Optimising care for women living with HIV

Laura Waters
Consultant GU/HIV Medicine
CNWL, Mortimer Market Centre
London, United Kingdom
Content

• Epidemiology
• Testing
• Antiretrovirals
  – Efficacy
  – Tolerability & toxicity
• Contraception
• Menopause
• Cardiovascular disease
• Additional considerations
Topics I will not cover today (but are VERY important)

• Bone disease
• Pregnancy & breastfeeding
• Mental health
• Social issues
  – Responsibility & care for others
  – Intimate partner violence
  – Female genital mutilation
  – Migration, asylum
# Global HIV epidemic: 2017

<table>
<thead>
<tr>
<th></th>
<th>People living with HIV in 2017</th>
<th>People newly infected with HIV in 2017</th>
<th>HIV-related deaths 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>36.9 million [31.1 million – 43.9 million]</td>
<td>1.8 million [1.4 million – 2.4 million]</td>
<td>940 000 [670 000 – 1.3 million]</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td>35.1 million [29.6 million – 41.7 million]</td>
<td>1.6 million [1.3 million – 2.1 million]</td>
<td>830 000 [590 000 – 1.2 million]</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>18.2 million [15.6 million – 21.4 million]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>16.8 million [13.9 million – 20.4 million]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Children (&lt;15 years)</strong></td>
<td>1.8 million [1.3 million – 2.4 million]</td>
<td>180 000 [110 000 – 260 000]</td>
<td>110 000 [63 000 – 160 000]</td>
</tr>
</tbody>
</table>

**Source:** UNAIDS/WHO estimates. Accessed 5th September 2018
ECDC: WHO European Region 2016

- >160,000 new diagnoses (>103,000 in Russia alone)
- Male:female ratio = 2.3 (3.2 if confine to EU/EEA)
- Late diagnosis similar by gender....
At time of review >165 000 papers mentioned “HIV” but <5% mentioned the word “female” or “women”
Undiagnosed HIV

• Overall
  – GLOBALLY\(^1\) 25% 2017
  – EU/EEA\(^2\) 15% 2015

• By gender
  – UK 6.6% women & 15.5% heterosexual men 2016
  – Europe More late diagnosis in heterosexuals 2016

• Impacted by nature of epidemic & antenatal testing coverage; national/local individualisation

1. [http://www.who.int/hiv/data/2017_hiv-continuum-care.png](http://www.who.int/hiv/data/2017_hiv-continuum-care.png) accessed 5th September 2018
More missed opportunities for women?

• **More use of medical services:**
  – Reproductive needs, cervical & breast cancer screening

• **Less access to services where testing is routine?**
  – Sexual health services
  – Community testing often MSM focused

• **Interventions**
  – More testing in primary care & other specialist services
  – Home-sampling & home-testing
  – **Simple guidelines: ALL HCP should be able to offer a test!**
HIV in migrant populations

• Survey of 2,009 patients in 9 EU countries, 2013-5¹
• Post-migration HIV acquisition:
  – 63% overall
  – 72% of men who have sex with men (MSM)
  – 58% of heterosexual men
  – 51% of heterosexual women
• Significant association between post-migration HIV acquisition in women and forced sex²
  – Women staying with ‘friends & family’, without stable housing & without a residence permit at higher risk

Antenatal screening for HIV, hepatitis B, syphilis and rubella susceptibility in the EU/EEA

Antenatal HIV screening

• 25/26 had a national infection screening guidance
  – Hungary did not at time of survey

• 24/26 (92%) recommend antenatal HIV testing
  – Hungary & Slovenia did not (reason = limited resources & national epidemiology not supporting need, respectively)
  – 60% publicly funded, 32% via insurance schemes
  – 15 = opt-out, 6 = opt-in (explicit consent), 3 = “universal”

• 23 countries reported type of test
  – 18 = Ab/Ag, 6 = lab Ab, 3 = POCT Ab, 2 = NAAT

