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DEPARTMENT OF OB/GYN

# Evidence on Hormonal Contraception & ART Interactions

HC-HIV Meeting
Lusaka, Zambia
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Jennifer Tang, MD, MSCR

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# Overview

- Antiretroviral Therapy (ART) drugs
- Hormonal Contraception (HC) drugs
- Introduction to Drug-Drug Interactions (DDI)
- DDI between HC & ART
- Clinical studies
- Guidelines for use of HC & ART
- Questions

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# ART Drugs

- Different classes of ART Drugs
  - **Nucleoside reverse transcriptase inhibitors (NRTIs)**
    - Zidovudine (AZT)
    - **Tenofovir (TDF)**
    - **Lamivudine (3TC)**
    - Abacavir (ABC)
    - Didanosine (DDI)
    - Emtricitabine (FTC)
    - Stavudine (D4T)

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# ART Drugs

- Different classes of ART Drugs
  - **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**
    - **Efavirenz (EFV)**
    - **Nevirapine (NVP)**
    - Etravirine (ETR)
    - Rilpivirine (RPV)

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# ART Drugs

- Different classes of ART Drugs
  - **Protease Inhibitors (PIs)**
    - **Ritonavir (RTV)**
    - Atazanavir (ATV)
    - Lopinavir (LPV)
    - Darunavir (DRV)
  - **Integrase inhibitors**
    - Raltegravir (RAL)

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# Hormonal Contraception Drugs

- Classes of Hormonal Contraception Drugs:
  - **Estrogens:**
    - Ethinyl estradiol (EE): COC, patch, ring
  - **Progestins:**
    - Levonorgestrel (LNG): COC, POP, EC, Jadelle® implant, Sino-Implant®, intrauterine contraception (Mirena®, Skyla®, Liletta®)
    - Etonorgestrel (ETG): Implanon® implant, Nuvaring®
    - Medroxyprogesterone acetate (MPA): 3-month injection
    - Norethindrone enanthate (NET-EN): 2-month injection
    - Norelgestromin (NGMN): COC, combined patch

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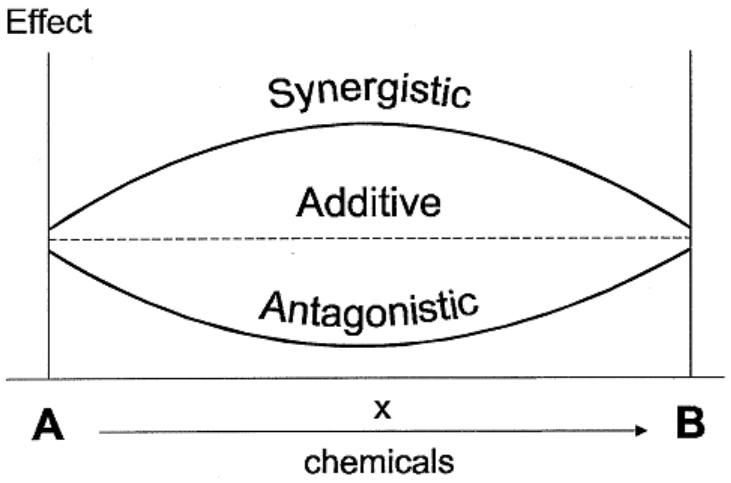
# Introduction to DDI

- What is a Drug-Drug Interaction (DDI)?
  - » Interaction between drugs that occurs when they are given at the same time.
    - Synergistic: drug *increases* levels of other drugs
      - » Could lead to overdose or increase in side effects
    - Antagonistic: drug *decreases* levels of other drugs
      - » Could lead to decreased effectiveness of drug



