is that it is very, very difficult to know whether any perceived association between hormonal contraceptive use and HIV incidence, progression, or transmissibility is in fact a real association, or rather the result of some unmeasured or inaccurately measure confounder. And knowing this makes a difference. The example cited above (on cigarette smoking, exercise, and lung cancer) may seem silly, but it is instructive, in that it shows how unmeasured confounding can lead to inaccurate conclusions and misguided interventions: Encouraging exercise to prevent lung cancer would have very little effect on cancer rates unless smoking were reduced, as well.

There is no “magic bullet” to fix this problem. All we can do is work to keep improving our study designs and measurement of confounders, use our best judgment when interpreting results, and be careful and cautious when recommending policy and service-delivery changes.

6. What should we do differently given what we know about the possible effects of hormonal contraception on HIV transmission?

As the discussion above makes clear, family planning programs and other providers of contraception should be cautious about changing what they do on the basis of what we know about this topic to date. Here are some important points to keep in mind:

- i) Although there is credible evidence for an association between hormonal contraceptive use and various aspects of HIV infection, this association cannot currently be said to be either proven or established as causal –especially for women in the general population. Even small errors in measuring confounding factors could overturn the conclusions of the studies conducted to date. We must use our best judgment in evaluating existing evidence, while remaining alert to any changes in our understanding that future studies may bring.
- ii) Even if the hormonal contraception/HIV association is confirmed and/or strengthened by future research, the best response to take is neither obvious nor uniform for all populations or all women. Some examples will help to make this point clear. Let us assume, for the moment, that using Depo-provera moderately increases a woman's risk of contracting HIV (remember – this is merely an assumption for argument's sake; we are not stating that such an increase in risk has actually been proved!). What this would mean would be very different for different women. For a woman in a relationship she has confidence is monogamous with an HIV-negative partner, for example, this finding would make almost no difference – her risk of acquiring HIV is very small to begin with, and a very small risk that is moderately increased remains very small. A similar situation might obtain for a woman who is less confident of her partner's fidelity, but who lives in a

community with low HIV prevalence and/or prevalence that is confined largely to one or two risk groups of which neither the woman nor her partner is a member. The implications of our hypothetical “finding” for a sex worker, on the other hand, or for a woman living in a community with high general prevalence of HIV, might be quite different. These women might have a large, ongoing risk of HIV acquisition, and moderately increasing this risk might very well be unacceptable. Thus, even if further research confirms an association between hormonal contraceptive use and increased HIV transmission, it is unlikely that any “one-size-fits-all” policy change will emerge as an appropriate response. This is all the more true when we consider that hormonal contraceptive use brings many benefits to women, as detailed below.

iii) In many parts of the world, women face a real, present, and grave danger of dying in childbirth. In some countries, this risk may be as great as 1 in 200 – or even 1 in 100 – for every child born. Furthermore, as evidence makes plain time and time again, women who have undesired pregnancies frequently seek to terminate them – even in countries where abortion is illegal and/or unsafe. In this context, it is easy to see that a dependable contraceptive method is not a “neutral” thing when it comes to women’s health. It is, rather, a means by which women can protect themselves from serious health risks associated with pregnancy and childbirth.

Hormonal contraceptives, when used correctly, are among the most dependable methods available. Beyond this, they provide a range of other benefits: They are woman-controlled, are easily reversible when a woman decides she wishes to become pregnant, and protect women against diseases such as ovarian cancer. They (especially Depo-provera) also offer women the possibility of concealing the fact that they are using contraception from others in their community – something which can be very important to women in places where family planning is frowned upon.

All in all, hormonal contraceptives offer a range of very important benefits to women around the world. Even if a hormonal contraceptive/HIV link is ultimately established, any risks from hormonal contraception must be weighed against these benefits – a process that will yield different conclusions for different populations and different women, as we saw above.

iv) Finally, it is important to keep any possible contribution of hormonal contraception to increased HIV risk in context. No matter what the findings ultimately are, it is important to remember that *hormonal contraceptives do not and cannot cause HIV infection*. HIV infection is caused by the HIV virus; other factors (possibly including hormonal contraceptive use) can increase or mitigate the risk, but they do not, in themselves, cause infection. And there are many, many factors – number of sexual partners (especially concurrent sexual partners); behavior of these partners; use of injecting drugs; use or nonuse of condoms during sex; type of sexual activity – that have a stronger effect on increasing or mitigating risk than hormonal contraceptives are likely to have under even a worst-case scenario. Furthermore, a woman who is at risk of contracting or spreading HIV when using hormonal contraception will also be at risk of contracting or spreading the virus if she stops using it. In focusing on the possibility that hormonal contraceptives might increase a woman’s HIV risk, we must be careful to remember that it is the whole complex of behaviors and situations facing a woman that determines her risk. Concentrating on ameliorating this entire complex, rather than on demonizing any one element in it, is the proper task for our anti-HIV efforts.

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