Women and HIV

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Women and HIV

- Epidemiology
- Women and HIV
- Antiretroviral drugs
- Conception and contraception
- Pregnancy
- Long term health
- Hot topics

Global HIV epidemic

Global estimates for adults and children | 2012

People living with HIV	**35.3 million** [32.2 million – 38.8 million]
New HIV infections in 2012	**2.3 million** [1.9 million – 2.7 million]
Deaths due to AIDS in 2012	**1.6 million** [1.4 million – 1.9 million]

World Health Organization

UNAIDS

Global HIV epidemic

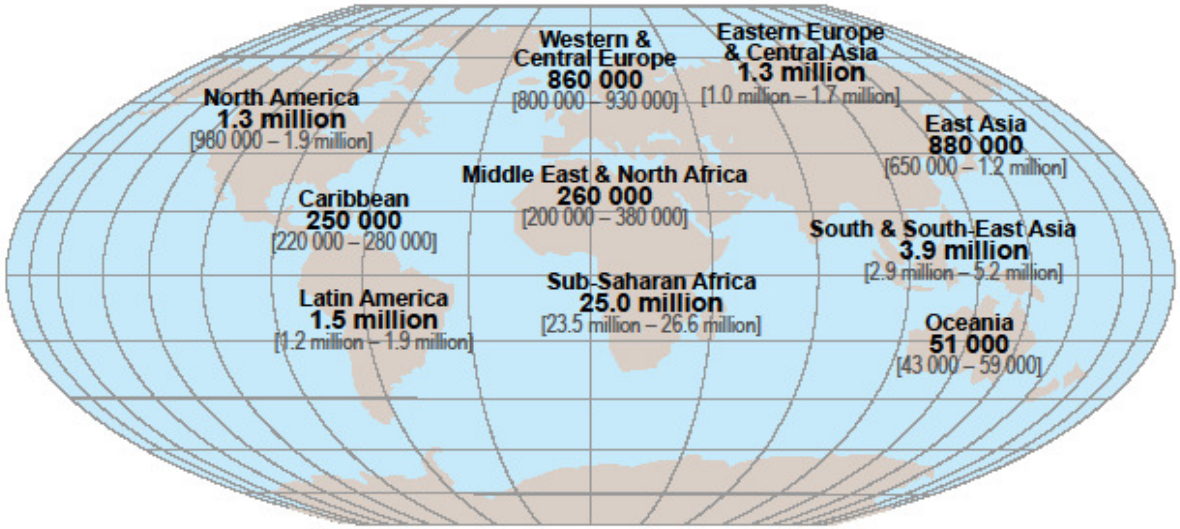
Global summary of the AIDS epidemic | 2012

Number of people living with HIV	Total	**35.3 million** [32.2 million – 38.8 million]
	Adults	**32.1 million** [29.1 million – 35.3 million]
	Women	**17.7 million** [16.4 million – 19.3 million]
	Children (<15 years)	**3.3 million** [3.0 million – 3.7 million]
People newly infected with HIV in 2012	Total	**2.3 million** [1.9 million – 2.7 million]
	Adults	**2.0 million** [1.7 million – 2.4 million]
	Children (<15 years)	**260 000** [230 000 – 320 000]
AIDS deaths in 2012	Total	**1.6 million** [1.4 million – 1.9 million]
	Adults	**1.4 million** [1.2 million – 1.7 million]
	Children (<15 years)	**210 000** [190 000 – 250 000]

World Health Organization UNAIDS

Global HIV epidemic

Adults and children estimated to be living with HIV | 2012



Total: 35.3 million [32.2 million – 38.8 million]

World Health Organization

UNAIDS

HIV in the United Kingdom (UK): 2013

- HIV now a treatable, chronic medical condition
- Over last decade, number living with HIV has increased due:
  - Improved long term survival with antiretroviral therapy (ART)
  - Ageing cohort
  - New infections
- UK epidemic largely among men who have sex with men (MSM) and black-African heterosexual men and women