## Coverage: 2011 or most recent year

<table>
<thead>
<tr>
<th>Country</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; trim</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; trim</th>
<th>Overall coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain*, Slovakia, Ireland*</td>
<td></td>
<td></td>
<td>99-100%</td>
</tr>
<tr>
<td>Luxembourg, Malta</td>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Netherlands</td>
<td></td>
<td></td>
<td>99.8%</td>
</tr>
<tr>
<td>France*</td>
<td></td>
<td>Risk groups</td>
<td>99%</td>
</tr>
<tr>
<td>Czech Republic</td>
<td></td>
<td></td>
<td>80% 1&lt;sup&gt;st&lt;/sup&gt; tri, 99% overall</td>
</tr>
<tr>
<td>Denmark*, Finland</td>
<td></td>
<td></td>
<td>98%</td>
</tr>
<tr>
<td>Sweden, UK*</td>
<td></td>
<td></td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Norway</td>
<td></td>
<td>Risk groups</td>
<td>95%</td>
</tr>
<tr>
<td>Germany*, Latvia*</td>
<td></td>
<td></td>
<td>Approx 90%</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td>90%</td>
</tr>
<tr>
<td>Estonia</td>
<td></td>
<td></td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Belgium</td>
<td></td>
<td></td>
<td>73-78%</td>
</tr>
<tr>
<td>Romania*</td>
<td></td>
<td></td>
<td>60% 1&lt;sup&gt;st&lt;/sup&gt; tri</td>
</tr>
<tr>
<td>Iceland</td>
<td></td>
<td></td>
<td>50%</td>
</tr>
</tbody>
</table>

*test at delivery if not tested earlier

No national testing rates for Greece or Poland
Cost-effectiveness of HIV screening in pregnancy

• Australian study 2004¹
  – Cost effective at undiagnosed HIV prevalence ≥0.0043%
  – Similar to the 0.0075% undiagnosed HIV prevalence considered cost-effective in a 2000 US study

• Systematic review 2018²
  – All papers confirmed cost-effectiveness of universal screening even in extremely low-prevalence countries
  – Targeted screening valuable if universal not possible
  – Rescreening in late pregnancy worthwhile even if low HIV burden, cost-saving in high prevalence countries

Key messages

KNOW your national/regional antenatal testing policies & rates & CHALLENGE these if necessary!

Use every opportunity to educate your colleagues about HIV testing, feed back about late (and timely!) diagnoses
TREATMENT & OUTCOMES
Gender differences

• Several studies show lower VL, higher CD4 & less inflammation & immune activation despite similar viral reservoir but no evidence of clinical benefit

• Benefit of early ART in START study numerically greater in women

• Women less likely to be diagnosed in early infection?
UNAIDS/WHO estimates:
2017 ART coverage by sex

<table>
<thead>
<tr>
<th>Region</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>53%</td>
<td>65%</td>
</tr>
<tr>
<td>Africa</td>
<td>50%</td>
<td>67%</td>
</tr>
<tr>
<td>W &amp; C Africa</td>
<td>29%</td>
<td>48%</td>
</tr>
<tr>
<td>Europe</td>
<td>54%</td>
<td>52%</td>
</tr>
<tr>
<td>SE Asia</td>
<td>45%</td>
<td>58%</td>
</tr>
<tr>
<td>W Pacific</td>
<td>61%</td>
<td>68%</td>
</tr>
<tr>
<td>America</td>
<td>67%</td>
<td>66%</td>
</tr>
<tr>
<td>E Mediterranean</td>
<td>18%</td>
<td>19%</td>
</tr>
</tbody>
</table>
UK ART coverage by risk group 2016

