

HIV in Women

Planning pregnancy



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Pregnancy-related issues in HIV

- Impact of HIV on fertility
- Impact of pregnancy on HIV
- MTCT
- Diagnosis in the child
- Obstetric concerns

Case Study Mrs BK

- 32-year-old woman
- Lived in Nigeria until age of 10, then the UK

Diagnosed with HIV (clade A) in 2005

- At diagnosis
 - CD4: 210/mm³
 - viral load: 63,000 copies/ml
- Immediately started on efavirenz, tenofovir and emtricitabine as Atripla

Background

- Non-smoker
- Does not drink alcohol or take recreational drugs
- Immune to hepatitis B after vaccination
- Previous LSIL on PAP
 - colposcopy normal, no therapy
- Partner HIV negative, recently married
- Condoms for intercourse

LSIL = low grade squamous intraepithelial lesion

Current health status

- Generally well
- Struggles with fatigue and occasional sleeplessness
- Some nausea with medications - so infrequently misses doses
- CD4 470 (28%), and viral load < 50 copies/ml
- Considerable weight gain since diagnosis
 - increased from 60 to 107 kg, mostly centripetal

Current Health status

January 2012

CD4 468 (28%), viral load < 50 copies/ml

Has missed her period

Pregnancy confirmed

Routine reproductive counselling for women with HIV is important

- In a survey of 700 women with HIV, 22% became pregnant after HIV diagnosis, but
 - 58% of these never discussed pregnancy or treatment options before pregnancy
 - 42% had limited / no knowledge of ART options during early pregnancy
- Among women considering pregnancy, or pregnant at the time of HIV diagnosis
 - 48% were never asked by a HCP if they had or were considering having children

Preconception counseling

- Should begin at the first visit for any HIV-infected woman of child-bearing age
 - Avoid undesired pregnancy (family planning)
 - Avoid potential teratogens (e.g. ribavirin, tobacco, alcohol, drugs)
 - Maximize physical and mental health before pregnancy
 - Discuss reproduction options that are safe to partner
 - Perform pelvic exam, pap smear, and sexually transmitted disease screening; treat abnormalities
- Encourage sexual partners to receive HIV testing, counseling, and care

General principles for pregnancy planning

- Take folic acid: 1–5 mg a day for 1–3 months before and during 1st trimester of pregnancy
- No smoking or drinking
- Maintain a balanced diet
- Terminate the use of recreational drugs



What would you recommend for her ARV?

1. Continue EFV/FTC/TDF
2. Switch therapy as on efavirenz
3. Continue efavirenz, switch backbone to AZT/3TC or ABC/3TC
4. Switch efavirenz to LPV or ATZ/r
5. Switch to a PI/r and AZT/3TC
6. Switch to RPV,DTG or Stribild

FDA classification: Antiretroviral toxicity

FDA categories

A: Controlled studies show no risk

B: No evidence of risk in humans, animal studies do not show toxicity

C: Risk cannot be ruled out- animal studies show toxicity or not done

D: Positive evidence of risk in humans

X: Contraindicated

Antiretroviral drug	FDA pregnancy classification
Atazanavir	B
Rilpivirine	B
Saquinavir	B
Dolutegravir	B
Tenofovir	B
Elvitegravir	B
Darunavir/r	C
Fosamprenavir	C
Lopinavir/r	C
Raltegravir	C
Abacavir	C
Lamivudine	C
Zidovudine	C
Efavirenz	D

ARVs used during pregnancy should be selected only if potential benefit justifies the potential risk.