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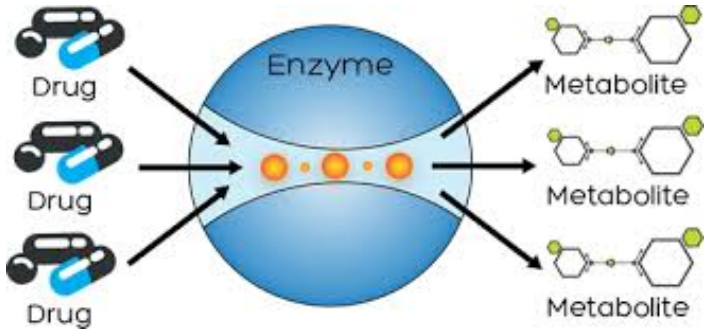
# Introduction to DDI

- Why do DDIs occur?
  - » Many reasons, but will focus on DDIs due to drug *metabolism* interactions.
  - » *Metabolism* refers to the chemical changes that occur within our cells.
    - One chemical is changed into another chemical through the action of enzymes.
    - Chemicals can be broken down or combine with other chemicals to create new chemicals or metabolites.

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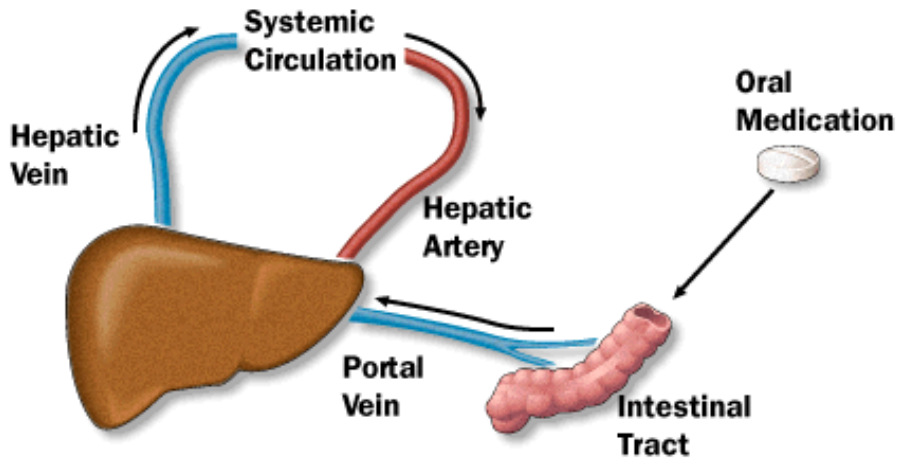
# Introduction to DDI

- Why do DDIs occur?
  - » Liver enzymes metabolize most drugs, including ART and hormonal drugs.
    - CYP3A4 liver enzymes metabolize the hormonal drugs.
  - » Some ART medications *induce or inhibit* the CYP3A4 liver enzymes.
  - » Therefore, when these ART medications and hormonal drugs are given at the same time, we have DDIs.

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# DDI between HC & ART

- Which ART medications induce or inhibit the liver enzymes?
  - » NRTIs have not been found to interact with hormonal contraceptives.
  - » Efavirenz and Nevirapine (NNRTIs): *induce* the CYP3A4 enzymes
    - Causes the enzyme to break down the hormonal drugs more rapidly.
    - Could lead to a *decrease* in hormone drug levels.

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# DDI between HC & ART

- Which ART medications induce or inhibit the liver enzymes?
  - Ritonavir (PI): *inhibits* the CYP3A4 enzymes
    - Causes the enzymes to break down the hormonal drugs more slowly.
    - Can lead to an *increase* in hormone drug levels.
  - Integrase Inhibitors have not been found to interact with hormonal contraceptives.

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# DDI between HC & ART

- What do pharmacokinetic studies show?
  - Efavirenz (EFV):
    - 2 studies found that EFV had *no effect* on MPA progestin levels.
      - Both evaluated DMPA injection. (Cohn, Nanda)
    - 5 studies found that EFV *decreased* progestin levels in other contraceptives.
      - 2 in COC users. (Sevinsky, Landolt)
        - No effect on EE.
      - 1 in EC users. (Carten)
      - 1 in Jadelle users. (Scarsi)
      - 1 in Implanon users. (Vieira)

