Conception and Pregnancy in HIV

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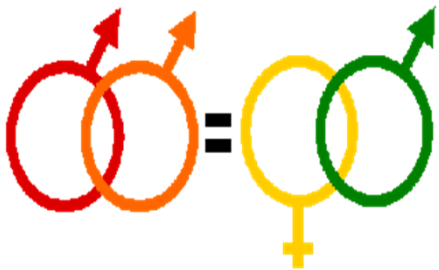
Definitions

HIV serodiscordant couples

Heterosexual or same sex (MSM) couples where one partner is HIV positive and the other is HIV negative



HIV +ve: Reproductive options

HIV+ woman & HIV- man

- Insemination of partner's sperm at ovulation (whether or not on ARVs / detectable viral load)
- Natural conception (if effective viral suppression)
- Assisted reproduction in case of fertility disorders
- Adoption

HIV+ man & HIV- woman

- IUI, IVF or ICSI following sperm washing
- Natural conception (if effective viral suppression)
- Insemination of donor sperm at ovulation
- Pre-Exposure Prophylaxis (PrEP)
- Adoption

Slide Courtesy Y Gilleece and S Taylor Nov 2011

Couple XX XY

- XY HIV positive 2002 when XX pregnant with their first child
- CD4 300, HIV VL 450,213 c/ml
- XX HIV negative
- Very shocked
- XY commenced ARVs as per BHIVA Guidelines

2012

- Referred to me for discussion regarding conception
- XX HIV testing phobia/OCD
- XY stable on ARVs, VL always <40c/ml
- Monogamous

Swiss Statement

"An HIV infected individual without an additional STD and on antiretroviral therapy with completely suppressed viraemia is sexually non-infectious i.e. he/she does not pass on HIV through sexual contact"

provided that the following conditions are fulfilled:
Complies with HAART, <50 for 6 months, no STI

BASHH PEPSE Guidelines 2011

Table 4 Situations when post-exposure prophylaxis (PEP) is considered (IV, grade C)

	Source HIV status			
	HIV-positive			
	Viral load detectable	Viral load undetectable	Unknown from high prevalence group/area*	Unknown from low prevalence group/area
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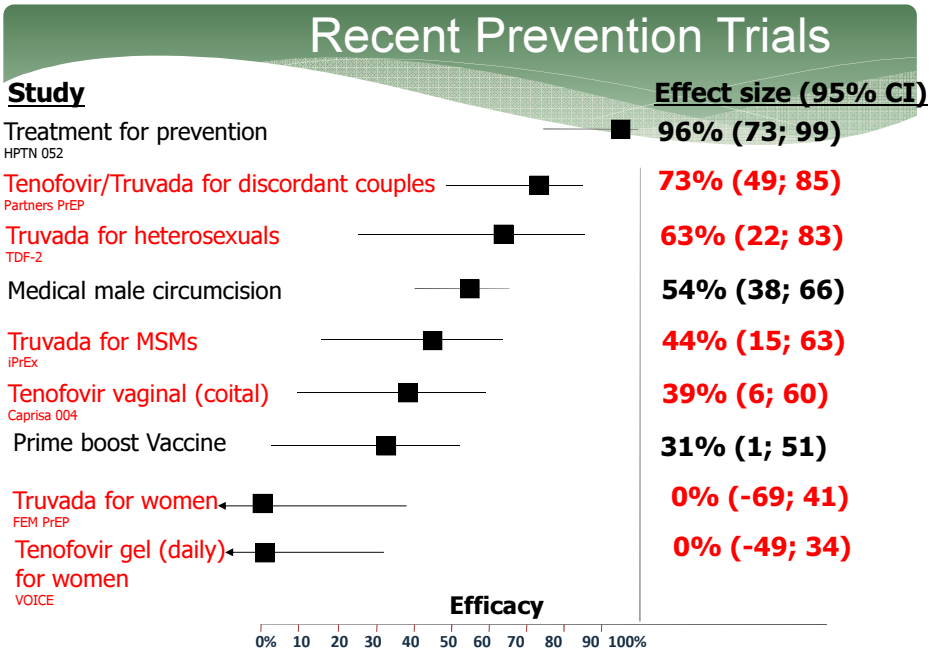
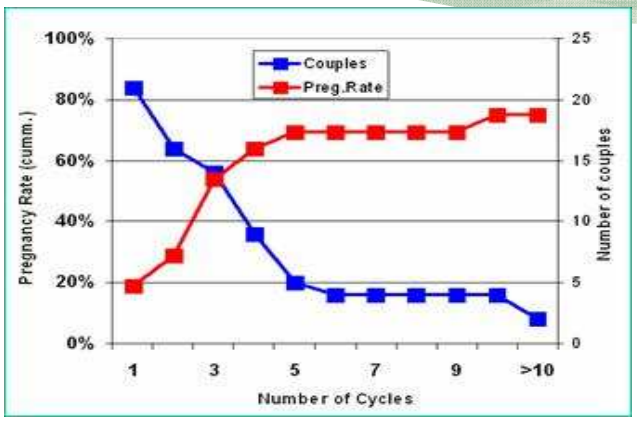
factors PEPSE *should not* be prescribed when the exposure is an undetectable plasma viral load.[102] In light of this evidence