Public Health Service Task Force Perinatal GL 2009. Available at <http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf>

Accessed; Sept 2012

First Trimester Exposure

Regimen	Defects/Live Births	Prevalence (95% CI)
Lamivudine	140/4485	3.1% (2.6%, 3.7%)
Zidovudine	132/4069	3.2% (2.7%, 3.8%)
Ritonavir	60/2542	2.4% (1.8%, 3.0%)
Tenofovir	53/2330	2.2% (1.7%, 3.0%)
Nelfinavir	47/1214	3.9% (2.8%, 5.1%)
Nevirapine	31/1083	2.9% (1.9%, 4.0%)
Lopinavir	29/1218	2.4% (1.6%, 3.4%)
Stavudine	21/810	2.6% (1.6%, 3.9%)
Abacavir	28/957	2.9% (1.9%, 4.2%)
Emtricitabine	41/1721	2.4% (1.7%, 3.2%)
Efavirenz	19/825	2.3% (1.4%, 3.6%)
Atazanavir sulfate	22/993	2.2% (1.4%, 3.3%)
Didanosine	20/423	4.7% (2.9%, 7.2%)
Indinavir	7/289	2.4% (1.0%, 4.9%)
Darunavir	8/293	2.7% (1.2%, 5.3%)

Antiretroviral treatment

- Tenofovir plus emtricitabine, abacavir plus lamivudine or zidovudine plus lamivudine are acceptable nucleoside backbones
- The third agent in HAART should be efavirenz or nevirapine (if the CD4 count is <250 cells/ μ L) or a boosted PI

TDF in Pregnancy

- Theoretical safety concerns: bone mineralization and renal function
- Animal studies: reversible bone abnormalities in some; dose, exposure, age, and species specific
- Case series of 76 women: well tolerated.
- In 20 TDF-exposed infants & 20 controls no differences in renal function, including cystatin C levels, through 2 years of age
- Retrospective review of 16 pregnancy outcomes in 15 heavily ARV experienced women: normal growth and development in TDF-exposed infants

Efavirenz Teratogenicity

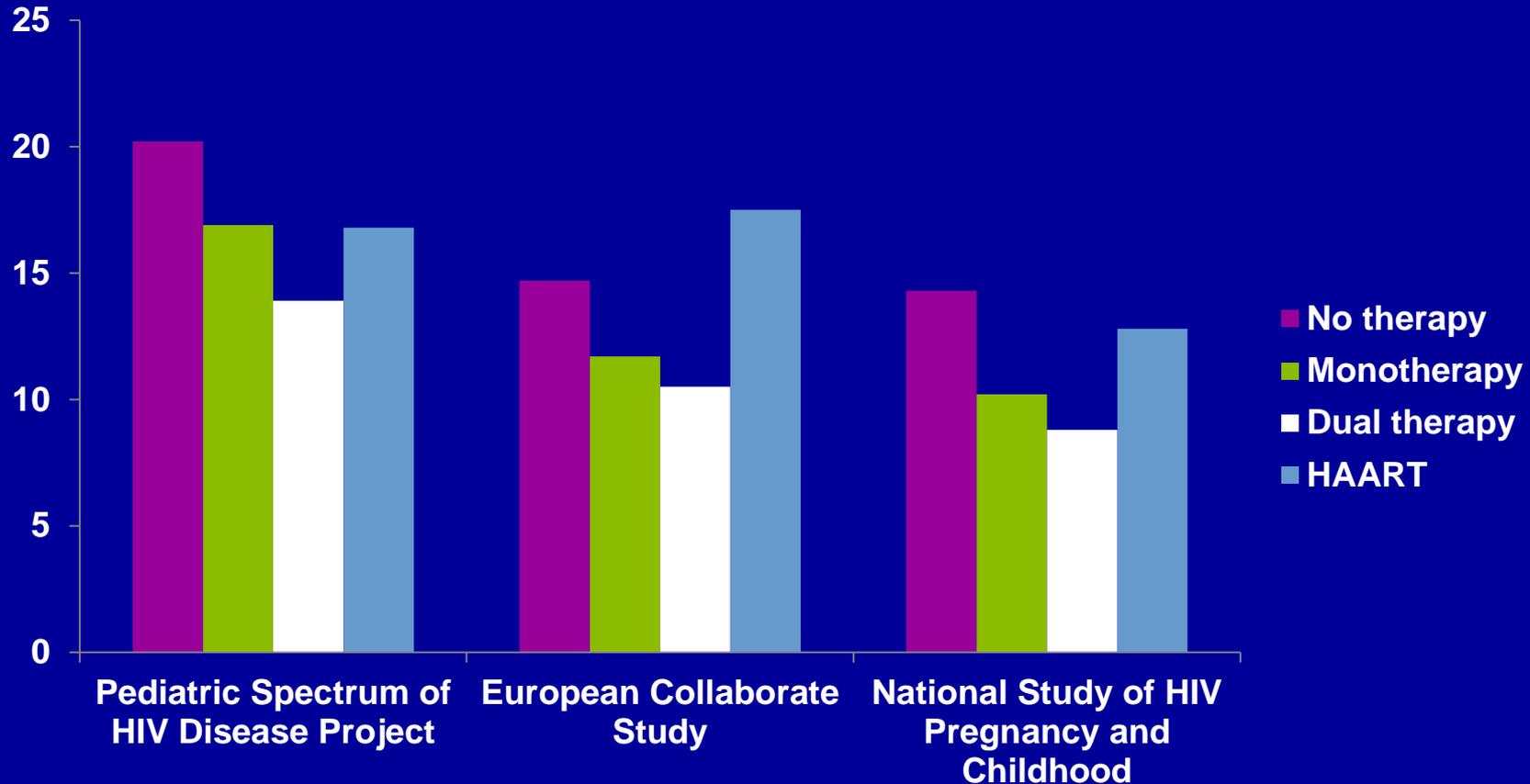
- Efavirenz teratogenicity
 - Teratogenic effects in cynomolgus monkeys
- Conflicting results in humans
 - Case reports on meningomyelocele in humans
 - Six birth defects in 10 women
 - Birth defects higher in EFV exposed vs unexposed children (15.6% vs 5%)
 - Birth defects 2%; neural tube defect 0.07%