<table>
<thead>
<tr>
<th>Region</th>
<th>Coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>96%</td>
</tr>
<tr>
<td>Outside London</td>
<td>95%</td>
</tr>
<tr>
<td>London</td>
<td>97%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gay/bisexual men</td>
<td>96%</td>
</tr>
<tr>
<td>Heterosexual men</td>
<td>96%</td>
</tr>
<tr>
<td>Heterosexual men</td>
<td>96%</td>
</tr>
<tr>
<td>PWID</td>
<td>93%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black African</td>
<td>96%</td>
</tr>
<tr>
<td>White</td>
<td>96%</td>
</tr>
<tr>
<td>Other</td>
<td>95%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age group</th>
<th>Coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>89%</td>
</tr>
<tr>
<td>25-34</td>
<td>93%</td>
</tr>
<tr>
<td>35-49</td>
<td>96%</td>
</tr>
<tr>
<td>50+</td>
<td>97%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>95%</td>
</tr>
<tr>
<td>Men</td>
<td>96%</td>
</tr>
</tbody>
</table>

% of people on ART with viral suppression (<200 copies/mL): UK 2012-2016

Gay and bisexual men
Heterosexual men
Heterosexual women
PWID

Delpech & Waters. BHIVA Autumn Conference 2017.
UK CHIC life expectancy: 2014

**Expected age at death**

---

**Men**

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>Viral load ≤400 copies/ml</th>
<th>Viral load &gt;400 copies/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥350</td>
<td>CD4 ≥350</td>
<td>CD4 ≥350</td>
</tr>
<tr>
<td>200–349</td>
<td>CD4 200–349</td>
<td>CD4 200–349</td>
</tr>
<tr>
<td>&lt;200</td>
<td>CD4 &lt;200</td>
<td>CD4 &lt;200</td>
</tr>
</tbody>
</table>

**Women**

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>Viral load ≤400 copies/ml</th>
<th>Viral load &gt;400 copies/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥350</td>
<td>CD4 ≥350</td>
<td>CD4 ≥350</td>
</tr>
<tr>
<td>200–349</td>
<td>CD4 200–349</td>
<td>CD4 200–349</td>
</tr>
<tr>
<td>&lt;200</td>
<td>CD4 &lt;200</td>
<td>CD4 &lt;200</td>
</tr>
</tbody>
</table>

*: Expected age at death for a person aged 35 years with different durations of antiretroviral therapy according to current CD4 count and viral load suppression

May M et al. AIDS 2014;28:1193–1202
ART-CC: life expectancy

http://dx.doi.org/10.1016/S2352-3018(17)30066-8
Key messages

Gender is no barrier to good HIV care outcomes amongst people retained in care.

We ALL have a responsibility to know our local outcomes by gender so we can take ACTION where differences emerge.
ANTIRETROVIRAL OUTCOMES
**Women are under-represented in clinical trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>New agent</th>
<th>Comparator</th>
<th>% Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINGLE</td>
<td>Dolutegravir</td>
<td>Efavirenz</td>
<td>16%</td>
</tr>
<tr>
<td>FLAMINGGO</td>
<td>Dolutegravir</td>
<td>Darunavir/r</td>
<td>15%</td>
</tr>
<tr>
<td>GS-104/111</td>
<td>Genvoya</td>
<td>Stribild</td>
<td>15%</td>
</tr>
<tr>
<td>GS-1489</td>
<td>BIC/FTC/TAF</td>
<td>Triumeq</td>
<td>10%</td>
</tr>
<tr>
<td>GS-1089</td>
<td>Descovoy</td>
<td>Continued Truvada</td>
<td>12%</td>
</tr>
</tbody>
</table>
In general no gender differences but not always....ACTG 5202

first RCT to identify significantly earlier time VF in women randomized to ATV/r vs EFV
Since then....

