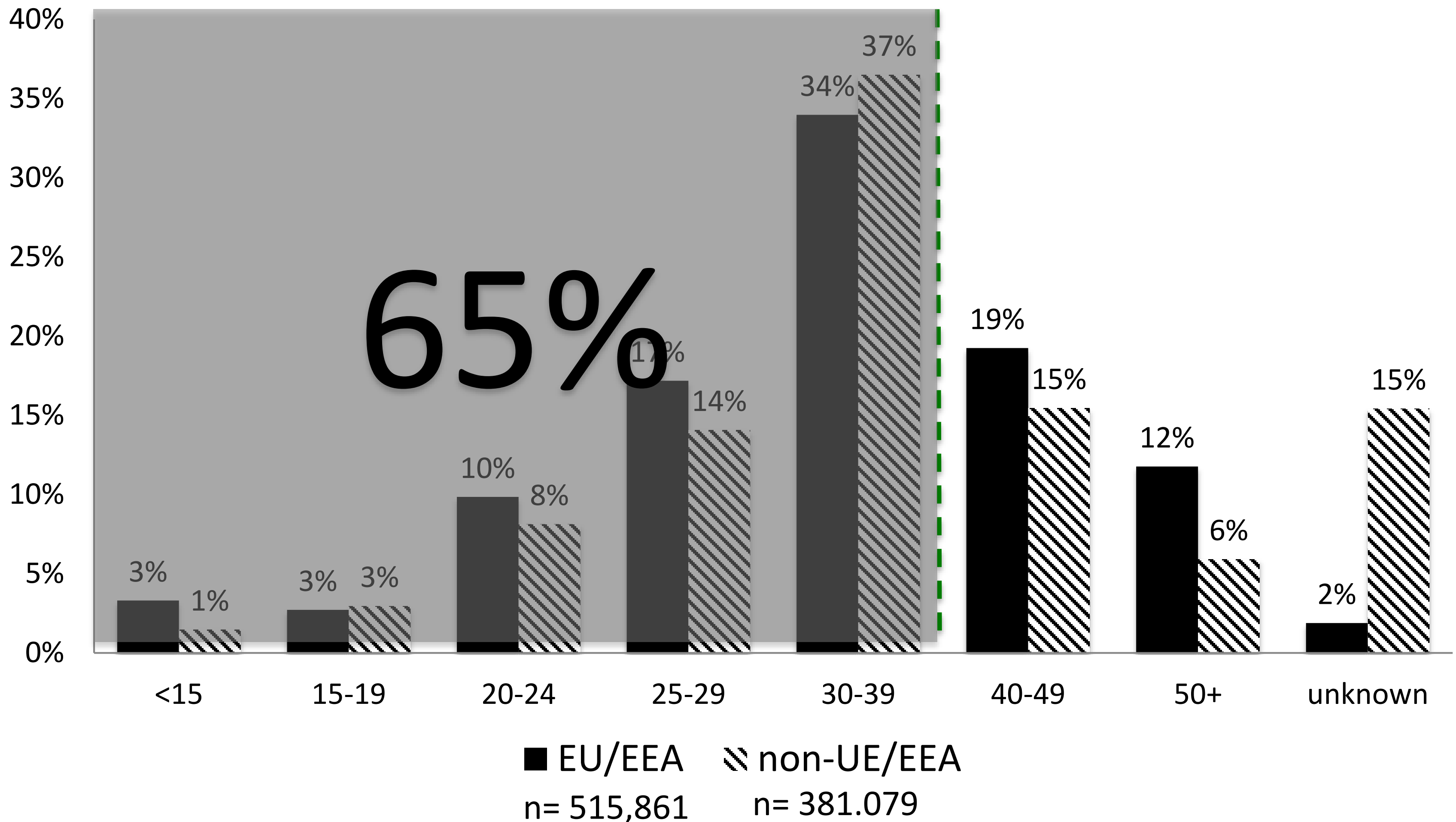
Case discussion: How do drugs/patients impact need and type of monitoring – CASE 1

Laura Waters
Lead HIV/hepatitis services
Mortimer Market Centre, CNWL, UK

Miss X

- 32 year old Black British woman
- Diagnosed HIV+ after regular male partner is tested following an admission with bacterial pneumonia
- CD4 540, VL 46,000, routines bloods normal
- Wild-type resistance test, HLA*B5701 negative
- HBV and HCV negative
- No plans for children

Age at diagnosis in women diagnosed 2006-2015



HIV/AIDS surveillance in Europe 2015

Miss X wants to start ART

- *“What ART should I take?”*
- *“Should I take the same as my partner?”*

Women living with HIV (WLWH)

- More than half of all PLWH globally are women
- Female recruitment to phase 3 trials is a lot less....