Nightingale SL. JAMA 1998; Fundaro C AIDS 2002; Saitoh A J Perinatol 2005 Khuong-Jossess MA EACS 2003; Brogly S, Pediatr Infect Dis 2010; Ford N, AIDS 2011-meta-analysis

EFV and Pregnancy

- Pregnancy recognition often occurs after the critical period of organogenesis (3–8 weeks post-conception)
- Development and closure of the neural tube usually complete by 28 days post-conception
- Changes to EFV-based regimens after four weeks post-conception will not reduce the risk of neural tube defects and after eight weeks will have minimal effect on risk for other structural malformations.

Protease Inhibitors: Preterm delivery rates by type of antiretroviral therapy



Use of ARV in pregnancy

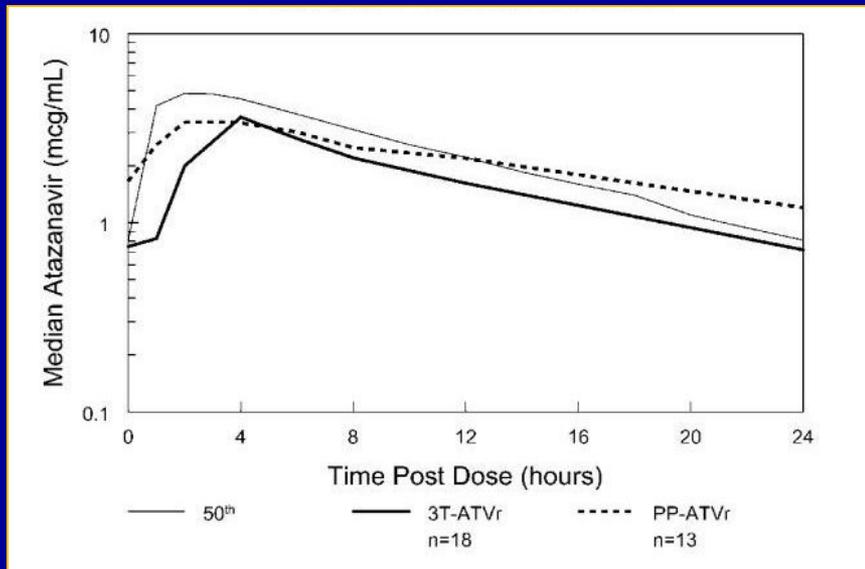
- For many of the PI, decreased concentration in the 3rd trimester
- Monitor Viral load carefully
- TDM only needed if viral load doesn't suppress
- ?increase doses
- Studies have not shown impact on transmission but too small