Recent Prevention Trials



PrEP-C with Tenofovir n=22



All women HIV negative 3/12 after last exposure
Maximum attempts 12*
Fertility investigations after 6 attempts*

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Why choose PrEP-C?

Reasons for	Reasons against
Ineligible for NHS funding	Co infection with Hepatitis
Unable to afford privately funded sperm washing	Detectable viral load in plasma or semen
Previous child	Sub fertility where natural conception cannot occur
More natural	High anxiety regarding HIV transmission
Less inconvenient	
Natural conception possible	

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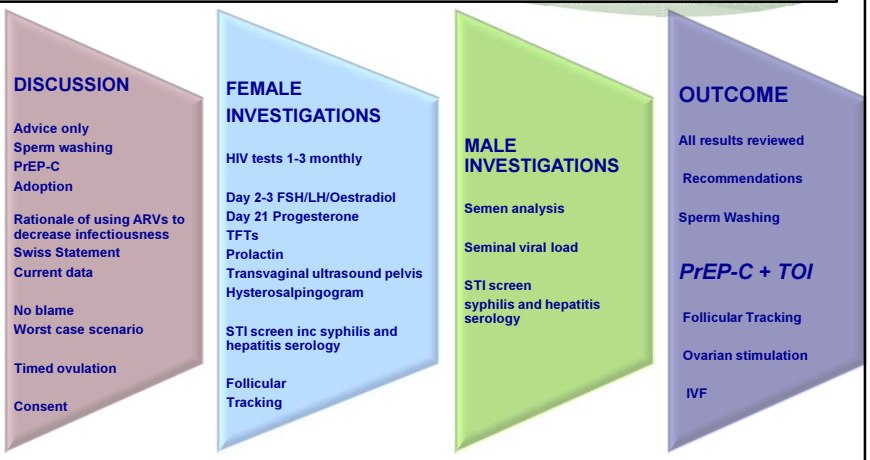
ARC

ANTI-RETROVIRALS FOR CONCEPTION DATABASE



Slide Courtesy of Y Gilleece and S Taylor adapted from BHIVA 2010

Couple XX XY

- Decide to go for PrEP-C
- XX baseline HIV test negative
- Semen analysis – poorly motile sperm, poor volume
- Gynaecologist suggests Selenium and ACE supplementation and stop alcohol/cigs
- Semen reanalysis 3 months later – now near normal motility and normal volume
- Given go ahead re natural conception

Protocol

Evidence based from human and animal models

- Prediction of ovulation
- Urine LH surge
- Follicle tracking

- 1-2 dosesTenofovir/Truvada 24-36hrs pre UPSI

- UPSI

- Tenofovir/Truvada 1-2 hrs post UPSI

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Brighton and Sussex University Hospitals NHS Trust

Couple XX XY

* Multiple attempts unsuccessful
* HIV testing very traumatic for XX
* Long discussion about whether or not they want to continue

* Tragedy – XY's son dies in accident

Couple XX XY

- Multiple attempts unsuccessful
- HIV testing very traumatic for XX
- Long discussion about whether or not they want to continue
- Tragedy – XY's son dies in accident
- They conceive