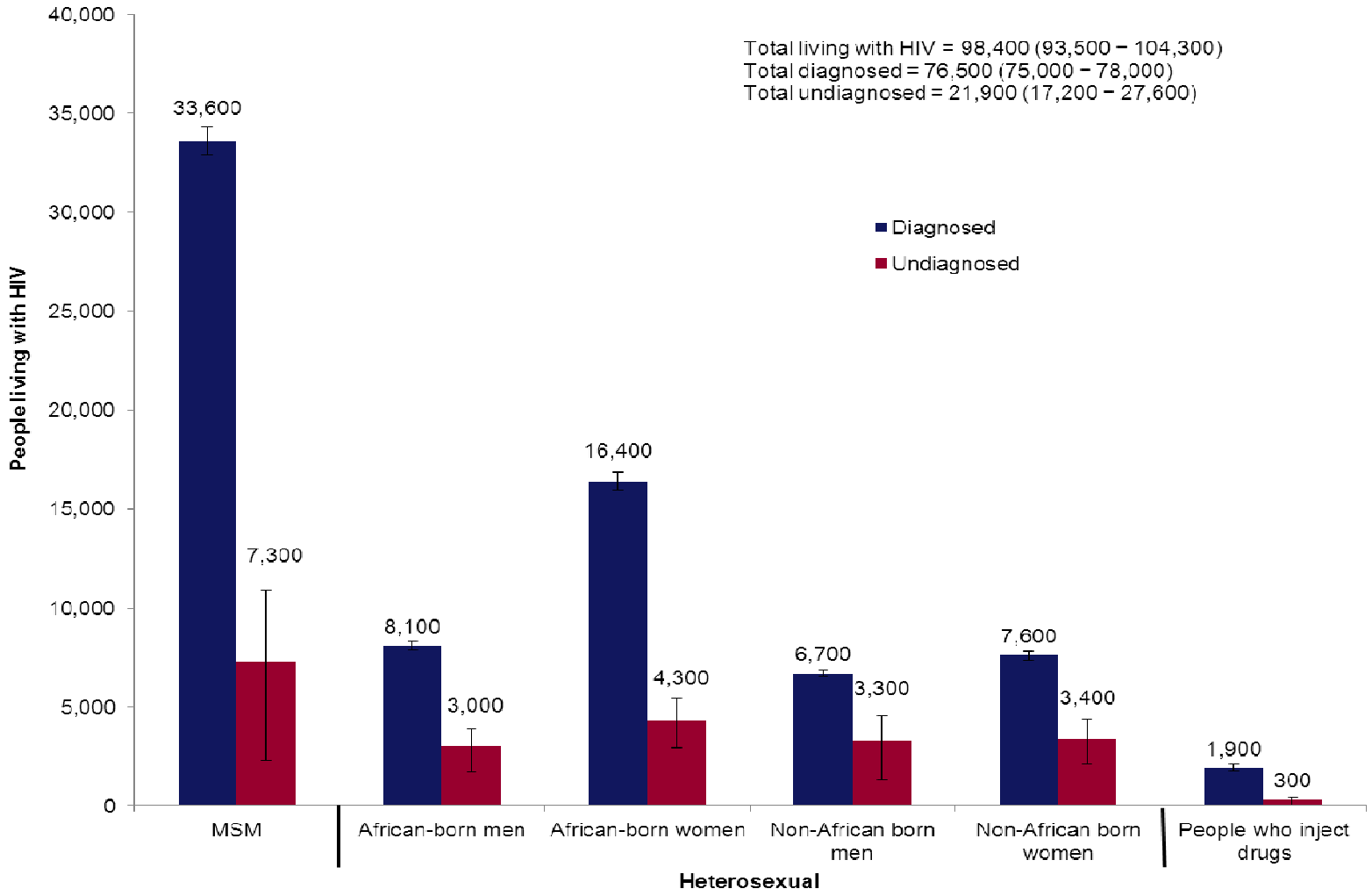
HIV in the UK: 2013*

- By the end of 2012: ~ 98,400 people living with HIV
- ~ 21,900 (22%) undiagnosed and unaware of infection

- 31,700 women
  - ~ 7700 (24%) undiagnosed
  - 20,700 (65%) African-born

* Public Health England. HIV in the United Kingdom: 2013

Estimated number of people living with HIV (both diagnosed and undiagnosed): UK, 2012



