HIV prevention for the HIV serodiscordant couple: opportunity for elimination?

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HIV prevention for the HIV serodiscordant couple: opportunity for elimination?
HIV prevention for the HIV serodiscordant couple: opportunity for elimination?
HIV serodiscordant couples are central to the African epidemic

Across a wide variety of settings, HIV serodiscordance has been demonstrated to be common. (➔)

In a couple in which one member is HIV+, there is a 50:50 chance that the other will be HIV-. In general, couples have equivalent likelihood that the HIV+ partner will be female/male.

Piot et al., Lancet 2008
HIV serodiscordant couples are central to the African epidemic

The frequency of serodiscordance follows underlying HIV prevalence: in lower-prevalence settings can be an important population to target for prevention, in higher-prevalence settings can be a substantial fraction of all couples.
HIV incidence is high in serodiscordant couples

In the absence of HIV testing – and most importantly, testing as a couple, with couples-based counseling and mutual disclosure – HIV risk is very high in serodiscordant couples.

Annualized incidence can be very high = >10% - driven by higher viral load and rare use of condoms. (Quinn et al. N Engl J Med 2000)
Survey and mathematical modeling studies have estimated that coupled relationships could account for up to half of HIV transmissions in Africa. (Dunkle et al. Lancet 2008)

In HIV serodiscordant couples, 65-85% of new infections are acquired from the married/cohabiting partner. (Campbell et al. PLoS One 2011; Eshleman et al. J Infect Dis 2011)
HIV testing of couples markedly reduces HIV risk

Couples-based HIV counseling and testing offers the opportunity to know one’s status and that of one’s partner, with facilitated disclosure and opportunity for counseling about serodiscordance and risk reduction.

Senator Barack Obama and his wife, Michelle Obama know their status...

Know your HIV status!

... DO YOU AND YOUR PARTNER KNOW YOURS?

For more information contact the Ministry of Health facility nearest you.
HIV testing of couples markedly reduces HIV risk

Ongoing retesting of HIV negative members of HIV serodiscordant couples has benefits:

Benefits of re-testing the HIV negative partner

- Motivates the negative partner to take-up prevention measures to maintain the negative HIV status
- In case of sero-conversion, early diagnosis of HIV infection enables linkage to care and treatment and other support services such as eMTCT to prevent further HIV transmission
- Re-testing may be offered as a prevention package for the negative partner and thus will facilitate better support to the partner living with HIV

WHO guidelines recommend retesting at least annually, more frequently if risk is higher (pregnancy, lack of condom use, etc).
HIV testing of couples markedly reduces HIV risk

Mutual disclosure of HIV status and ongoing HIV testing can be accompanied by substantial behavior change (particularly increases in condom use, and reductions in sexual activity), resulting in reduced HIV risk. *Also, better linkage and use of PMTCT services.

However, testing alone does not eliminate HIV risk in couples:

Drivers of ongoing risk in HIV serodiscordant couples

Ongoing risk in HIV serodiscordant couples is driven by biologic and behavioral factors:

- High viral load / lack of viral suppression
- Inconsistent condom use (“condom fatigue”)
- Lack of male circumcision
- Outside partnerships
- Genital tract infections / sexually transmitted infections (minority)
- Fertility desires
Quantifying risk in HIV serodiscordant couples

HIV risk is heterogeneous, even in at-risk populations

An objective risk scoring tool for serodiscordant couples identifies those with higher risk (Kahle et al. JAIDS 2013)

- Components of the score: younger age, fewer children, lack of circumcision (HIV- men), cohabiting, unprotected sex in the prior month, and high plasma HIV RNA levels in HIV+ partner

<table>
<thead>
<tr>
<th>Age of HIV-1–uninfected partner</th>
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<tbody>
<tr>
<td>20 years or less</td>
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<tr>
<td>21-30 years</td>
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<tr>
<td>More than 30 years</td>
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<table>
<thead>
<tr>
<th>Number of children</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>1–2</td>
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<tr>
<td>3 or more</td>
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<table>
<thead>
<tr>
<th>Male HIV-1–uninfected partner uncircumcised</th>
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<tr>
<td>Yes</td>
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<tr>
<td>No</td>
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<table>
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<tr>
<th>Married and/or cohabiting</th>
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<tr>
<td>Yes</td>
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<tr>
<td>No</td>
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<table>
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<tr>
<th>Unprotected sex within partnership, prior 30 days</th>
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</thead>
<tbody>
<tr>
<td>Yes</td>
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<tr>
<td>No</td>
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<table>
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<tr>
<th>HIV-1 plasma viral load, HIV-1–infected partner</th>
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<tbody>
<tr>
<td>50,000 copies or higher</td>
</tr>
<tr>
<td>10,000-49,999 copies</td>
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<tr>
<td>Less than 10,000 copies</td>
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Total score
Fertility desire as a driver of HIV risk in serodiscordant couples