Couple XX 2012

- XX test HIV negative at pregnancy and 3/12 later
- Healthy baby boy born 2013

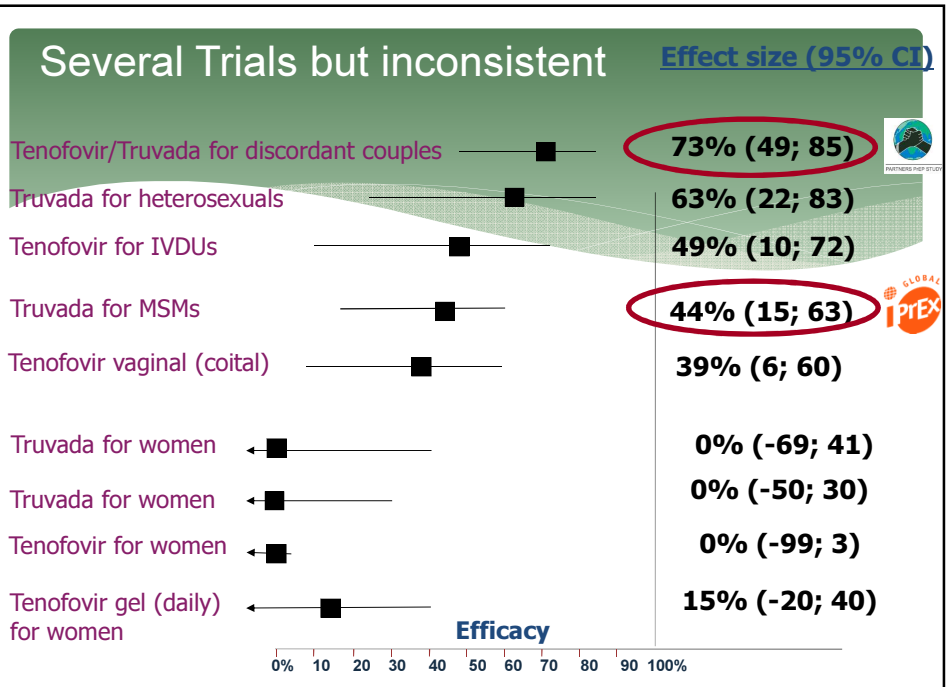
2015

Couple XX XY

- Son 18 months old
- Want a sibling of similar age for him to grow up with
- Referred again to me
- Long discussion
- They want PrEP-C again
- Gynae happy with that
- Trial of 3 months
- Erectile dysfunction XY when has “to perform”

What's new in 2015?

Several Trials but inconsistent



Why so different? Adherence…

	% of blood samples with tenofovir detected	HIV protection efficacy in randomized comparison	HIV protection estimate with high adherence
Partners PrEP FTC/TDF arm	81%	75%	90% (tenofovir in blood)
TDF2	79%	62%	78% (prescription refill)
BTS	67%	49%	70% - 84% (tenofovir in blood / pill count)
iPrEx	51%	44%	92% (tenofovir in blood)
FEM-PrEP & VOICE	<30%	No HIV protection	N/A

PROUD Pilot

PROUD

GMSM reporting UAI last/next 90days; 18+;
and willing to take a pill every day

↓

Randomize HIV negative MSM
(exclude if treatment for HBV/Truvada contra-indicated)

↓

Risk reduction includes Truvada **NOW**

Risk reduction includes Truvada **AFTER 12M**

↓

Follow **3 monthly** for up to 24 months

Main endpoints in Pilot: recruitment and retention
From April 2014: HIV infection in first 12 months

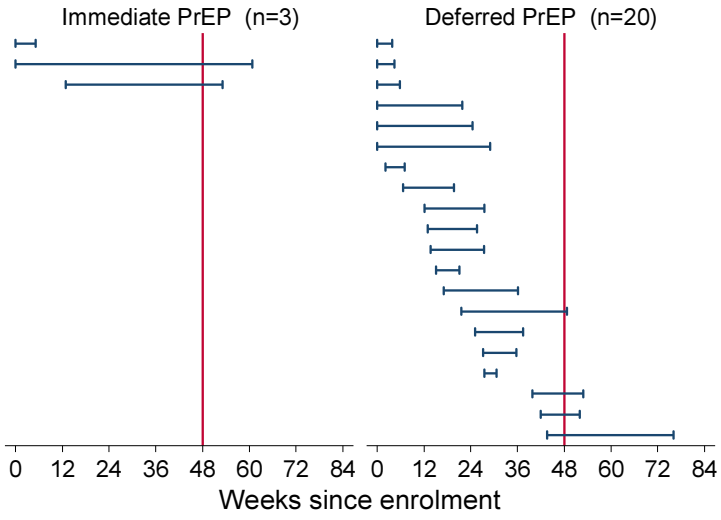
HIV Incidence

Group	No. of infections	Follow-up (PY)	Incidence (per 100 PY)	90% CI
Overall	23	465	4.9	3.4–6.8
Immediate	3	245	1.2	0.3–3.0
Deferred	20	220	9.1	6.2–12.9

Efficacy =86% (90% CI: 65 – 96%)
P value =0.0001

Rate Difference =7.9 (90% CI: 4.3 – 11.4)
Number Needed to Treat =13 (90% CI: 9 – 23)