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# DDI between HC & ART

- What do pharmacokinetic studies show?
  - Nevirapine (NVP):
    - 3 PK studies found that NVP did not have an effect on COC users. (Stuart, Midvan, Landolt)
    - 1 clinical study found that NVP did not increase ovulation or pregnancy rates among COC users. (Nanda)

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# DDI between HC & ART

- What do pharmacokinetic studies show?
  - Ritonavir:
    - 2 studies found it *decreased* progestin levels in combined COC users. (Sekar, Kasserra)
    - 1 study found it *increased* progestin levels in POP users. (Atrio)
    - 1 study found it *increased* progestin levels in combined patch users. (Vogler)
    - 1 study found it *increased* progestin levels in Implanon users. (Vieira)
    - 2 studies found *no effect* on progestin levels in DMPA injection users. (Cohn, Nanda)

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# Clinical Studies

- Focus on implant since 1 SSA country has restricted its use among women using EFV.
- 5 clinical studies:
  - Kreitchmann 2012 (Brazil, Implanon)
  - Perry 2014 (Swaziland, Jadelle)
  - Scarsi 2015 (Uganda, Jadelle)
  - Patel 2015 (Kenya, Implanon & Jadelle)
  - Pyra 2015 (7 SSA countries, implant)

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# Clinical Studies

- Kreitchmann prospective cohort study (*IJGO* 2012):
  - 79 HIV+ Brazilian women had Implanon inserted b/t March 2004 – Sep 2007.
  - Followed-up every 6 months over 3 years.
  - 56 (71%) on ART
    - 25 (32%) on NNRTI
    - 31 (39%) on PI
  - 5 women had removal prior to 3 years of use.
  - 2 women died prior to 3 years of use.
  - No pregnancies occurred.

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# Clinical Studies

- Kreitchmann prospective cohort study (*IJGO* 2012):
  - Limitations:
    - Small sample size
    - Did not specify specific ART regimen
    - No comparison group

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# Clinical Studies

- Perry retrospective cohort study (*AIDS* 2014):
  - 570 HIV+ women in Swaziland had Jadelle placed between September 2010-May 2012.
    - 347 (61%) on ART
      - 208 (36%) on NVP-based regimens
      - 121 (21%) on EFV-based regimens
      - 18 (3%) on LPV/r-based regimens
    - 16 pregnancies occurred with 16.4-month mean time between Jadelle insertion and pregnancy. (SD 5.5 months)
      - 15 among EFV users
      - 1 among non-ART user

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# Clinical Studies

- Perry retrospective cohort study (*AIDS* 2014):
  - » EFV use at time of pregnancy associated with pregnancy ($p<0.001$).
  - » TB treatment during study trended towards association, but not enough power:
    - 31/554 (5.6%) in non-pregnant women vs. 3/16 (18.8%) in pregnant women ($p=0.064$).
      - » 2 pregnancies in women on EFV
      - » 1 pregnancy in woman not on ART
    - Mean age, mean CD4 count, reported condom use, and provider placing implant (4 providers) not different between 2 groups.

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# Clinical Studies

- Limitations of Perry study
  - » Selection bias
    - Women who were on EFV-based regimens may have been different than others.
  - » Retrospective, so unable to collect data on other confounders:
    - Sexual frequency, BMI, breastfeeding, ART adherence, length of time on ART, etc.
  - » Different follow-up times after Jadelle insertion without systematic evaluation for pregnancy
    - No pregnancy rate calculation
  - » Small sample size
  - » No comparison to other contraceptives

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# Clinical Studies

- Recommendation from Perry study:
  - "The Jadelle implant is widely-used in Sub-Saharan Africa. New 2013 WHO guidelines suggest moving toward TDF/3TC/EFV as first-line treatment for all women of childbearing age."
  - "As countries incorporate these recommendations, **further investigation of the interactions on all family planning choices, in both larger cohorts and with different family planning options, is essential to making informed policy decisions**."