Antiretroviral treatment

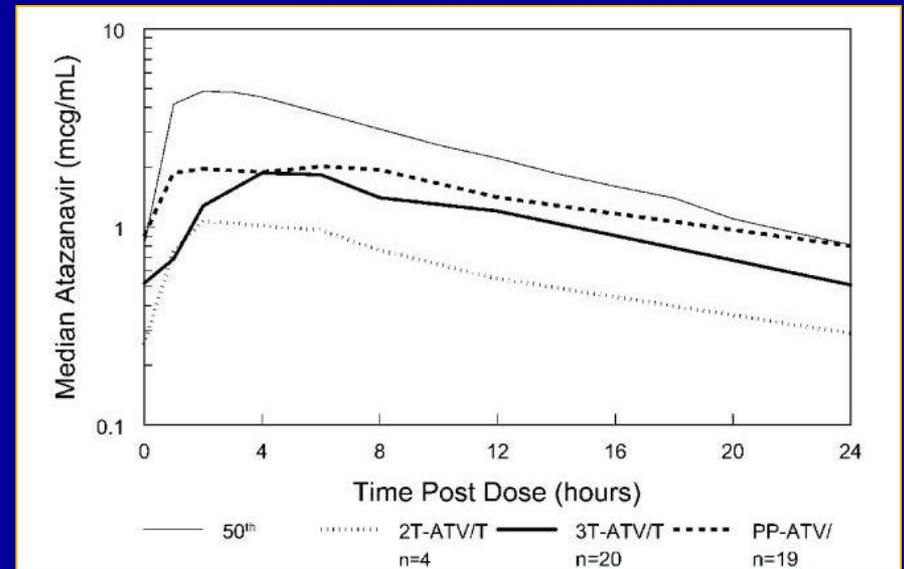
- Darunavir (which should be dosed twice daily) is the only adult-dose ARV that should have a dose alteration during pregnancy
- Consider third trimester TDM, particularly if combining tenofovir and atazanavir or if using a non-standard dose of ARV or darunavir

Atazanavir pharmacokinetics with and without tenofovir during pregnancy

Atazanavir without tenofovir



Atazanavir with tenofovir

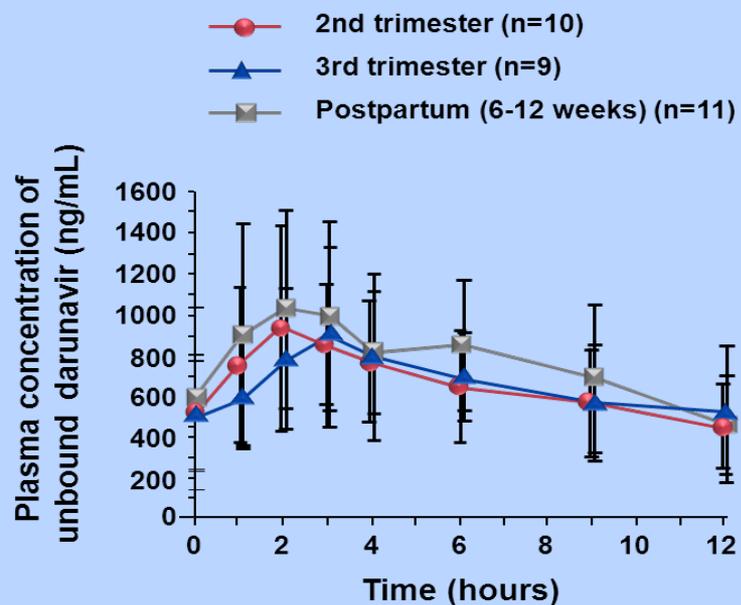
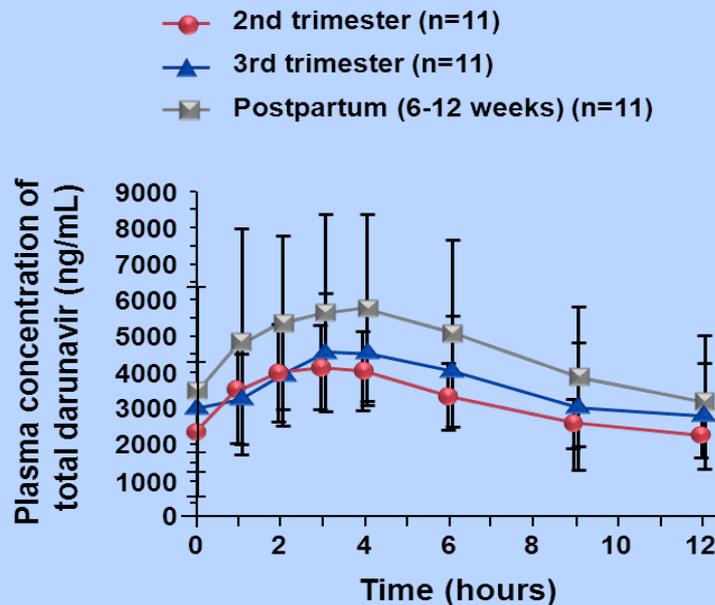