Individual incident HIV infections



ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

www.ipergay.fr

Study Design

Double-Blinded Randomized Placebo-Controlled Trial

- HIV negative high risk MSM
- Condomless anal sex with ≥ 2 partners within 6 m
- eGFR > 60 mL/mn

→ **Full prevention services* TDF/FTC before and after sex**

→ **Full prevention services* Placebo before and after sex**

* Counseling, condoms and gels, testing and treatment for STIs, vaccination for HBV and HAV, PEP

- End-point driven study : with 64 HIV-1 infections, 80% power to detect a 50% relative decrease in HIV-1 incidence with TDF/FTC (expected incidence: 3/100 PY with placebo)
- Follow-up visits: month 1, 2 and every two months thereafter

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Agence autonome de l'Inserm

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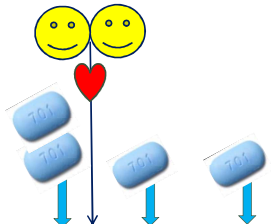
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

Ipergay : Event-Driven iPrEP

- ✓ 2 tablets (TDF/FTC or placebo) 2-24 hours before sex
- ✓ 1 tablet (TDF/FTC or placebo) 24 hours later
- ✓ 1 tablet (TDF/FTC or placebo) 48 hours after first intake



Friday | Saturday | Sunday | Monday | Tuesday | Wednesday | Thursday | Friday | Saturday | Sunday

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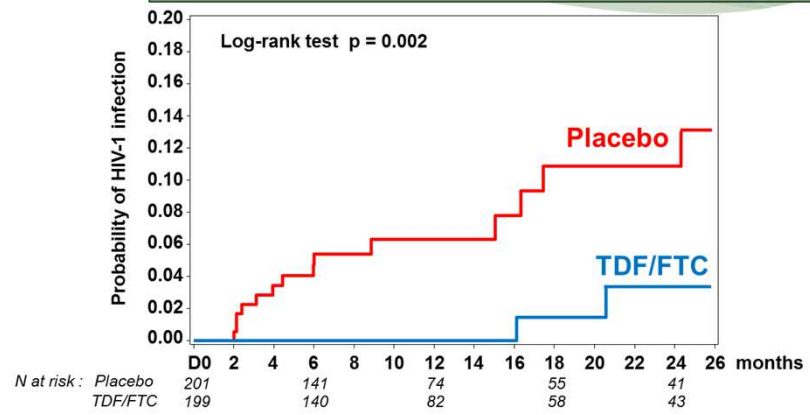
KM Estimates of Time to HIV-1 Infection (mITT Population)



Mean follow-up of 13 months: 16 subjects infected
14 in placebo arm (incidence: 6.6 per 100 PY), **2 in TDF/FTC arm** (incidence: 0.94 per 100 PY)

86% relative reduction in the incidence of HIV-1 (95% CI: 40-99, p=0.002)
NNT for one year to prevent one infection : 18

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Reminder of concerns around PrEP

- Cost (including delivery costs) precludes universal access
- Not funded in the UK
- Viral resistance
- Toxicity
- Possibility that biological efficacy of PrEP could be negated by behavioural changes:
  - replacement of condom use by less effective pharmacological prevention methods
  - increase in risky behaviour by alteration of individuals' perceptions of their HIV risk
- These concerns are widely shared: gay community, regulatory authorities, commissioners, clinicians, research community

Is PrEP-C safe?
Partners PrEP study

- Not set up to examine the safety of PrEP for conception or during pregnancy - pregnant women were specifically excluded
- During each year of the study 1 in 10 women became pregnant
- Fetuses estimated exposure to TFV max 6 weeks
- Data was collected on 288 pregnancies, with follow-up visits every 3 months throughout the infant's first year of life
- Comparing women who received placebo, tenofovir, or Truvada, the investigators found no statistically significant differences in terms of:
  - Number of pregnancies/ Miscarriages/ Stillbirths
  - Preterm delivery/ Birth weight/ Congenital abnormalities Infant growth
  - Safe but further study of PrEP taken throughout pregnancy would be valuable

N Mugo, T Hong, C Celum, E Bukis, et al (Partners PrEP Study). 7th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. Kuala Lumpur, June 30-July 3, 2013. Abstract WEAC0101.