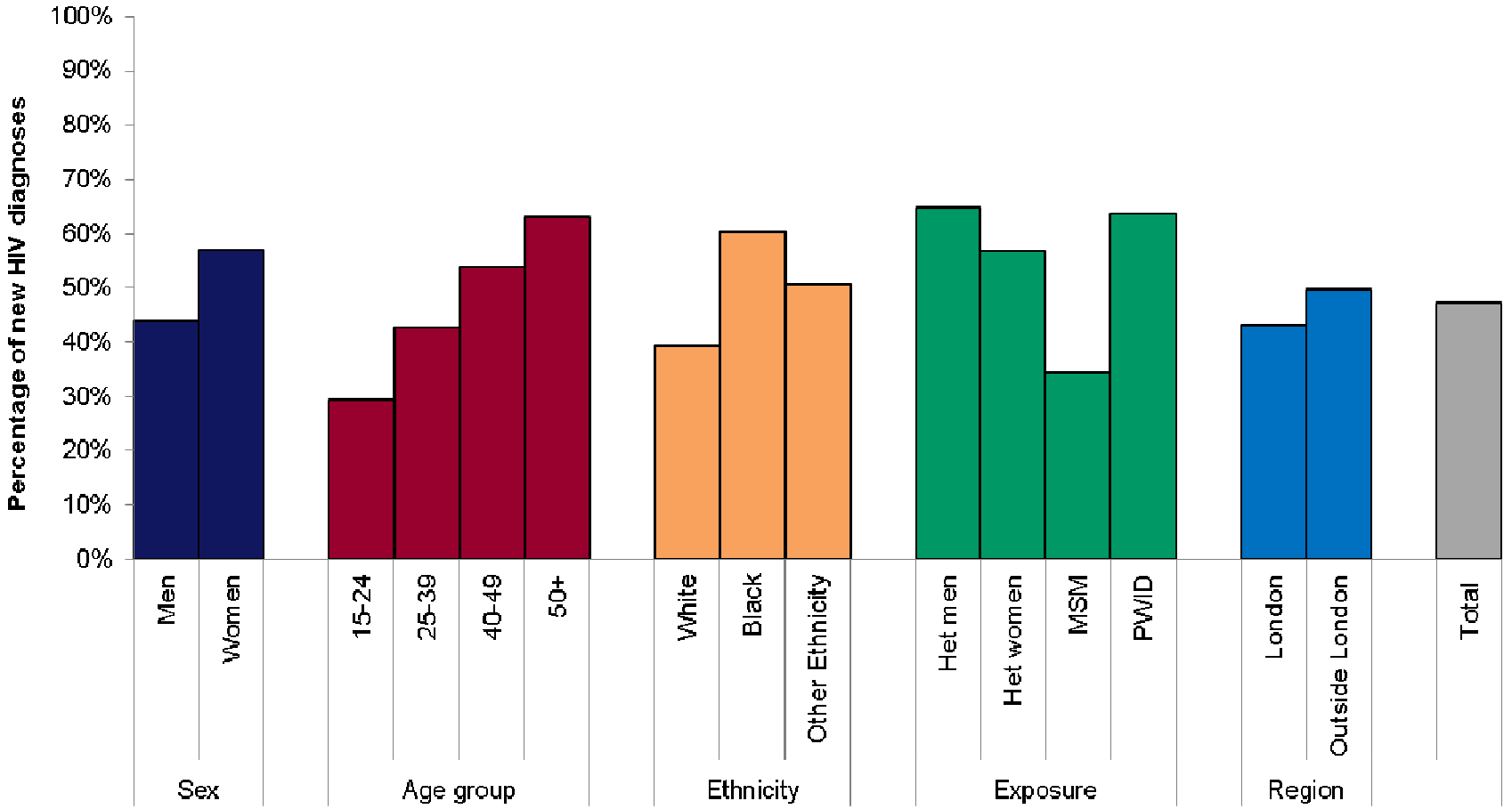
Late Diagnosis

- Defined as CD4<350 cells/mm³ within 3 months of diagnosis
- Associated with poorer prognosis and outcomes
- Over last decade: 81% of 2000 AIDS related deaths in England and Wales due to late diagnosis[1]
- 2012[2]:
  - 47% new diagnoses were late
  - 28% severely immunocompromised (CD4<200 cells/mm³)
  - **~ 57% women diagnosed late**

[1]Simmons RD, Ciancio BC, Kall MM, Rice BD and Delpech VC. Ten-year mortality trends among persons diagnosed with HIV infection in England and Wales in the era of antiretroviral therapy: AIDS remains a silent killer. HIV Med 2013 Nov; 14(10):596-694