Safety of ATZ/r in pregnancy

- N=41 (n=20, 300/100mg; n=21 400/100mg)
- Grade 3–4 bilirubin in mother: 6/20; 13/21
- All infants had normal bilirubin at birth through day 14
- Then seven developed grade 3–4 bilirubin consistent with physiologic changes in normals
- Maternal bilirubin, cord ATZ levels poorly predictive of infant bilirubin

DRV PK parameters after administration of DRV/rtv 600/100mg twice daily as part of an ARV regimen during pregnancy and postpartum

- Phase IIIb, multicenter, single-arm, open-label trial
- 16 HIV-1–infected pregnant women (18–26 weeks of gestation) received DRV/r (600/100mg) plus an optimized background regimen
- Unbound concentrations of DRV remained relatively unchanged during pregnancy relative to postpartum suggesting no a priori dose adjustment is needed in DRV/r (when dosed twice daily) in pregnant women



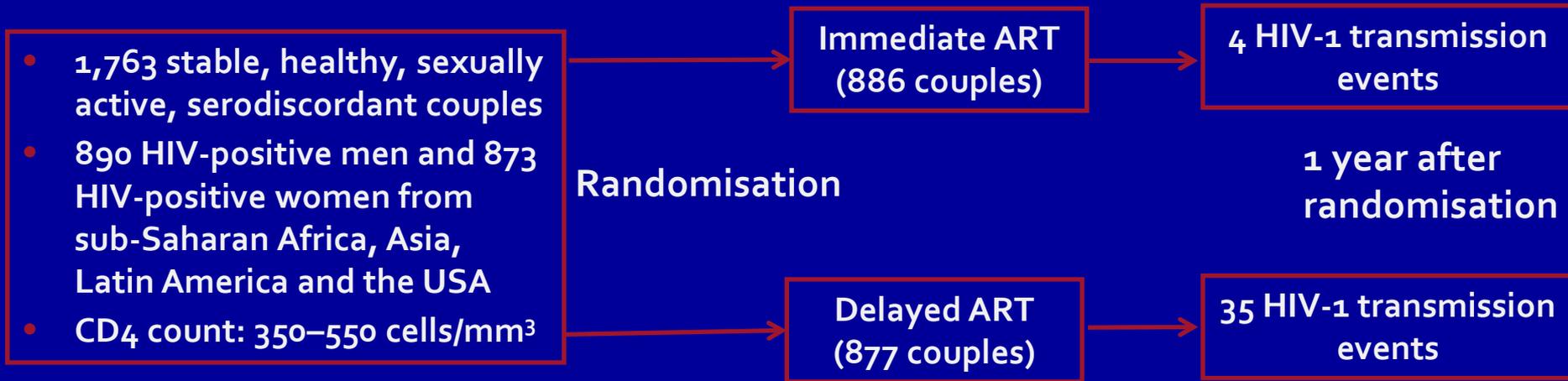
How would you have advised her on becoming pregnant if she had discussed this prior to getting pregnant?