Study	New agent	Comparator	% Women
SINGLE	Dolutegravir	Efavirenz	16%
FLAMINGO	Dolutegravir	Darunavir/r	15%
GS-104/111	Genvoya	Stribild	15%
GS-1489	BIC/FTC/TAF	Triumeq	10%
GS-1089	Descovy	Continued Truvada	12%

Trials: Meta-analysis of FDA registrational studies

Included developed and developing settings
Around the globe, females with HIV-1 infection have **slightly improved survival** outcomes vs males

No clear sex disparity in:

HIV-1 disease progression (including AIDS)
Treatment effects (viral or immune markers)

8.15% men
4.25% women*

Soon GG et al. AIDS Patient Care STDS. 2012 Aug;26(8):444-53.

*from presented abstract, not included in published paper

By and large outcomes are the same for women….EXCEPT…..

- **Atazanavir-based ART**
  - Fast time to virological failure for vs EFV in ACTG 5202
  - Inferior to alternatives in women-only trial:
    - TDF/FTC + ATV/r vs E/C/F/TDF in WAVES
    - TDF/FTC + ATV/r vs ABC/3TC/DTG in ARIA
- **Why?**
  - Differences driven be adverse events
  - Jaundice = main adverse event
  - Black African individuals more likely to have polymorphisms that confer reduced UGT1A1 activity

http://www.humgenomics.com/content/pdf/1479-7364-4-4-238.pdf accessed 7th October 2015

Possible sex differences in PK parameters relevant to ARVs

Pharmacokinetics

Bioavailability

- ↓acid, slower gastric emptyi (OCP, preg)
- Diet difference
- No consistent differences in gut CYP or p-gp

- Less organ flow
- Oestrogen has effects on plasma binding proteins

Elimination

- maller organs
- lepC and liver tatus

What does it mean?

We ‘overdose’ anyway

Monitor efficacy, tolerability and toxicity

- Administration of concomitant medications can affect each stage & vary by sex

Gandhi *Annu Rev Pharm Tox* 2004; Mirfazaellan EJ *Clin Pharm* 2002; Wobold *Hepatol* 2003

Other ART considerations

- **CRANIum Study:**
  - Survey in Western Europe, n=2,863, 38% women
  - Female subjects:
    - More unemployment
    - Lower education status
    - More depression by HADS (17.9% vs 14.3%; p=0.01)
- **Issues that *may* affect women more:**
  - Stigma, disclosure, shared housing, immigration, finance
  - Need vs preference for a single tablet regimen
- **These issues will be detected in a good consultation**

Bayon C et al. 2nd International Workshop on HIV & Women. Abstract O_1.

BHIVA 2015/2016

8.7.3 What to start

8.7.3.1 Recommendations

- There are insufficient data to support specific recommendations for HIV-positive non-pregnant women. We therefore recommend therapy-naïve HIV-positive women start ART as per general guidelines (1A).
- We recommend both HIV-positive women of childbearing potential and healthcare professionals who prescribe ART are conversant with the benefits and risks of ARV agents for both the health of the HIV-positive woman and for that of an unborn child (GPP)
- We recommend that potential pharmacokinetic interactions between ARVs, hormonal contraceptive agents and hormone replacement therapy are checked before administration (GPP)

What do we do?