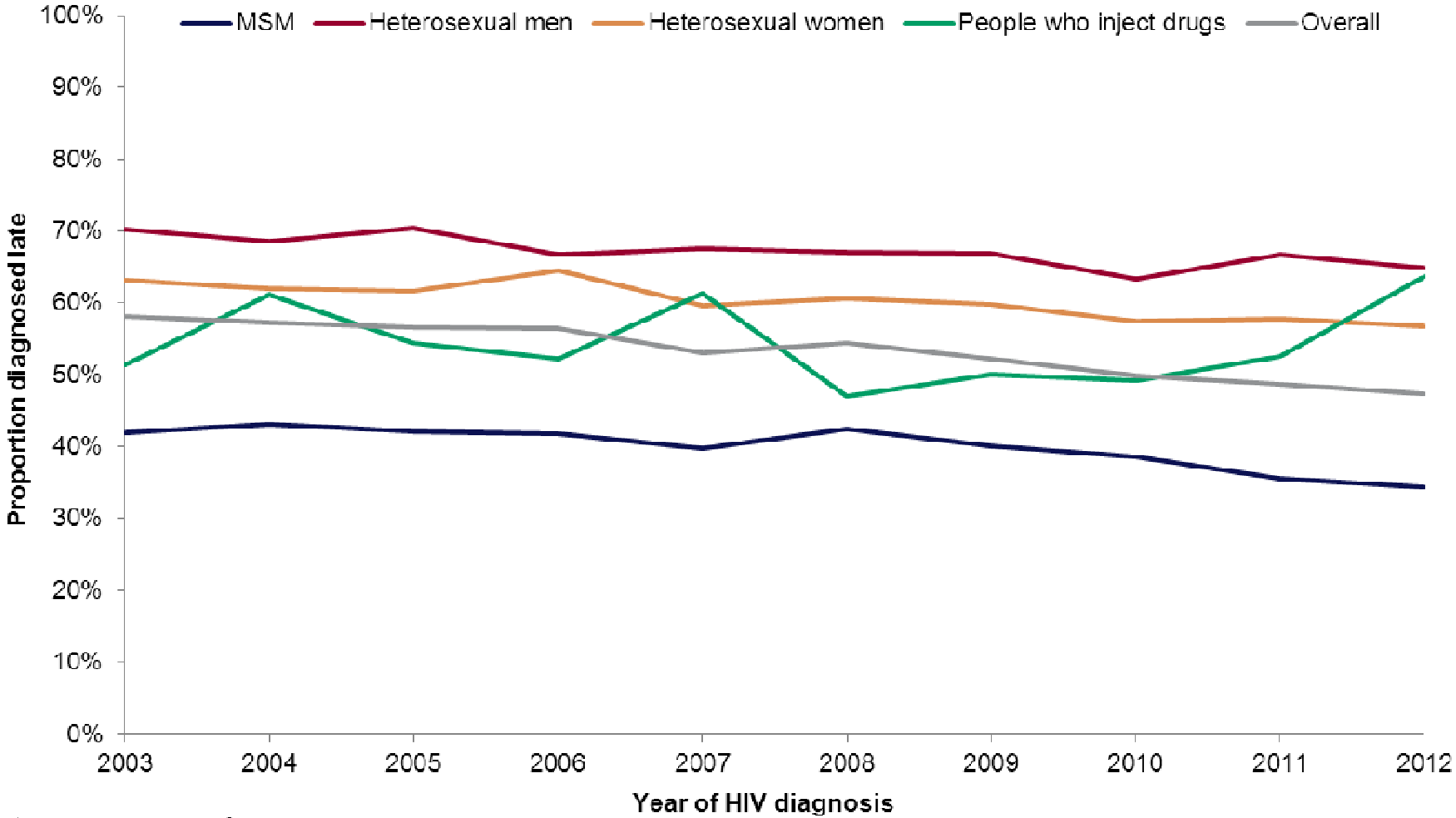
[2] Public Health England. HIV in the United Kingdom: 2013