Fertility intentions are common in HIV serodiscordant couples:

•~1/3 of HIV- partners at any one point in time, mostly in agreement with HIV+ partner (Mujugira et al JAIDS 2013)

•Commonly fluctuated over time (Heffron et al. AIDS2016 abstract)

•In prospective studies off HIV serodiscordant couples, pregnancy incidences mirror that of the general population
“We just said even if we have the virus, we will still get the baby.”

- HIV+ woman with an HIV- male partner

Ngure et al. AIDS Care 2014
Risk-reduction strategies for safer conception

- HIV prevention
  - Pre-exposure prophylaxis (PrEP)
  - Antiretroviral therapy (ART)
  - Condomless sex during peak fertility; condoms at other times
  - Treatment of genital infections
  - Vaginal self-insemination (if HIV+ woman)
  - Semen washing (if HIV+ man)
  - Medical male circumcision (if HIV+ woman and HIV- man)

- Pregnancy optimization
  - Identification of peak fertility using fertility awareness methods
  - Simple fertility screening
  - Fertility workup and fertility services

Antiretrovirals work for prevention in couples

Antiretroviral-based prevention – as antiretroviral treatment (ART) for HIV+ partners and pre-exposure prophylaxis (PrEP) for HIV- partners – demonstrated high HIV protection in trials done among HIV serodiscordant couples.

Global guidelines recommending ART and PrEP rest on the tremendous motivation and dedication of couples.
## Antiretrovirals work for prevention in couples

<table>
<thead>
<tr>
<th>HIV prevention effect</th>
<th>ART for HIV prevention</th>
<th>PrEP for HIV prevention</th>
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<tbody>
<tr>
<td></td>
<td>69% all events</td>
<td>75% vs. placebo</td>
</tr>
<tr>
<td></td>
<td>93% linked events</td>
<td>90+% adherent</td>
</tr>
<tr>
<td></td>
<td>100% w/ viral supp</td>
<td>(Partners PrEP, with objective evidence of good adherence)</td>
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<td></td>
<td>(HPTN 052, near-universal adherence)</td>
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Neither PrEP nor ART is perfect

- **Partners PrEP Study**: ART initiation delay/decline was 30% @ 12 months after reaching eligibility (CD4 < 350) (Mujugira et al, JAIDS 2014)

- **HPTN 052 delayed arm**: ~20% declined ART when offered after the trial demonstrated ART efficacy (Batani et al, CROI 2013)

- **Partners PrEP Study**: PrEP use was ~80% and was consistent – those not using PrEP one month after starting the study rarely ever used (Baeten et al. Lancet Infect Dis 2014)
Undoing the meaning of “early” ART as un-health, rather than health-preserving

Among HIV+ members of serodiscordant couples in Kenya, 40% said they would not start ART for prevention. A key theme for refusal was the message that starting ART signaled death. (Heffron et al, JAIDS 2013; Curran et al., AIDS 2013)

“Like me, if I am given ARVs I will think I am nearing the grave.”

- HIV+ woman, Kenya
Antiretrovirals work for prevention in couples

In the clinical trials of PrEP and ART for HIV prevention, access to these potent tools markedly reduced HIV risk, above and beyond the benefits of mutual disclosure, behavior change, and other risk-reduction messaging.

So, didn’t you say “elimination”??
ART and PrEP protect completely/nearly completely against HIV transmission – but, they are not always used, and as a result neither can work alone.

An integrated program of prevention options, built on ART and PrEP and bolstered by other prevention interventions, could virtually eliminate incident HIV infection in couples.
Delivering an integrated program of prevention for couples

The Partners Demonstration Project was an open-label, prospective interventional study of integrated prevention services for heterosexual HIV serodiscordant couples in Kenya and Uganda.