- We follow the London regional guidelines
- No contra-indications to abacavir
- Declines efavirenz
- Starts **Kivexa + raltegravir 400mg BID**
- Tolerates well
- Switches to **raltegravir 800mg OD** once suppressed

BHIVA 2015/2016

8.7.3 What to start

8.7.3.1 Recommendations

- There are insufficient data to support specific recommendations for HIV-positive non-pregnant women. We therefore recommend therapy-naïve HIV-positive women start ART as per general guidelines (1A).
- We recommend both HIV-positive women of childbearing potential and healthcare professionals who prescribe ART are conversant with the benefits and risks of ARV agents for both the health of the HIV-positive woman and for that of an unborn child (GPP)
- **Pharmacokinetic interactions**

Miss X

- On depot progestogen injection
- Takes no other medication

ART & contraception

Coloured boxes: European SPC advice; grey boxes: my opinion NR = not recommended)

	Oral	DMPA[a]	Implanon[b]
EFV	Barrier too	No impact but levels vary so barrier too	Not studied, ↓exposure expected, cases of failure
NVP	Not sole method	No impact – OK	Interaction unlikely but NR
RPV	No dose adjustment	Likely fine but no data	Likely fine but no data
ETR	No dose adjustment	No dose adjustment	No dose adjustment
ATV/r	At least 30mcg EE. If prog other than norgestimate, NR	Not studied therefore NR	Not studied therefore NR
DRV/r	Oestrogen-based use alt/additional (no POP advice)	Likely fine	Interaction unlikely but NR
LPV/r	Additional methods if oestrogen containing	Likely fine	Interaction unlikely but NR
MVC	No dose adjustment	Likely fine	Likely fine
RAL	No dose adjustment	No dose adjustment	No dose adjustment
DTG	No dose adjustment*	Likely fine	Likely fine
EVG/c	**Similar PK effects to boosted ATV ie approximate doubling in norgestimate and reduction in ethinyl oestradiol (approx 40% reduction in Cmin)**		

a) **DMPA: clearance = hepatic blood flow, inducers unlikely to impact efficacy**

b) **Implanon: failures on EFV & AED; SPC says efficacy may be affected by enzyme inducers**

*no impact on LH or FSH

COCP & ATV

EE = Ethinylestradiol; NE = norethindrone; NG = Norgestimate

ATAZANAVIR

- ↑EE: Cmax AUC Cmin
  15% 48% 91%
- ↑NE: Cmax AUC Cmin
  1.67x 2.1x 3.62x

ATAZANAVIR/r (300/100)

- ↓EE: Cmax AUC Cmin
  19% 16% 37%
- ↑NG: Cmax AUC Cmin
  1.68x 1.85x 2.02x

"If an oral contraceptive is administered with REYATAZ(atazanavir)*/ritonavir, it is recommended that the oral contraceptive contain at least 30µg (EUROPE) or 35µg (FDA) of ethinyloestradiol and that the patient be reminded of strict compliance with this contraceptive dosing regimen."*

Atazanavir SmPC. Available at:http://emc.medicines.org.uk/document.aspx?documentId=14145. Accessed January 2010

Should we be concerned?

- WLWH have an elevated with of CVD
- Most CVD risk assessments focus on over 40s
- BHIVA guidelines don’t recommend lipids or HbA1C unless over 40
- **My view**
  - I ignore the BHIVA lipid guidelines and **follow EACS**
  - Check glucose or HbA1C in women on progestogen-based contraception with ATV/r or Stribild/Genvoya annually

Overall advice

- Long-acting reversible methods are preferred
- Caution at times of method change
- Be aware of emergency contraception advice
  - *Do you routinely ask WLWH of child-bearing potential if they know how to access emergency contraception?*

Emergency contraception

- **Copper intrauterine device**
  - Most effective method, 1st choice
  - Up to 120 hours after UPSI or within 5 days ovulation
  - Only method not affected by enzyme inducers

Dolutegravir Raltegravir Rilpivirine	Ullapristal metabolised by 3A4 (1A2 & C2D6) LNG metabolised by CYP3A4 EFV may ↓ Boosters may ↑

Miss X

- All going well
- Sees you in clinic
- Says her primary care doctor has refused to do annual smear test

Cervical screening recommendations

- **EACS v8.2**
  - Cervical cytology every 1-3 years
- **CDC**
  - Start 1 year after sexarche, then annually
  - After 3 consecutive normal annual smears 3 yearly
  - If smear normal + hrHPV negative, 3 yearly after a single normal/negative result
- **BHIVA draft**
  - Annually
  - 3 yearly if hrHPV negative, normal smear and CD4 >500

Harris TG, Burk RD, Palefsky JM, et al. JAMA. Mar 23 2005;293(12):1471-1476
Keller MJ, Burk RD, Xie X, et al.. JAMA. Jul 25 2012;308(4):362-369.