Is PrEP-C necessary?
Mathematical modelling

- HIV negative woman taking antiretroviral drugs as PrEP in addition to her HIV positive male partner taking similar drugs as treatment, giving birth to a child while remaining HIV negative
- Circumstances examined included
  - using PrEP/ using HIV treatment/ using both/ using neither
  - Timed versus regular intercourse
  - women of different ages
  - couples who had intercourse more or less often
- The investigators fed in a series of assumptions, derived from previous studies
  - the transmission risk during both the first years of HIV infection and late-stage disease
  - the effectiveness of HIV treatment and PrEP in reducing transmissions
  - the impact of sexually transmitted infections
  - the probability of conception by age
  - the probability of successful delivery by age
  - and the number of unprotected sex acts to achieve successful conception

R Hoffman, R Vardavas, A Jaycocks, R Landovitz, et al.. 7th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. Kuala Lumpur, June 30-July 3, 2013.Abstract TUAC0104.

Is PrEP-C necessary? Mathematical modelling

- Best outcome: For couples who limited unprotected sex to fertile days: ARVS>PrEP>Neither. No additional benefit ARVS +PrEP.
- For couples who had unprotected sex throughout the month, adding PrEP on top of HIV treatment did confer some benefit
- Younger women needed to have unprotected intercourse on far fewer occasions to achieve a pregnancy – very significant
- Couples can achieve the desired results without needing PrEP, as long as they limit unprotected sex to the time of ovulation, screen for and treat sexually transmitted infections, and the positive partner adheres to antiretroviral therapy

Evolution of PrEP-C

- Hold off radiological investigations unless clinically indicated
- No routine semen HIV VL
- Protocols for HIV negative men and women
- Protocol includes use of daily Truvada
- ARC UK database

BASHH PEPSE Guidelines 2015

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700 International Journal of STD & AIDS Volume 22 December 2011

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HIV transmission through condomless sex if the HIV positive partner is on suppressie ART: PARTNER study

PARTNER Study

The PARTNER study is an observational multi-centre study of HIV serodifferent couples in which the positive partner is on ART, taking place in 75 European sites

Aim

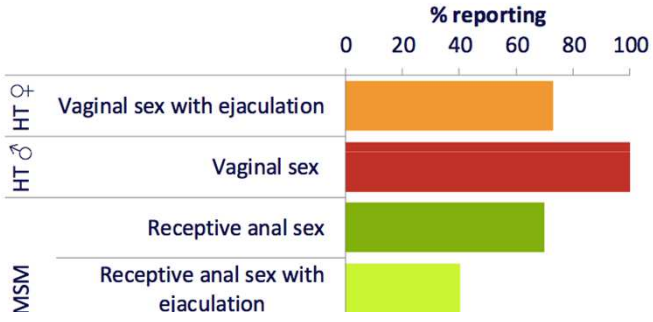
To evaluate the risk of within-couple HIV transmission (HT and MSM) during periods where condoms are not used consistently

	MSM couples (n=282)	Heterosexual couples (n=445)	
		M -ve (n=245)	W -ve (n=240)
At study entry			
Age, median (IQR)	40 (32-47)	45 (37-50)	40 (34-46)
Yrs CL sex, median (IQR)	1.5 (0.5-3.5)	2.7 (0.6-6.9)	3.5 (0.7-10.6)
During follow up			
Years in the study, median (IQR)	1.1 (0.7-1.9)	1.5 (1.0-2.0)	1.5 (0.9-2.0)
Diagnosed with STI, %	16%	5%	6%
CL sex with other partners, %	34%	3%	4%
CL sex acts/year, median (IQR)	43 (18-79)	37 (14-77)	38 (14-71)

Partner Study

	MSM couples (n=282)	Heterosexual couples (n=445)	
		W +ve (n=245)	M +ve (n=240)
At study entry			
Age, median (IQR)	42 (36-47)	40 (34-46)	45 (40-49)
Years on ART, median (IQR)	5 (2-11)	7 (3-14)	10 (4-15)
Self-reported adherence >=90%, %	97%	94%	94%
Self report undetectable VL, %	94%	86%	85%
CD4>350 cells/mm³, %	90%	88%	84%
During follow-up			
Having missed ART for more than 4	2%	7%	4%

Partner Study



Without ART: expected 15 transmissions in heterosexual and 86 transmissions in MSMs