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# Clinical Studies

- Scarsi prospective cohort study (CROI 2015):
  - 40 Ugandan women with Jadelle inserted at enrollment:
    - 20 not yet on ART (Control group)
      - 3 excluded from analysis:
        - 1 for pregnancy in Week 1
        - 1 for ART initiation at Month 3
        - 1 for removal of implant at Week 1
    - 20 on EFV-based ART for at least 30 days
      - Median (range) of EFV use: 10 (5-66) months

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# Clinical Studies

- Scarsi prospective cohort study (CROI 2015):
  - 40 Ugandan women with Jadelle inserted at enrollment
    - Could not be using drug with potential interaction with LNG or EFV.
    - LNG sampling done day 0 and at weeks 1, 4, 12, 24, 36, and 48 weeks post-insertion.

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# Clinical Studies

- Scarsi prospective cohort study (CROI 2015):
  - At enrollment, women on EFV had lower body weight (59 vs. 73 kg, $p<0.01$) and lower CD4 (568 vs. 758, no p-value).
  - Over 48 weeks of combined LNG-EFV use:
    - LNG concentrations in EFV group were 45-57% lower than in Control group.
    - 3 pregnancies occurred in EFV group (at ~Weeks 38, 41, and 46) vs. 0 in Control group.

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# Clinical Studies

- Scarsi prospective cohort study (CROI 2015):
  - At Week 36, only 1 woman who become pregnant had LNG concentrations <180 pg/mL (122 vs. 299 and 303), previously thought to be the LNG efficacy threshold.

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# Clinical Studies

- Limitations of Scarsi study:
  - » Small sample size:
    - Powered only to find a difference in LNG concentrations, not pregnancy rates.
    - Couldn't adjust for confounding factors.
  - » Selection bias
    - Women on EFV may have been different than others.
  - » No comparison to other contraceptives.

- Recommendation:
  - » Further investigation is urgently needed.

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# Clinical Studies

- Summary so far:
  - Drug interactions between Jadelle and EFV lead to decreased LNG concentrations.
  - Decreased LNG concentrations *may* lead to decreased efficacy of Jadelle, although 2 of the pregnant women in Scarsi study did not have the lowest LNG concentrations.
  - Not all women on Jadelle & EFV become pregnant.
    - Need to determine which women are at-risk and when they become at-risk.
  - Is Jadelle still better than alternative contraceptives, such as pills or DMPA, which typically have a much higher pregnancy rate?

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# Clinical Studies

- Jadelle vs other contraceptives:
  - 1st year typical-use pregnancy rates:
    - Jadelle: 0.1%
    - Depo: 6%
    - Pills: 9%
- Why does Jadelle have much lower rates:
  - Less visits required -> less risk for stock-outs and other problems with contraceptive access:
    - 1st year continuation rates:
      - Jadelle: 87-91%
      - Depo: 31-78%
      - Pills: 67%-84%

Sivin 2002; Trussell 2011; Grimes 2009; Haddad 2013; Nanda 2011; Tolley 2005

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# Clinical Studies

- Patel retrospective cohort (*Lancet* 2015):
  - 24,560 Kenyan HIV+ women enrolled in longitudinal cohort from Jan 2011-Dec 2013.
    - Followed every 1-6 months.
      - Implant: 3,047 W-Y of follow-up
  - Compared pregnancy rates among women on different contraceptive/ART combinations.
    - Pregnancy determined by self-report or presenting while gravid.

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# Clinical Studies

- Patel retrospective cohort (*Lancet* 2015):
  - Adjusted Poisson models with robust SEs to estimate incident pregnancy rates per 100 woman-years (W-Y).
    - Age
    - Educational attainment
    - Marital status
    - # living children
    - HIV disclosure to partner
    - Condom use
    - Health: BMI, WHO stage, CD4 count
    - Self-reported ART adherence
    - TB drug use