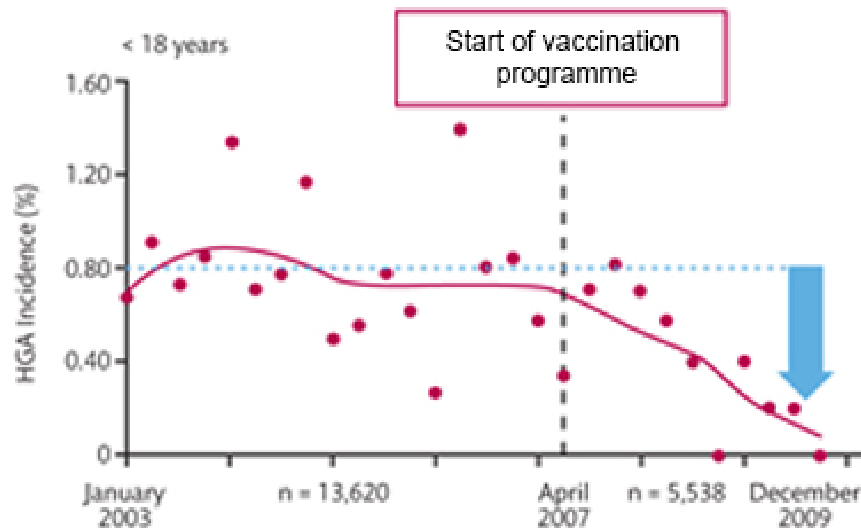
Questions

- What cervical screening frequency do you recommend to WLWH?
- Do you have access to hrHPV screening as part of your cervical screening programme?
- Do you recommend HPV vaccination to WLWH?
- Do you administer HPV vaccination to WLWH?

Reduction of high-grade cervical abnormalities in Australia

Within 3 years after the start of the national HPV vaccination programme with the 4HPV vaccine the incidence of high-grade cervical abnormalities almost halved in girls aged <18 years in Victoria