Partner Study

HIV status and sexual orientation of couples	Type of sex without a condom by HIV negative partner	Linked trans-missions (n)	Couple-years of follow up (CYFU)	Approx. no. of sex acts without condoms	Risk per contact (95% CI)*	Rate per 100 CYFU (95% CI)	10 year risk (95% CI)
Study overall	All types of sex (VL <200)	0	894	44,450	0 (0 – 0.00008)	0 (0 0.40)	0 (0 – 3.9%)
	All types of sex (VL < 50)	0	836	41,480	0 (0 – 0.00009)	0 (0-0.43)	0 (0 – 4.2%)
	Anal sex	0	374	21,030	0 (0 – 0.00017)	0 (0-0.96)	0 (0 – 9.2%)
Straight couples (man positive)	Sex	0	288	13,730	0 (0 – 0.00028)	0 (0-1.25)	0 (0 – 11.7%)
	Vaginal sex with ejaculation	0	191	8,910	0 (0 – 0.00043)	0 (0-1.88)	0 (0 – 17.1%)
	Vaginal sex without ejaculation	0	174	6,380	0 (0 – 0.00060)	0 (0-2.07)	0 (0 – 18.7%)
Straight couples (woman positive)	Sex	0	298	14,300	0 (0 – 0.00027)	0 (0-1.21)	0 (0 – 11.4%)
	Vaginal sex	0	272	14,150	0 (0 – 0.00027)	0 (0-1.32)	0 (0 – 12.4%)
Gay male couples	Anal sex	0	308	16,420	0 (0 – 0.00023)	0 (0-1.17)	0 (0 – 11.0%)
	Receptive anal sex (with or without ejaculation)	0	182	7,750	0 (0 – 0.00050)	0 (0-1.97)	0 (0- 17.9%)
	Insertive anal sex	0	262	11,750	0 (0 – 0.00033)	0 (0-1.37)	0 (0 – 12.8%)

There is no documented HIV transmission from an individual with HIV RNA <40c/ml

There is no documented HIV transmission from an individual with HIV RNA <40c/ml

Ever!

START study


"All the News That's Fit to Print"
The New York Times
Late Edition
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Couple XX XY 2015

- We discuss the data…again
- We discuss her concerns
- We discuss his ED

- They are now trying UPSI…..

Summary

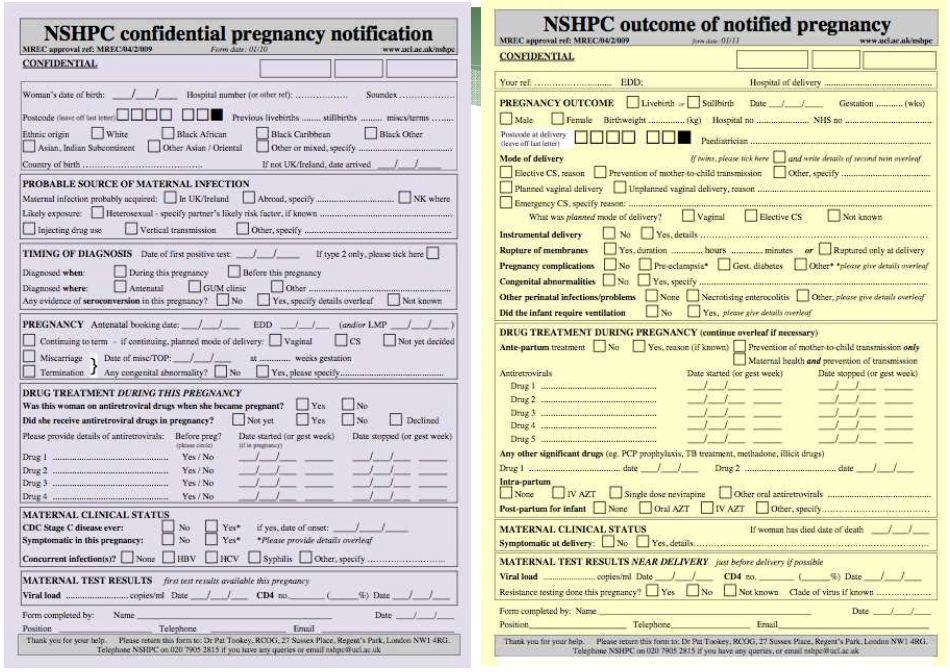
- Multitude of data on transmission
- Long term data is what we need
- Individual discussion is really important
- MDT care is essential for couples wishing to conceive
- PrEP is safe and may be indicated for some couples
- Normalisation of conception is most important

Acknowledgements

* Lawson Unit Team and Patients
* Tracey Buckingham
* Mark Roche

BHIVA Audit 2015
Pregnancies in women with HIV:
A collaboration between BHIVA and the National Study [illegible] Pregnancy and Childhood

* The National Study on HIV in Pregnancy and Childhood (NSHPC) provided BHIVA with anonymised data on pregnancies in the UK and Ireland
* Pregnancies with an estimated date of delivery (EDD) between 1 January 2013 and 30 June 2014 were included
* BHIVA audited the data against outcomes specified in its 2012 pregnancy guidelines



NSHPC confidential pregnancy notification

MREC approval ref: MREC/04/2/089 *Form date: 01/10* www.ucl.ac.uk/nshpc

CONFIDENTIAL

Woman's date of birth: ___/___/___ Hospital number (or other ref): ..... Soundex .....