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# Clinical Studies

- Patel retrospective cohort (*Lancet* 2015):
  - Adjusted Pregnancy Rates:
    - Implant users:
      - 1.1/100 W-Y for NVP-users (95% CI 0.7-1.5)
      - **3.3/100 W-Y for EFV-users (95% CI 1.8-4.8)**
        - Adjusted RR: 3.0 (95% CI 1.3-4.6)
      - 0.95/100 W-Y for LPV/r users (95% CI 0-2.3)
        - Adjusted RR: 0.9 (95% CI 0-2.1)
    - Depo users:
      - 4.5/100 W-Y for NVP-users (95% CI 3.7-5.2)
      - **5.4/100 W-Y for EFV-users (95% CI 4.0-6.8)**
        - Adjusted RR: 1.2 (95% CI 0.9-1.5)
      - 4.5/100 W-Y for LPV/r users (95% CI 2.5-6.2)
        - Adjusted RR: 1.0 (95% CI 0.6-1.5)

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# Clinical Studies

- Patel retrospective cohort (*Lancet* 2015):
  - Adjusted Pregnancy Rates:
    - Implant users:
      - 1.1/100 W-Y for NVP-users (95% CI 0.7-1.5)
      - **3.3/100 W-Y for EFV-users (95% CI 1.8-4.8)**
        - Adjusted RR: 3.0 (95% CI 1.3-4.6)
      - 0.95/100 W-Y for LPV/r users (95% CI 0-2.3)
        - Adjusted RR: 0.9 (95% CI 0-2.1)
    - Pill users:
      - 5.8/100 W-Y for NVP-users (95% CI 4.0-7.6)
      - **9.3/100 W-Y for EFV-users (95% CI 4.6-14.0)**
        - Worse than those on less effective/no FP.
        - Adjusted RR: 1.6 (95% CI 0.7-2.5)
      - 7.6/100 W-Y for LPV/r users (95% CI 0.2-14.9)
        - Adjusted RR: 1.3 (95% CI 0-2.6)

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# Clinical Studies

- Patel retrospective cohort (*Lancet* 2015):
  - » Limitations:
    - Retrospective: limited in accounting of FP use to electronic records available from clinic visits.
    - Social desirability bias: women may have falsely reported FP use.
    - Unable to determine FP initiation dates and that pregnancies occurred within efficacy periods of each method.
    - Unable to account for important covariates: sexual activity, actual ART adherence, length of time on ART.

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# Clinical Studies

- Patel retrospective cohort (Lancet 2015):
  - Conclusions:
    - "In women using either ETG or LNG implants, adjusted pregnancy rates were 3-times higher with EFV-based ART than with NVP-based ART."
    - **"However,** even in women who use EFV-based ART, implant use was associated with lower pregnancy rates than were alternative contraceptive methods, except intrauterine devices and permanent methods."

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# Clinical Studies

- Patel retrospective cohort (Lancet 2015):
  - Conclusions:
    - "HIV programs and providers need to actively engage women in conversations about the potential risks and benefits of each contraceptive method because **greater choice exists with options for contraceptives** than with choice of ART regimens currently available in resource-limited settings."
    - "Prospective studies and pharmacokinetic **studies which account for contraceptive and ART adherence and pregnancy ascertainment better** than does the present study design are **urgently needed** to further explore the interactions between hormonal contraceptive and ART."

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# Clinical Studies

- Pyra prospective cohort (*AIDS* 2015):
  - » 5,153 HIV+ women followed in 3 HIV prevention studies:
    - Partners PrEP
    - Partners in Prevention HSV/HIV Transmission
    - Couples Observation
  - » Enrolled from 2004-2013 in 7 SSA countries:
    - Botswana
    - Kenya
    - Rwanda
    - South Africa
    - Tanzania
    - Uganda
    - Zambia

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# Clinical Studies

- Pyra prospective cohort (*AIDS* 2015):
  - Compared pregnancy rates between users of pills, DMPA, implants, and no FP.
    - Stratified the rates by ART use:
      - None
      - Any ART
      - NVP
      - EFV
        - Few women on implant & EFV: 16.7 W-Y

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# Clinical Studies

- Pyra prospective cohort (*AIDS* 2015):

Table 1: Adjusted Hazard Ratios (aHR) for ART users

| FP method | # preg | Woman-Years | Preg rate (per 100 W-Y) | aHR (95% CI), p-value* |
|---|---|---|---|---|
| None | 111 | 843.5 | 13.2 | Referent |
| Implant | 1 | 94.1 | 1.1 | 0.06 (0.01-0.45), p=0.005 |
| Injectable | 11 | 332.8 | 3.3 | 0.18 (0.10-0.35), <0.001 |
| Pills | 5 | 81.2 | 6.2 | 0.37 (0.15-0.91), p=0.03 |

*p-value versus no contraception and ART use; adjusted for site, study, age, unsafe sex, CD4 count.