Attributes of late* HIV diagnosis, UK 2012



* CD4 <350 cells/mm^3 within three months of diagnosis

Trends in late diagnosis* by exposure group: UK, 2003-2012



* CD4 <350 cells/mm^3 within three months of diagnosis

Late diagnoses, AIDS and deaths*

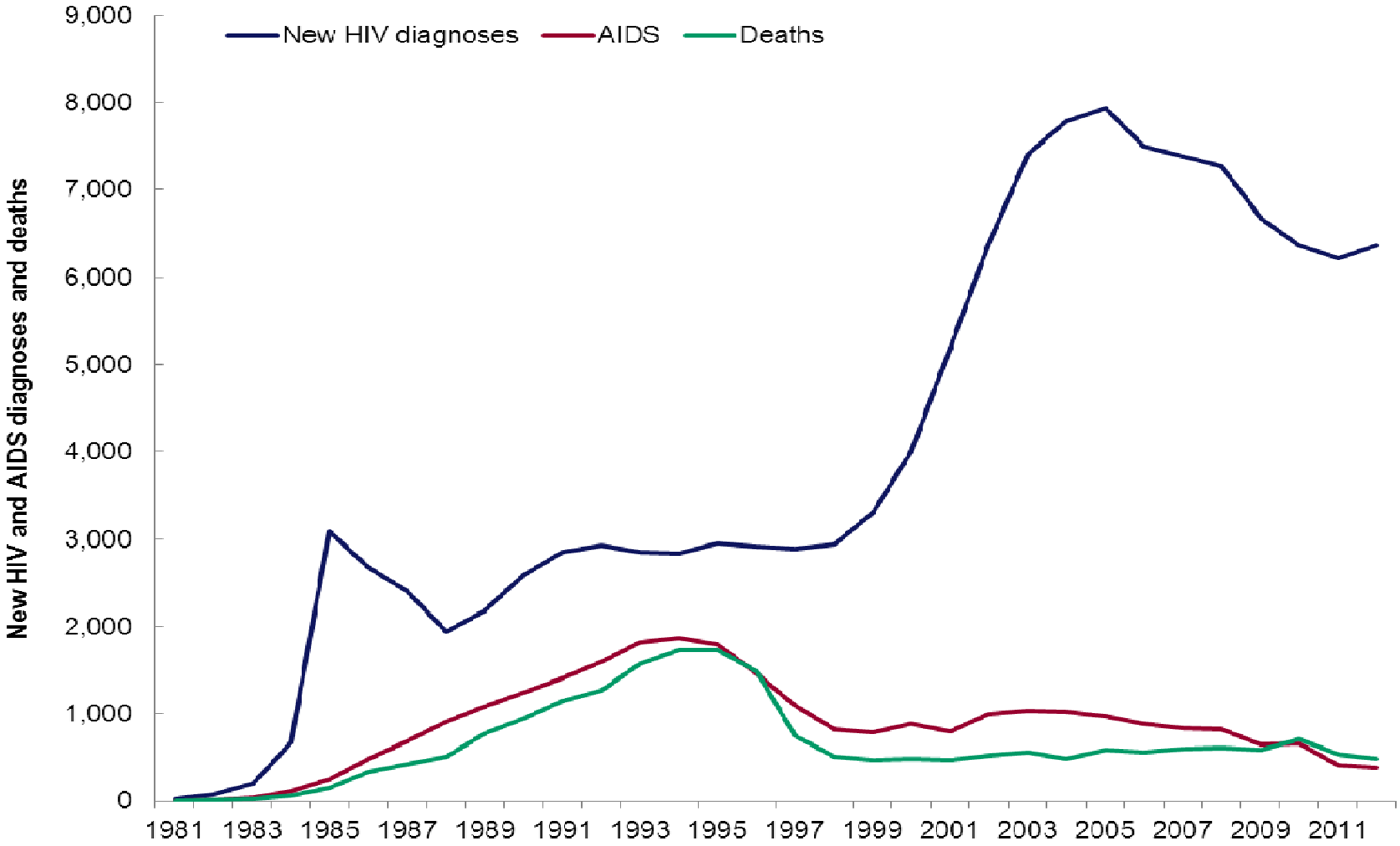
- Decline over last decade
- Deaths mostly in late presenters- x10 increase within first year of diagnosis

- Most common AIDS defining illnesses between 2010-2012:
  - Pneumocystis jirovecii pneumonia (33%)
  - Mycobacterium Tuberculosis (TB) (15%)
  - Kaposi's Sarcoma (7%)
  - Oesophageal candidiasis (9%)

- Important to test, diagnose and treat early
- UK national guidelines: test everybody if HIV prevalence >2/1000
- Leicester City: 3.55 per 1000 (sixth highest outside London)