1. Natural conception- her viral load is $< 50/\text{ml}$
2. Artificial insemination with husband sperm- “turkey baster”
3. Natural conception- provide PreP to her husband
4. Something else

Conception options for HIV concordant and discordant couples

HIV– woman and HIV+ man	<ul style="list-style-type: none">• IUI following sperm washing• Timed natural conception (only at ovulation, only with effective viral suppression)• Natural conception (only with effective viral suppression)• IVF or ICSI following sperm washing• Insemination of donor sperm at ovulation• PrEP with timed natural conception (only at ovulation, only with effective viral suppression)
HIV+ woman and HIV– man	<ul style="list-style-type: none">• Home artificial insemination with partner's sperm during ovulation• Timed natural conception (only at ovulation, only with effective viral suppression)• Natural conception (only with effective viral suppression)• Assisted reproduction in case of fertility disorders• PrEP with timed natural conception (only at ovulation, only with effective viral suppression)
HIV+ woman and HIV+ man	<ul style="list-style-type: none">• Timed natural conception (only at ovulation, only with effective viral suppression)• Natural conception (only with effective viral suppression)• IUI following sperm washing• Insemination of donor sperm at ovulation• Assisted reproduction in case of fertility disorders

Early cART prevents HIV transmission to sexual partners: HPTN052 study



- At 1 year after randomisation, 90% had suppression in the delayed arm vs 93% in the immediate arm
- 28/39 transmission events were linked
 - One in the ART immediate arm and 27 in the cART delayed arm (P<0.001)
- 96% reduction in HIV transmission to the uninfected partner when comparing immediate to delayed treatment

PARTNER Study:

HIV transmission risk through condomless sex if the HIV positive partner is on suppressive ART

- **Aim:**

- To evaluate the risk of within-couple HIV transmission (HT and MSM) during periods where condoms are not used consistently & the HIV+ partner is on suppressive ART

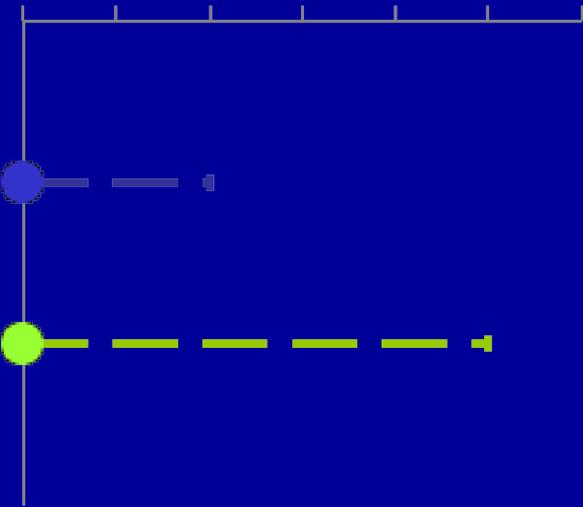
HIV transmission rate by sexual behaviour reported by the negative partner

Rate of within couple transmission (per 100 CYFU)

0 0.2 0.4 0.6 0.8 1 1.2

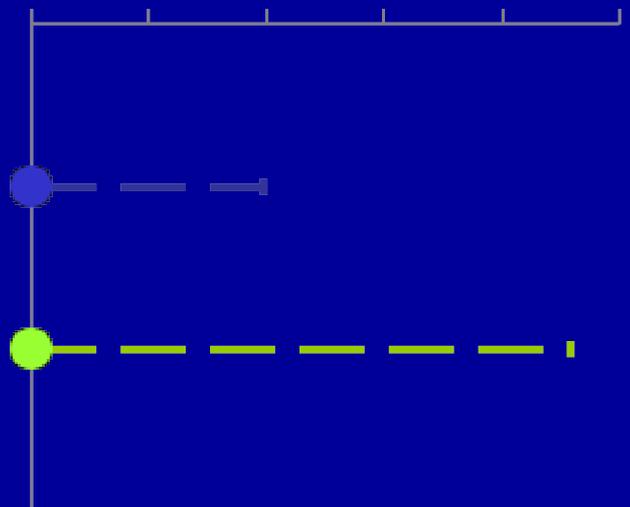
Any sex
(CYFU=894)