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# Clinical Studies

- Pyra prospective cohort (*AIDS* 2015):

Table 2: Adjusted Hazard Ratios (aHR) for EFV users

| FP method | # preg | Woman-Years | Preg rate (per 100 W-Y) | aHR (95% CI), p-value* |
|---|---|---|---|---|
| None | 16 | 127.5 | 12.6 | Referent |
| Implant | 1 | 16.7 | 6.0 | 0.43 (0.07-2.50), p=0.34 |
| Injectable | 2 | 52.2 | 3.8 | 0.3 (0.07-1.22), p=0.09 |
| Pills | 1 | 7.7 | 12.9 | 0.9 (0.86-6.76), p=0.88 |

*p-value versus no contraception and ART use; adjusted for site, study, age, unsafe sex, CD4 count.

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# Clinical Studies

- Pyra prospective cohort (*AIDS* 2015):
  - Conclusions:
    - "**All hormonal methods had point estimates suggesting lesser effectiveness among EFV users**, although the sample size for analyses limited to EFV users was small."
    - "**Implants**, which have the lowest adherence requirements out of these 3 methods, **showed the greatest reduction on pregnancy rates, including for women concurrently using ART**."

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# Clinical Studies

- Pyra prospective cohort (*AIDS* 2015):
  - Conclusions:
    - "As national policies evaluate the potential pharmacokinetic interactions between ART and hormonal contraception, **prospective studies such as this, which comparatively evaluate the real-world effectiveness of contraceptive methods, are essential."**

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# Summary of Evidence

| Contraceptive | EFV/NVP (NNRTI) | Protease Inhibitor |
|---|---|---|
| **Pills** | **Some Concern** | **Some Concern** |
| Progestin Only Pills (POPs) | No Data | No Current Concern |
| NET-EN, DMPA (2 month or 3 month injection | No Current Concern | No Current Concern |
| **Implants (Jadelle, Implanon)** | **Some Concern** | **Some Concern** |
| **Emergency Contraceptive Pills (ECPs)** | **Some Concern** | **No Data** |

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# Guidelines for use of HC & ART

- How has this translated into recommendations for use of HC with ART?
  - 5th Edition WHO Medical Eligibility Criteria (MEC) for Contraceptive Use, 2015

| Category | Explanation |
|---|---|
| **1** | **A condition for which there is no restriction for the use of the contraceptive method.** |
| **2** | **A condition where the advantages of using the method generally outweigh the theoretical or proven risks.** |
| 3 | A condition where the theoretical or proven risks usually outweigh the advantages of using the method. |
| 4 | A condition which represents an unacceptable health risk if the contraceptive method is used. |

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# Guidelines for use of HC & ART

- WHO Medical Eligibility Criteria (MEC) categories for contraceptive eligibility:
  - In situations where resources for clinical judgement are limited, the 4-category classification framework can be simplified into 2 categories.
  - Thus, a woman with a Category 1 or 2 condition can use the contraceptive method, whereas if the woman has a Category 3 or 4 condition, she should not use the method.