* Public Health England. HIV in the United Kingdom: 2013

Annual new HIV and AIDS diagnoses and deaths: UK, 1981-2012



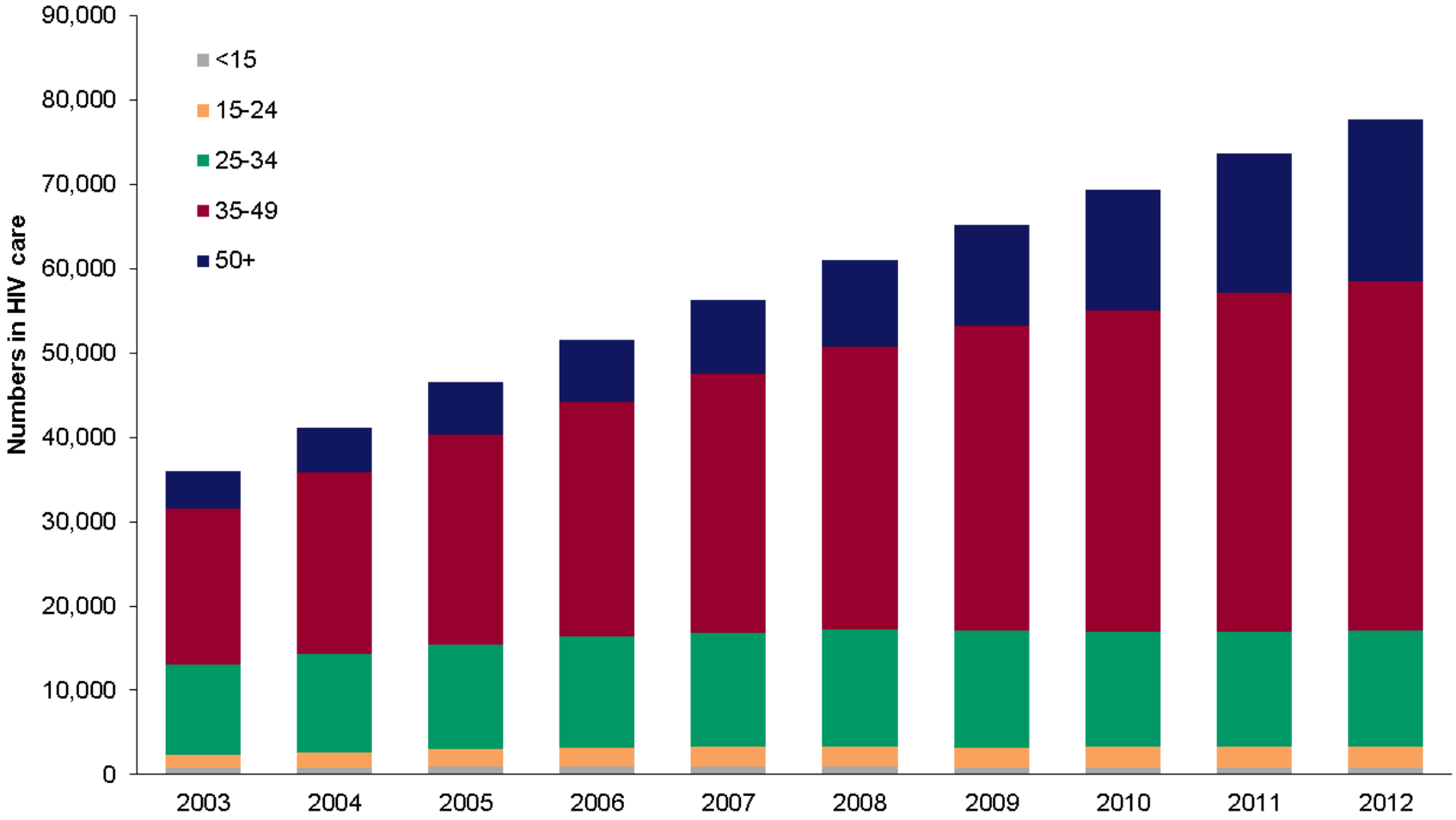
Public Health England. HIV in the United Kingdom: 2013

Number of people accessing HIV Care*

- More than doubled over last decade
- 2012:
  - 77,610 with HIV received care
  - 52,060 men
  - 25,550 women
- Increase due to improved long term survival and on-going transmission
- Increase in number of people age 50 and over accessing HIV related care
- In 2012: one in four adults accessing care were over 50 compared to one in eight in 2003