Anal sex
(CYFU=374)



10 year risk (%) of within couple transmission

0 2 4 6 8 10



● estimated rate/risk

--- 95% confidence interval

Case study: RF

- Diagnosed HIV+ve 2012
- CD4 905
- VL 65,000
- HepB/HepC –ve
- No resistance

Case study: RF

- CD4 remained stable
- VL 2013 180,000
- Pt's partner HIV +ve
- Pt keen to avoid starting antiretroviral therapy

Case study RF

- RF wants advice as she is now keen to get pregnant
- Has a sexual health screen and has an up to date negative PAP screen
- Should she start ARV's now?

Residual Transmission in France, 1997-2007

- Case control study in France: 19 cases (transmitters despite antenatal VL on ART <500); 60 controls (non-transmitters with same)
- Cases less likely to be on ART at conception (16% vs 45%)
- Viral load <500 copies/mL cases vs. controls:
 - 14 weeks: 0% vs. 38.1%
 - 28 weeks: 7.7% vs. 62.1%
 - 32 weeks: 21.4% vs. 71.1%
- Multivariate analysis (VL, CD4+, timing of ART initiation): viral load only factor independently associated with MTCT
- **Earlier and sustained** control of viral load is associated with a decreasing “residual” risk of HIV MTCT

MTCT in the UK and Ireland 2000-2006 (HAART era)

- Among 2117 infants born to women on HAART, with VL < 50, only three (0.1%) were infected, two with evidence of in-utero transmission
- Longer duration of HAART was associated with reduced transmission after adjusting for VL, mode of delivery and sex (adjusted odds ratio 0.90, or 10% reduction, per week of HAART (P=0.007))
- Among women on HAART, there was no difference in MTCT rates between elective CS (0.7%, 17/2286) and planned vaginal delivery (0.7%, 4/559); adjusted for sex and viral load

Stopping ART Post-Partum

- Controversial issue. ART given for MTCT alone – could individualize. PROMISE study ongoing
- If Nadir CD4 falls within guidelines to treat – continue
- most would recommend continuing in all in resource rich settings, as treatment interruption not recommended in other settings
- Consider transmission to partner
- Modifications welcome- especially if AZT used
- If discontinued, stop all drugs simultaneously, unless significant differences in half-life
-
- Do not stop in HBV co-infected (reactivation risk)

Consider the scenario:

Couple HIV concordant or discordant

Review all different options for insemination & continuum of risk including:

- Unprotected intercourse
- Unprotected intercourse with timed ovulation
- Home insemination (i.e. turkey baster method)
- Intrauterine insemination (IUI) (in fertility clinic)
- Sperm washing followed by IUI
- Other: in vitro fertilization, intra-cytoplasmic sperm injection, gestational carrier, adoption

Are there any questions?

Pregnancy

- May 2013 – pregnant
 - Estimated delivery on January 3, 2014
- Referred to obstetrics, ultrasound, specialist paediatrics counselling and services
- Increase in fatigue
- Added chronic suppressive therapy with acyclovir for genital herpes

She expresses the desire to have a vaginal delivery. What actions would you take?

1. Tell her to elect for a c-section because she sometimes fails to take her medication
2. Discuss the risks and advise that this is an option if her viral load remains undetectable
3. Tell her to elect for a c-section as this has been shown to reduce the risk of MTCT
4. Treat as you would an HIV negative mother- delivery mode determined by obstetrical circumstances

Mrs B Conception

- Instructed on 'turkey baster' approach to impregnation
- Efavirenz switched to lopinavir/r
- Initially considerable problems with gas and diarrhoea
- Modified diet and when she took tablets an improvement was noticed



What would you do to the dose of ART now she is pregnant?