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# Guidelines for use of HC & ART

## WHO MEC for Contraceptive Use, 5th edition, 2015

| ART | POP | DMPA/ NET-EN | LNG/ ETG implant |
|---|---|---|---|
| **NRTIs** | 1 | 1 | 1 |
| **Integrase Inhibitors** | | | |
| **Raltegravir** | 1 | 1 | 1 |
| **NNRTIs** | | | |
| **Etravirine** | 1 | 1 | 1 |
| **Rilpivirine** | 1 | 1 | 1 |

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# Guidelines for use of HC & ART

## WHO MEC for Contraceptive Use, 5th edition, 2015

| ART | POP | DMPA/ NET-EN | LNG/ ETG implant | Clarifications/ Evidence |
|---|---|---|---|---|
| **EFV** | 2 | DMPA=1<br>NET-EN=2 | 2 | Clarification: ART have the potential to either decrease or increase the levels of steroid hormones in women using HC. PK data suggest potential drug interactions between some ART and some hormonal contraceptives. These interactions may reduce the effectiveness of the hormonal contraceptive. |
| **NVP** | 2 | DMPA=1<br>NET-EN=2 | 2 | |

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# Guidelines for use of HC & ART

## WHO MEC for Contraceptive Use, 5th edition, 2015

| ART | POP | DMPA/ NET-EN | LNG/ ETG implant | Clarifications/ Evidence |
|---|---|---|---|---|
| **ATV/r or LPV/r or DRV/r** | 2 | DMPA=1<br>NET-EN=2 | 2 | Clarification: ART have the potential to either decrease or increase the levels of steroid hormones in women using HC. PK data suggest potential drug interactions between some ART and some hormonal contraceptives. These interactions may reduce the effectiveness of the hormonal contraceptive. |
| **RTV** | 2 | DMPA=1<br>NET-EN=2 | 2 | |

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# Guidelines for use of HC & ART

- WHO Technical Brief, July 2014:
  - *Hormonal contraceptive methods for women at high risk of HIV and living with HIV*
    - 3.4. Recommendations for women living with HIV using ART
      - Women using ART containing either efavirenz or nevirapine can generally use COC, patches, rings, combined injectables, POPs, NET-EN, and implants (MEC Category 2).
      - Women using efavirenz or nevirapine can use Depo without restriction (MEC Category 1).

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# Guidelines for use of HC & ART

- WHO Technical Brief, July 2014:
  - Remarks:
    - **Consistent and correct use of condoms**, male of female, is critical for prevention of HIV transmission to non-infected sexual partners.
    - **Voluntary** use of contraception by women living with HIV who wish to prevent pregnancy is critical for upholding their reproductive rights and continues to be an important strategy for reducing vertical HIV transmission.
    - Women living with HIV and using ARVs should **discuss the potential impact of certain ARVs on contraceptive efficacy** with their health-care provider.

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# Guidelines for use of HC & ART

- WHO Technical Brief, July 2014:
  - » Executive Summary
    - **WHO strongly supports the need for further research to identify definitive answers** to these issues, with particular emphasis on potential associations between use of progestogen-only injectables and HIV acquisition, as well as **potential interactions between some hormonal contraceptives and some ARVs**.

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# Guidelines for use of HC & ART

- USAID Technical Brief, October 2014:
  - *Drug interactions between hormonal contraceptive methods and anti-retroviral medications used to treat HIV*
    - Joint brief produced in collaboration between USAID, PEPFAR, the U.S. Department of Health and Human Services, and the CDC, with technical input from FHI 360.
    - Who should read this brief?
      - **HIV and family planning implementing partners, practitioners, researchers, and professional societies.**

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# Guidelines for use of HC & ART

- USAID Technical Brief, October 2014:
  - » Programmatic Implications:
    - The contraceptive efficacy of the LNG and ETG implants may potentially be reduced among HIV-infected women on EFV-based antiretroviral regimens, **though more definitive data are needed.**
    - Even if drug interactions lead to slightly decreased efficacy for implants, **overall efficacy may still be reasonably high compared to other contraceptive choices; more studies are needed.**

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# Guidelines for use of HC & ART

- USAID Technical Brief, October 2014:
  - Programmatic Implications:
    - HIV-infected women using LNG implants or ETG implants and EFV-based ART should be **informed about the possibility of decreased contraceptive efficacy, counseled on dual contraceptive use** including correct and consistent use of male of female condoms (to provide back-up pregnancy protection in case of implant failure, in addition to reducing the risk of onward HIV transmission).

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# Thank you

- Questions


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