*Public Health England. HIV in the United Kingdom: 2013

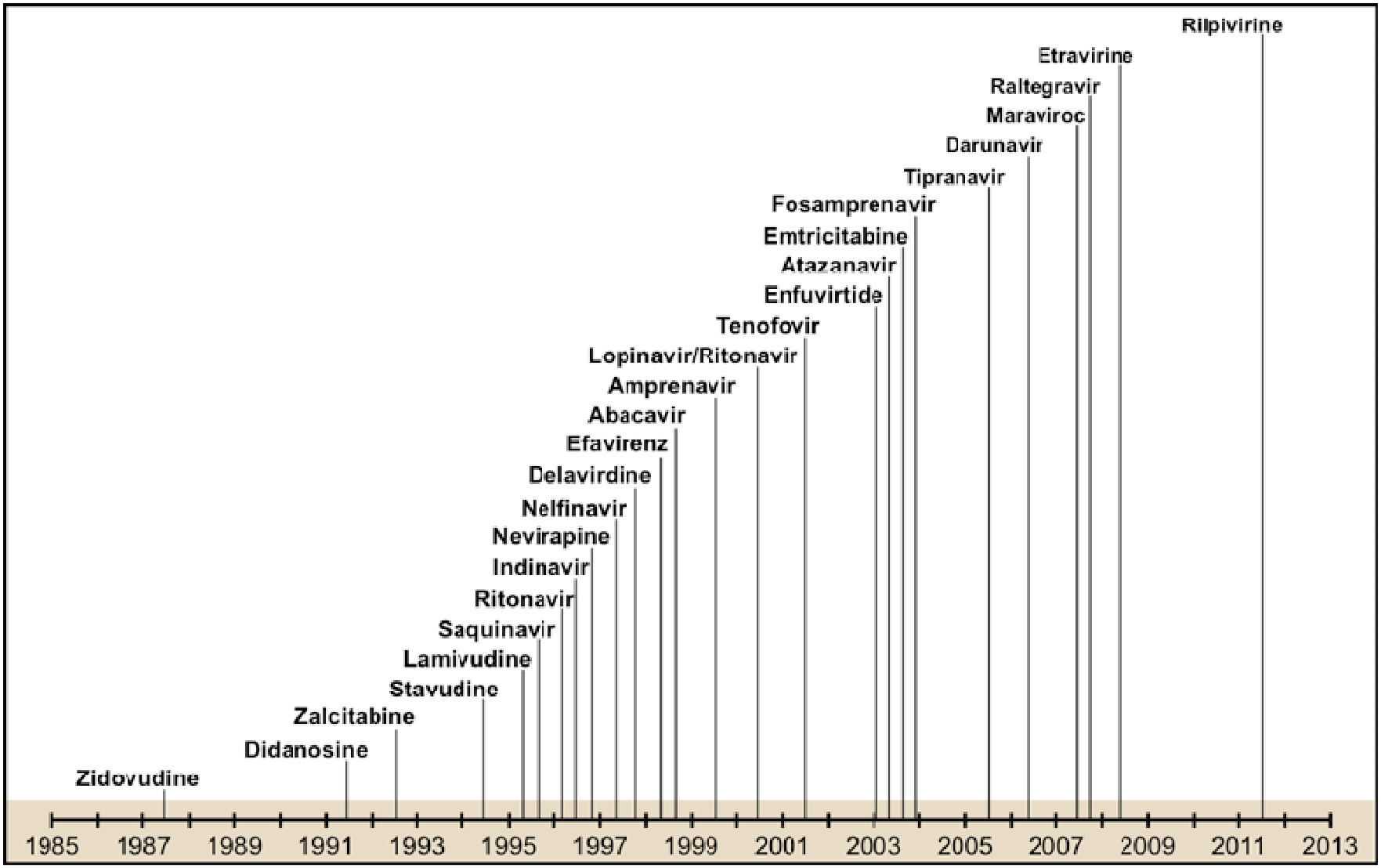
Trends in people diagnosed with HIV accessing care by age group: UK, 2003 – 2012



Antiretroviral Drugs

- HIV is now a treatable medical condition
- Over 20 drugs approved for use
- 5 main drug classes:
  1. Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)
  2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
  3. Protease inhibitors (PIs)
  4. Entry inhibitors
  5. Integrase strand transfer inhibitors