1. Decrease it for the first trimester to protect the foetus from toxicity
2. Increase it if her viral load increases significantly
3. Nothing - dose adjustment is usually not required with lopinavir/r although may be required with other PIs during the 2nd and 3rd trimesters

Delivery and post-pregnancy

- Spontaneous vaginal delivery
- Baby HIV negative

What would you do with her ARV?

1. continuing current ARV
2. switching back to efavirenz
3. Discontinue as she does not require them for her own health

BK informs you that she is going to breast feed, as this is “best for baby” and consistent with her cultural and religious beliefs. What do you do?

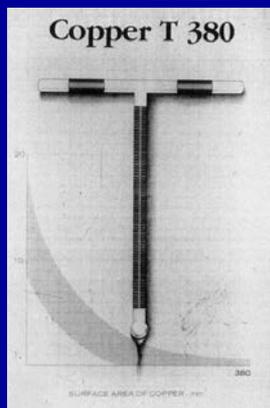
1. State that her beliefs are dangerous and she must not breast feed
2. Tell her not to breast feed and inform the child protection authorities if she still insists on breast feeding
3. Discuss the risks again, and ask her to tell you more about her beliefs and why she wants to breastfeed
4. Advise that if she cannot limit breast feeding, chronic ART prophylaxis in the infant should be initiated

Following delivery, Mrs BK asks for advice on contraception. What would you recommend?

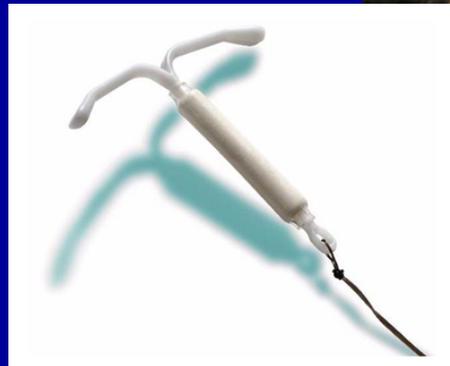
1. Non-barrier methods are possible if her VL remains undetectable
2. She must continue to use condoms at all times, to prevent transmission of HIV and other STDs
3. Avoid oral contraceptives due to potential interactions with her current HIV regimen
4. Avoid injectable contraception as there is evidence to suggest this increases the risk of transmission and progression

Contraception options

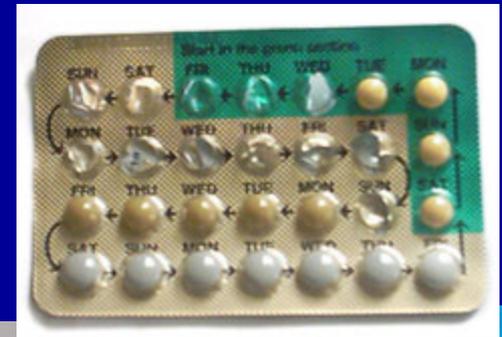
Non-hormonal



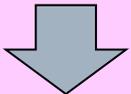
Progestins



Combination Hormones



ARVs and oral contraceptives: Drug interactions

ARV Drug	Effect on EE* AUC	Comment
EFV	 None	Barrier contraception should always be used in combination with other methods of contraception
NVP, LPV/r, SQV/r, DRV/r, NFV		Alternative or additional contraceptive measures are recommended when co-administered with oestrogen-based contraceptives
ATV/r	 19%	Oral contraceptives need to contain >30ug EE
FPV/r	 36%	Coadministration with oral contraceptives may increase the risk of hepatic transaminase elevations, alternative contraception methods are recommended
MVC	 None	Can coadminister with EE
RAL	 2%	Can be co-administered without dose adjustment

No data on PK/PD interactions, ie what is the impact on ovulation

*EE = Ethinylestradiol

Does hormonal contraception biologically alter risk of HIV acquisition or progression ?

- Several potential biological mechanisms postulated
- Unclear which biological mechanisms might be relevant
- Some possible mechanisms supported by animal data
- Unclear how existing animal data extrapolates to humans
- Some studies in women suggest increased risk
- Findings are inconsistent with other studies in women