Postcode (leave off last letter) ☐☐☐☐ ☐☐☐ Previous livebirths ..... stillbirths ..... miscs/terms .....

Ethnic origin ☐ White ☐ Black African ☐ Black Caribbean ☐ Black Other ☐ Asian, Indian Subcontinent ☐ Other Asian / Oriental ☐ Other or mixed, specify .....

Country of birth ..... If not UK/Ireland, date arrived ___/___/___

PROBABLE SOURCE OF MATERNAL INFECTION

Maternal infection probably acquired: ☐ In UK/Ireland ☐ Abroad, specify ..... ☐ NK where

Likely exposure: ☐ Heterosexual - specify partner's likely risk factor, if known .....

☐ Injecting drug use ☐ Vertical transmission ☐ Other, specify .....

TIMING OF DIAGNOSIS Date of first positive test: ___/___/___ If type 2 only, please tick here ☐

Diagnosed **when**: ☐ During this pregnancy ☐ Before this pregnancy

Diagnosed **where**: ☐ Antenatal ☐ GUM clinic ☐ Other .....

Any evidence of **seroconversion** in this pregnancy? ☐ No ☐ Yes, specify details overleaf ☐ Not known

PREGNANCY Antenatal booking date: ___/___/___ EDD ___/___/___ (*and/or* LMP ___/___/___)

☐ Continuing to term - if continuing, planned mode of delivery: ☐ Vaginal ☐ CS ☐ Not yet decided

☐ Miscarriage ☐ Termination } Date of misc/TOP: ___/___/___ at ..... weeks gestation

Any congenital abnormality? ☐ No ☐ Yes, please specify .....

DRUG TREATMENT *DURING THIS PREGNANCY*

Was this woman on antiretroviral drugs when she became pregnant? ☐ Yes ☐ No

Did she receive antiretroviral drugs in pregnancy? ☐ Not yet ☐ Yes ☐ No ☐ Declined

Please provide details of antiretrovirals:	Before preg? (please circle)	Date started (or gest week) (if in pregnancy)	Date stopped (or gest week)
Drug 1	Yes / No	___/___/___ ____	___/___/___ ____
Drug 2	Yes / No	___/___/___ ____	___/___/___ ____
Drug 3	Yes / No	___/___/___ ____	___/___/___ ____
Drug 4	Yes / No	___/___/___ ____	___/___/___ ____

MATERNAL CLINICAL STATUS

CDC Stage C disease ever: ☐ No ☐ Yes* if yes, date of onset: ___/___/___

Symptomatic in this pregnancy: ☐ No ☐ Yes* **Please provide details overleaf*

Concurrent infection(s)? ☐ None ☐ HBV ☐ HCV ☐ Syphilis ☐ Other, specify .....

MATERNAL TEST RESULTS *first test results available this pregnancy*

Viral load ..... copies/ml Date ___/___/___ **CD4** no.____ (____%) Date ___/___/___

Form completed by: Name _____ Date ___/___/___

Position _____ Telephone _____ Email _____

Thank you for your help. Please return this form to: Dr Pat Tookey, RCOG, 27 Sussex Place, Regent's Park, London NW1 4RG. Telephone NSHPC on 020 7905 2815 if you have any queries or email nshpc@ucl.ac.uk

NSHPC outcome of notified pregnancy

MREC approval ref: MREC/04/2/089 *form date: 01/11* www.ucl.ac.uk/nshpc

CONFIDENTIAL

Your ref: ..... EDD: Hospital of delivery .....

PREGNANCY OUTCOME ☐ Livebirth *or* ☐ Stillbirth Date ___/___/___ Gestation ..... (wks)

☐ Male ☐ Female Birthweight ..... (kg) Hospital no ..... NHS no .....

Postcode at delivery (leave off last letter) ☐☐☐☐ ☐☐☐ Paediatrician .....

Mode of delivery *If twins, please tick here* ☐ *and write details of second twin overleaf*

☐ Elective CS, reason ☐ Prevention of mother-to-child transmission ☐ Other, specify .....

☐ Planned vaginal delivery ☐ Unplanned vaginal delivery, reason .....

☐ Emergency CS, specify reason: .....

What was *planned* mode of delivery? ☐ Vaginal ☐ Elective CS ☐ Not known

Instrumental delivery ☐ No ☐ Yes, details .....