• Two women only RCTs have shown Truvada + atazanavir/ritonavir is INFERIOR:
  – Stribild (WAVES)
  – Triumeq (ARIA)

• Both these large, women only RCTs were presented at international conferences as POSTERS
Trials in women

• How to improve recruitment?
  – Address prohibitive inclusion criteria (e.g. contraception)
  – Flexible appointments, child care
  – Empower people to ask about trials

• How far can RCTs address concerns about treating women with HIV?
  – Rare outcomes (e.g. teratogenicity)
  – Stigma, social exclusion etc
  – Relative benefits beyond viral suppression
CONTRACEPTION
Emergency contraception: Copper IUD, Levonorgestrel or Ulipristal

- Copper intra-uterine device is the most effective method of emergency contraception

**Levonorgestrel**
- Up to 72 hours after UPSI
- Double dose if enzyme inducers within 28 days
  - Efavirenz CONTRA-INDICATED
  - Boosters may increase levels (no data)

**Ulipristal**
- Up to 120 hours after UPSI
- Efficacy may be reduced by enzyme inducers
  - Efavirenz
  - Boosters may increase levels, unlikely clinically important

FSRH Guidelines for Emergency Contraception (Dec 2017 update); https://www.hiv-druginteractions.org/checker accessed 7th September 2018
Other methods

• **IUD & IUS**
  – Intra-uterine devices & progestogen-based intra-uterine system effective and safe, no DDI

• **DMPA (depot progesterone injection)**
  – No DDI, same dosing interval for women with HIV
  – Reversible BMD loss; concern during adolescence and early adulthood....unknown if use by younger women will reduce peak bone mass & increase fracture risk in later life

• **Implant....**
Efavirenz decreases etonogestrel exposure: a PK evaluation of implantable contraception with antiretroviral therapy

Key messages

ASK women about contraception & ensure they can access information about contraceptive choices

We have enough antiretroviral choice to support women to have any contraceptive method of their choice
MENOPAUSE
Dr Shema Tariq: Queen of menopause & HIV
Menopause: Definitions

• The average age at menopause is 50 years:
  – 95% of women have final period between ages 44 and 56

• Early menopause: ≥12 consecutive months of amenorrhoea due to natural causes at ≤45 years

• Premature menopause: ≥12 consecutive months of amenorrhoea due to natural causes at ≤40 years

• Clinical implications of early/premature menopause:
  – Altered mood & sexual function, decreased quality of life
  – Comorbidities: CVD, bone disease, earlier mortality

Age, Menopause and HIV

• Age of menopause in women living with HIV 46-50 years of age, similar to HIV negative women\(^1-4\)

• Differences in rates of:
  – **Early menopause** reported in these studies as occurring in **22-35%** of women living with HIV\(^1-3\)
  – **Premature menopause** which occurred in **12%**\(^3\)
  – Studies in HIV negative women suggest **early menopause** occurs in 5-10% and **premature menopause** in 1% of the general population\(^1,5\)

---

4. Tariq S et al. BHIVA 2016, P174
Menopause & ART

• ART-näive postmenopausal women have same response to ART as premenopausal women\(^1,2\)

• Pharmacokinetics of some ARVs changes with age:
  – This has been **not** been demonstrated in postmenopausal women compared to premenopausal women taking tenofovir-DF\(^3\) or raltegravir\(^4\)

Confounders?

• Many associations between HIV & various endpoints are attenuated with *appropriate adjustment*

• **Factors associated with age at menopause:**
  - **Smokers:** menopause occurs 1-2 years earlier
  - **Depression:** earlier menopause
  - **Low BMI:** earlier menopause
  - **Injecting drug use:** earlier menopause
  - **Higher socio-economic status:** later menopause
  - **Employment:** later menopause

Primary care management

• Questionnaire study of 88 UK primary care practitioners attending two sexual and reproductive health conferences
• No association between confidence in managing menopause in HIV and respondent gender, age, clinical role, practice size or region (all p>0.05)

<table>
<thead>
<tr>
<th>How confident do you feel managing menopause symptoms?</th>
<th>HIV-negative women, n (%)</th>
<th>HIV-positive women, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confident</td>
<td>85 (97)</td>
<td>40 (47)</td>
</tr>
<tr>
<td>Not confident</td>
<td>3 (3)</td>
<td>46 (53)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Where should menopause be routinely managed?</th>
<th>HIV-negative women, n (%)</th>
<th>HIV-positive women, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mainly within primary care</td>
<td>84 (96)</td>
<td>40 (53)</td>
</tr>
<tr>
<td>By a specialist service</td>
<td>3 (3)</td>
<td>17 (22)</td>
</tr>
<tr>
<td>HIV specialist teams</td>
<td>n/a</td>
<td>18 (24)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
PRIME Study: Positive Transitions Through the Menopause
Headlines