The overall goal was to evaluate a scalable delivery system for PrEP and ART for HIV prevention in couples

Initiated November 2012 & concluded follow-up June 2016

**Prescriptions for ART and PrEP:**
- Continuous ART for the infected partner
- Time-limited PrEP for the uninfected partner—until 6 months after ART initiation by the infected partner.
PrEP as a bridge to ART in couples

ART and PrEP together:

ART offered per Kenya/Uganda guidelines, which recommend ART for all infected partners in serodiscordant couples, regardless of CD4 count.

PrEP (daily oral FTC/TDF, Truvada®) offered to the uninfected partner until the infected partner has been on ART for 6 months, permitting time to achieve viral suppression (=PrEP as a bridge to ART)
Delivering an integrated program of prevention for couples

At the outset, both partners use medications and both partners have role in supporting each other's medication use and adherence.

PrEP has a short term role to protect the negative partner during the time before the positive partner starts ART and while the positive partner is getting used to taking ART and reducing the amount of HIV in their blood (about 6 months).

When couples attend HIV counseling together, they have the opportunity to talk with a counselor about prevention strategies and strengthen their relationship.

When it is time for PrEP use to stop, ART use by the positive partner and the support for ART use provided by the negative partner are habits and are likely to continue.
Combination prevention messages – HIV+ partner

**ART as HIV treatment.** ART use treats HIV infection and improves health; starting as soon as possible after diagnosis and continuing for life is the best strategy.

**ART as HIV prevention.** ART is also an HIV prevention strategy. ART reduces the amount of HIV in the body. Because of this, it makes someone less likely to pass their infection to other people.

**Adherence.** In order for ART to work as treatment and prevention, it must be taken daily without interruptions. It is important to plan ahead to make sure ART does not run out.

**Viral suppression.** It takes 3-6 months of ART used daily for someone to decrease the amount of HIV in their body to a level where they will not pass on their infection.

**Resistance.** If there are inconsistencies in ART use, one problem may be the development of resistance and the need to change ART medications. There are a limited number of ART medications.

**Pregnancy.** ART is safe to use for people who are planning to get a baby, pregnant and breastfeeding. It is important to use ART to prevent HIV infection from passing to the baby.

**Side effects.** All medications have side effects. Side effects from ART may affect each person differently. Most side effects will lessen after the first 1-2 months of regular use, once the body gets used to the medications.

**Condoms.** When ART is used, condoms have a role to prevent other sexually transmitted infections and pregnancy as well as being another HIV prevention method.
Combination prevention messages – HIV+ partner
**Combination prevention messages – HIV- partner**

- **PreP for HIV prevention.** PrEP prevents HIV infection in men and women.
- **PreP discontinuation.** PrEP should be used when someone has a risk of getting HIV. When this risk is no longer there, PrEP can be stopped.
- **Daily use.** PrEP must be taken every day to prevent HIV infection.
- **Adherence.** Counselors can talk about the best strategies to help people take their daily pills. They help people find ways to take their pills during difficult times such as travel, in the face of stigma, or when there are new partners.
- **HIV testing.** Individuals who are taking PrEP need to have regular HIV testing.
- **Side effects.** Side effects from PrEP affect each person differently. Most side effects will lessen after the first 1-2 months of regular use, once the body gets used to the medications.
- **Pregnancy.** PrEP is safe to use when trying to become pregnant.
- **Condoms.** When PrEP is used, condoms have a role to prevent other sexually transmitted infections and pregnancy as well as being another HIV prevention method.

Morton et al. JAIDS 2017
“Every day, every time thinking to yourself, how will it be when I go back there? When you test yourself, you know your status; you relax.”

“… otherwise there would be no hope for people whose status are not the same, maybe I would have gotten infected with the virus or we would have broken up, but now that we know and with the doctor’s advice we can continue together and plans for our life will continue as planned.”
Virtual elimination of HIV

- Given the risk score distribution of the enrolled population, the counterfactual simulations predicted 83 HIV infections would be predicted in this population, at an overall incidence of 4.9 per 100 person-years.

- However, only four incident HIV infections were observed, for an HIV incidence of 0.2 per 100 person-years.

- Predicted and expected results were compared using simulations.

PrEP and ART in couples’ lives

“I knew I would be safer, because when we came here we were told we can … she will be using those ARVs and I will be using Truvada and we will continue protecting.”