Rupture of membranes ☐ Yes, duration ..... hours ..... minutes *or* ☐ Ruptured only at delivery

Pregnancy complications ☐ No ☐ Pre-eclampsia* ☐ Gest. diabetes ☐ Other* **please give details overleaf*

Congenital abnormalities ☐ No ☐ Yes, specify .....

Other perinatal infections/problems ☐ None ☐ Necrotising enterocolitis ☐ Other, *please give details overleaf*

Did the infant require ventilation ☐ No ☐ Yes, *please give details overleaf*

DRUG TREATMENT DURING PREGNANCY (continue overleaf if necessary)

Ante-partum treatment ☐ No ☐ Yes, reason (if known) ☐ Prevention of mother-to-child transmission ***only*** ☐ Maternal health ***and*** prevention of transmission

Antiretrovirals	Date started (or gest week)	Date stopped (or gest week)
Drug 1	___/___/___ ____	___/___/___ ____
Drug 2	___/___/___ ____	___/___/___ ____
Drug 3	___/___/___ ____	___/___/___ ____
Drug 4	___/___/___ ____	___/___/___ ____
Drug 5	___/___/___ ____	___/___/___ ____

Any other significant drugs (eg. PCP prophylaxis, TB treatment, methadone, illicit drugs)

Drug 1 ..... date ___/___/___ Drug 2 ..... date ___/___/___

Intra-partum

☐ None ☐ IV AZT ☐ Single dose nevirapine ☐ Other oral antiretrovirals .....

Post-partum for infant ☐ None ☐ Oral AZT ☐ IV AZT ☐ Other, specify .....

MATERNAL CLINICAL STATUS If woman has died date of death ___/___/___

Symptomatic at delivery: ☐ No ☐ Yes, details.....

MATERNAL TEST RESULTS *NEAR DELIVERY* *just before delivery if possible*

Viral load ..... copies/ml Date ___/___/___ **CD4** no. _____ (_____%) Date ___/___/___

Resistance testing done this pregnancy? ☐ Yes ☐ No ☐ Not known Clade of virus if known .....

Form completed by: Name _____ Date ___/___/___

Position_____ Telephone_____ Email_____

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1483 pregnancies in 1469 women

	Number of women	Percent of women
Ethnicity:		
Black African	1083	73.7%
White	250	17.0%
Black Caribbean	46	3.1%
Other/not stated	90	6.1%
Age at EDD:		
16-19	12	0.8%
20-29	344	23.4%
30-39	952	64.8%
40 or over	161	11.0%
HIV acquisition:		
Heterosexual	1251	85.2%
Vertical	21	1.4%
Injecting drug use	17	1.2%
Other/not stated	180	12.3%

Conclusions & Recommendations

Limited data, particularly regarding VL, affected this audit but:

- Initial ART regimens were nearly all in accordance with guidelines
- Combination ART was initiated in over 80% of cases
- Only 27.2% of newly diagnosed women with CD4 <350 cells/mm^3 started ART within 2 weeks
- Many women started ART late, and in most cases this was not explained by late booking
- Use of ART should be consistently reported to the Antiretroviral Pregnancy Registry (APR) to increase confidence of ART use in pregnancy

Conclusions & Recommendations

- More than half of deliveries were by CS
- 27.4% of women with VL <50 copies/ml measured at ≥36 weeks planned for CS
- National survey of management of pregnancy in women living with HIV, presented at autumn BHIVA 2014 confirmed some centres have very high rates of CS
- Maternity and HIV services should review and agree pathways to ensure swift assessment and prompt ART initiation
- Clinicians should encourage women to plan vaginal delivery unless obstetric factors or insufficient virological control present a clear indication for CS

Safety of ARVs in Pregnancy

- Further data on safety of Efavirenz in pregnancy
  - 2014, a systematic review and meta-analysis of observational cohorts reported birth outcomes among women exposed to efavirenz during the first trimester [57]. The primary endpoint was a birth defect of any kind with secondary outcomes including rates of spontaneous abortions, termination of pregnancy, stillbirths and preterm delivery
  - Twenty-three studies met the inclusion criteria
  - The analysis found no increased risk of overall birth defects among 2026 women exposed
  - Only one neural tube defect was observed giving a prevalence of 0.05% (95% CI <0.01–0.28%)
  - Furthermore, the prevalence of overall birth defects with first-trimester efavirenz exposure was similar to the ranges reported in the general population
- Antiretroviral Pregnancy Register
  - Insufficient safety data on first trimester exposure to
    - Etravirine
    - Rilpivirine
    - Maraviroc
    - Raltegravir
    - Elvitegravir
    - Cobicistat
    - Plus Saquinavir, T20, Fosamprenavir, Tipranavir