• Menopause symptoms COMMON & UNDER-TREATED
• 47% had not received sufficient information

8% of women (n=21) with hot flushes reported using hormone replacement therapy (HRT)

3% of women (n=10) with vaginal and/or urinary symptoms reported using topical vaginal oestrogens
Hormone replacement therapy (HRT)

• Several modes of delivery
  – Oral, vaginal pessaries, gels/creams, implants

• Indications (may vary by region)
  – Premature menopause (≥40 years)
  – Menopause symptoms (review after 3/12 then annually)

• Dose should be titrated symptoms
HRT

- Pendulum of concerns over the years (GOOD! BAD!)
- Good for symptoms, QoL, fractures
- **Absolute risks if started <10 years post-menopause:**
  - Breast cancer 0
  - Ovarian cancer + 1/1000
  - Thrombosis + 5/1000
  - Stroke + 4/1000
  - Coronary artery disease - 8/1000
  - Death - 6/1000

- **Lowest effective dose for shortest duration possible**

Information courtesy Dr Shema Tariq, UCL
Analysis of 2 major RCTs (combined and oestrogen only HRT)

N=27,347 with 18 years follow-up

All cause, CVD and cancer mortality not increased in either group (compared to placebo)
Additional HRT issues for WLWH

• Drug-drug interactions
  – May influence route of administration?
  – Limited data on HRT & it may differ from hormonal contraception in terms of dose and route so we cannot necessarily extrapolate the results

• Lack of data for relative benefits/risks
  – Bone health
  – Cardiovascular disease
  – Symptom control
Key messages

ASK women about their menstrual cycle & menopause symptoms

HIV and ART are not be a barrier to HRT use or symptom control
CARDIOVASCULAR DISEASE
Cardiovascular disease

- Ageing population
- Multifactorial increased risk of CVD in PLWH
- Women vs men...??
- Additional factors?
  - Lower androgens & oestradiol in pre-menopausal HIV-positive vs HIV-negative women; hormone levels correlate with arterial distensibility
  - DDI between ART and hormones
  - Lack of understanding about hormonal changes over life course and interplay with CV risk

Karim R et al. J Clin Endocrinol Metab. 2013
CVD and HIV

• Little data on CV outcomes by gender
• Early data suggests women post menopause have a rapid increase in CVD
• Ensure you assess CVD risk in ALL patients even if you think the risk is low

<table>
<thead>
<tr>
<th>BHIVA 2016</th>
<th>EACS 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Annual screening in established CVD and those at increased risk of CVD (10 year CVD risk &gt;10%): for hypertension, diabetes, dyslipidaemia &amp; CKD</td>
<td>• 2 yearly risk assessment (Framingham score) Should be performed in all men &gt; 40 years and women &gt; 50 years without CVD</td>
</tr>
<tr>
<td>• Annual review BMI, smoking status and ARVs</td>
<td></td>
</tr>
</tbody>
</table>
POPPY: CVD risk factor management

% that met eligibility criteria for LLDs but were not on them

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>79%</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>n=49</td>
<td>n=66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$p = 0.16$

% that met eligibility criteria for anti-hypertensives but were not on them

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56%</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>n=23</td>
<td>n=25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$p = 0.25$

Tariq S et al. BHIVA 2017 P91
CERVICAL SCREENING
Guidelines

• EACS
  – Screen for all HIV-positive women > 21 years of age or within one year after sexual debut
  – 1-3 yearly interval

• CDC-US
  – Can move to 3 yearly smears after:
    1. Three consecutive normal annual smears
    2. Single normal smear + high risk HPV negative
LAST....BUT FAR FROM LEAST
UNDETECTABLE = UNTRANSMITTABLE
Thank you!

lwaters@nhs.net
@drlaurajwaters