“… otherwise there would be no hope for people whose status are not the same, maybe I would have gotten infected with the virus or we would have broken up, but now that we know and with the doctor’s advice we can continue together and plans for our life will continue as planned.”

Ngure et al. AIDS Pt Care & STDs 2016
Combination prevention messages


HIV testing. Individuals who are taking PrEP need to have regular HIV testing.

PrEP discontinuation. PrEP should be used when someone has a risk of getting HIV. When this risk is no longer there, PrEP can be stopped.

Side effects. Side effects from PrEP affect each person differently. Most side effects will lessen after the first 1-2 months of regular use, once the body gets used to the medications.

Daily use. PrEP must be taken every day to prevent HIV infection.

Pregnancy. PrEP is safe to use when trying to become pregnant.

Adherence. Counselors can talk about the best strategies to help people take their daily pills. They help people find ways to take their pills during difficult times such as travel, in the face of stigma, or when there are new partners.

Condoms. When PrEP is used, condoms have a role to prevent other sexually transmitted infections and pregnancy as well as being another HIV prevention method.
Pregnancy and HIV risk

- Pregnancy increases the risk of HIV
  - Approximately 2-fold for HIV- women
  - WHO systematic review and meta-analysis found an HIV incidence in pregnancy of 4.7/100 woman-years
    - Comparable or higher than sex worker incidence rates in many settings

- HIV retesting in pregnancy is a priority intervention for at-risk women … but it is arguably insufficient as prevention

- Nevertheless, HIV prevention interventions are often not tested in women who might become or who are pregnant

Mugo et al. AIDS 2011
Weighing pregnancy research risks/benefits

- When is an intervention ready for evaluation in pregnancy? (research, policy, program)

“Pregnant women are a vulnerable group and just like other vulnerable groups, they must be protected….while we need more information for research, pregnancy is very sensitive…, so it’s a balancing act.”

Beima-Sofie et al. AIDS2016 abstract
PrEP and fertility/pregnancy safety

- PrEP safety in women prior to, during, and after pregnancy has been built across multiple studies:
  - No statistically significant differences between PrEP and placebo in terms of:
    - Pregnancy incidence (in both couples in which women used PrEP and couples in which men used PrEP)
    - Birth outcomes
    - Infant growth
  - Periconception adherence to PrEP was high, emphasizing that PrEP is an option for safer conception in women with HIV+ partners

Mugo et al. JAMA 2014
Were et al. AIDS 2014
Matthews et al. JAIDS 2013
PrEP and fertility/pregnancy safety

• In the Partners Demonstration Project, pregnancy incidence was high (~20% per year, in both couples with HIV- female partners and those with HIV+ female partners)

• Most used PrEP in pregnancy:

More data at CROI 2017 (Heffron et al. poster)

Heffron et al. AIDS2016 abstract
TFV transferred in milk in very small quantities (3.2 ng/mL or ~3% MP conc.)

In infant plasma, TFV was unquantifiable in 94% of the samples.

Based on milk conc., a breastfeeding infant would have TFV exposures <0.01% of the proposed infant therapeutic dose (6 mg/kg)
PrEP and fertility/pregnancy safety

• “Given available safety data, there does not appear to be a safety-related rationale for prohibiting PrEP during pregnancy/lactation or for discontinuing PrEP in HIV-uninfected women receiving PrEP who become pregnant and are at continuing risk of HIV acquisition.”

• Ongoing questions:
  – Can PrEP be implemented in ANC and similar settings
  – Can integrated prevention – including HIV testing for women and partners, PrEP, and ART – be deliverable in the context of pregnancy
  – Can we use novel technologies (e.g., HIV self-testing, including partner-delivered self-tests) to make PrEP and ART initiation and PrEP continuation easier?

Mofenson et al. AIDS 2016
Ngure et al. JIAS 2017
Thirumurthy et al. Lancet HIV 2016
Integrated prevention for HIV elimination in serodiscordant couples

An integrated program of prevention options for couples can virtually eliminate incident HIV infection in couples, including in those who desired and became pregnant.

Elimination?
HIV prevention for couples: opportunity for elimination

HIV risk in couples is high

Testing and disclosure are the beginning of prevention

Fertility desires drive risk

Integrated, multicomponent prevention can virtually eliminate risk