Incidence of high-grade cervical abnormalities in girls aged <18 years



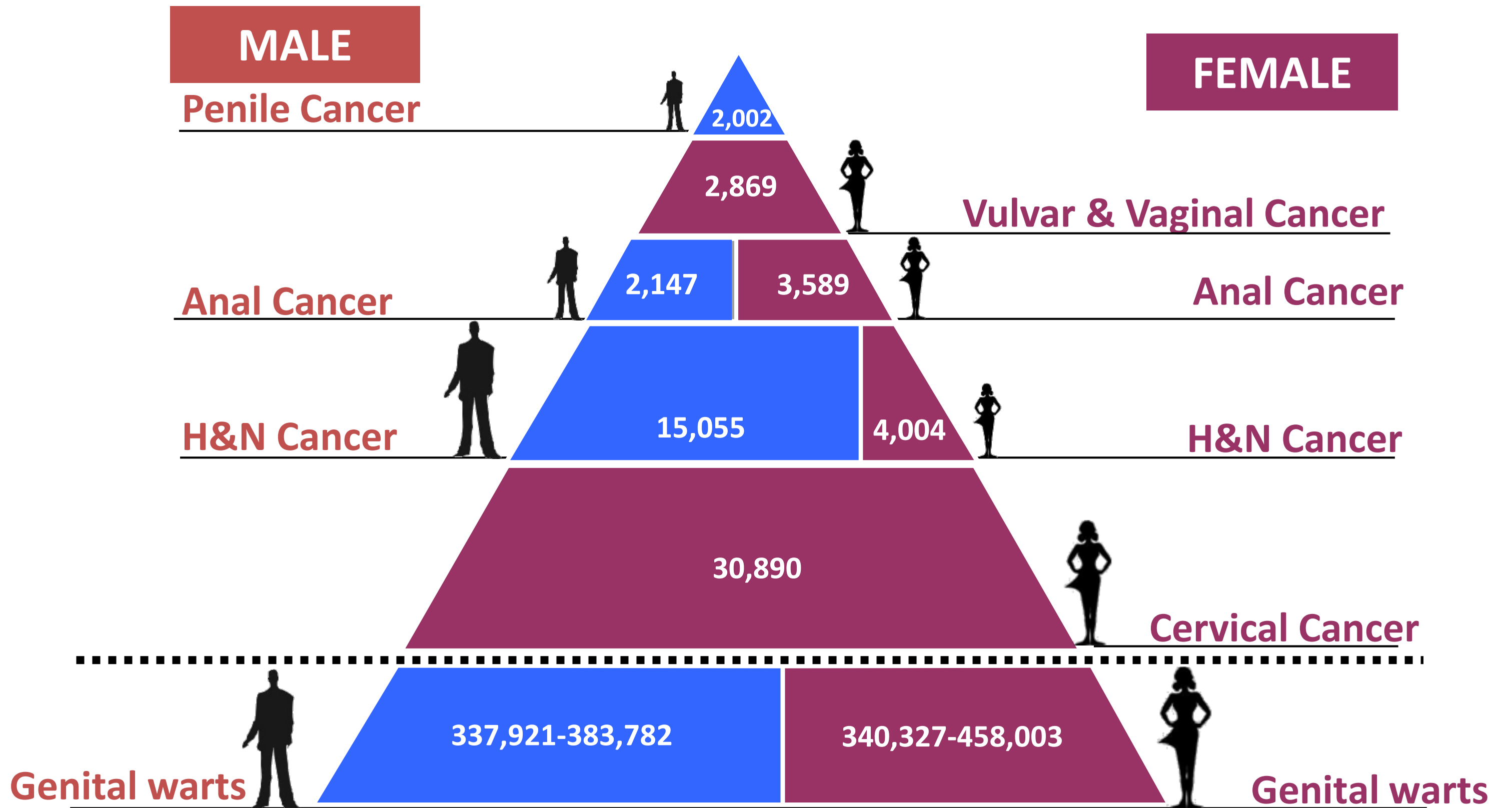
-47.5% decrease in incidence of HGAs (between Jan 2003- Mar 2007 & April 2007-Dec 2009)

High grade cervical abnormalities (HGA) = CIN 2 or worse or adenocarcinoma in situ

Brotherton, J. M. L., Fridman, M., May, C. L., Chappell, G., Saville, A. M., and Gertig, D. M. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. The Lancet, 377[9783], 2085-2092. 2011.

HPV ano-genital Disease Burden Europe

Estimated Annual New Cancers Related to HPV* and Genital Warts Cases Related to HPV#



* HPV 16/18/31/33/45/52/58
\# HPV 6/11

Adapted from Hartwig S et al. Papillomavirus Research 2015

FINAL THOUGHTS

Intimate Partner Violence

- Quantitative, questionnaire
- 350 women with HIV at an East London clinic
- Half the women with HIV (n=191) had experienced intimate partner violence (cf 1:4 UK population)
- 1:7 women reported IPV in the previous year
- 1:7 women reported IPV in pregnancy

Dhairyawan R et HIV Medicine 2012

Disclosure

- Danish questionnaire study 2013-2014
- 234 participants:
  - **Perceived stigma:** >2/3 stated fear of rejection and of being talked about as reasons for non-disclosure
  - **Experienced stigma:** less frequent; 7% encountered negative reactions at disclosure, 23% felt others were frightened and kept a physical distance
  - 75% felt **better** at making life decisions post-disclosure
  - **Internalised stigma** 30% felt infectious and 40% who no longer 'dared' to have sex

Wessman M et al. J Virus Erad. 2017 Jul; 3(3): 140–144.

Undetectable = uninfectious (U=U)

- **Do you routinely discuss U=U with patients?**
  A. Always
  B. Only those who are sexually active
  C. Sometimes
  D. Only if asked by patent

Undetectable = uninfectious (U=U)

- **Do you routinely discuss U=U with patients?**

A. Always