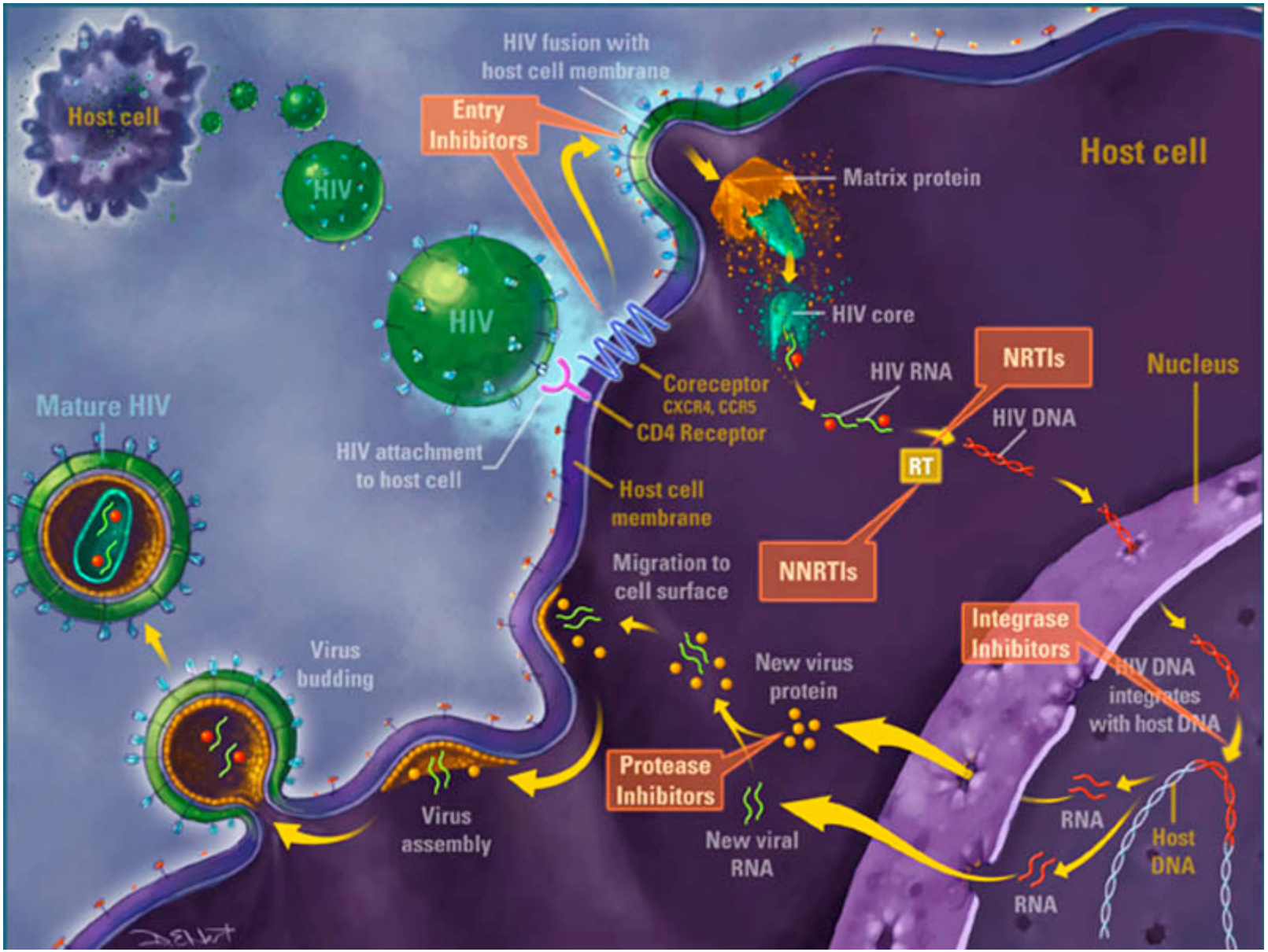
Current Antiretroviral drugs with timeline for FDA (USA) approval



Antiretroviral Drugs

- All drugs work at various points of HIV life cycle to stop replication
- **Always used in combination**
- Usually 2 NRTIs (backbone) + 1 drug from another class
- Examples:
- Truvada (Tenofovir + Emtricitabine) and Efavirenz
- Kivexa (Abacavir + Lamivudine) and Darunavir (+ Ritonavir)

- Compliance very important
- Resistance develops if non-adherence


Host cell
HIV
HIV fusion with
host cell membrane
Entry
Inhibitors
HIV
Host cell
Matrix protein
HIV core
HIV RNA
NRTIs
Nucleus
HIV DNA
RT
Coreceptor
CXCR4, CCR5
CD4 Receptor
Mature HIV
HIV attachment
to host cell
Host cell
membrane
Migration to
cell surface
NNRTIs
Integrase
Inhibitors
HIV DNA
integrates
with host DNA
Virus
budding
New virus
protein
Protease
Inhibitors
Virus
assembly
New viral
RNA
RNA
Host
DNA
RNA

Women and HIV

Why consider women living with HIV as a group?

Women living with HIV

- HIV affects women at various stages of their lives:
- As **Children**
- In **Adolescence**
- **Women of childbearing potential**
- **Menopause**
- **Old age**

Women living with HIV

- HIV can affect women at every stage of their lives
- Different challenges in managing HIV positive women when compared to men
- There is still a high unmet medical need to understand the differences between men and women with HIV
- Women are under-represented in clinical trials for HIV drugs

Women living with HIV

- Many challenges
- Biological and physiological differences between men and women
- Lifetime hormonal changes
- Differences in response to ART
- Limited gender specific data
- Lack of specific guidelines
- Stigma, fear of disclosure
- Social, economic, legal and cultural issues

More discontinuations in women

- Cohort studies- UK Collaborative HIV Cohort Study (UK CHIC)[1] , Swiss HIV Cohort Study[2] and also some randomised controlled drug trials show more discontinuations in women
- Discontinuations due to toxicity
- Differences in ARV pharmacokinetics and pharmacodynamics between men and women
- Some studies demonstrate that for some ARVs, women achieve higher plasma concentrations than men[3’]

1. Barber TJ, et al. Antivir Ther. 2011;16:805–14 . 2.Rosin et al. EACS 2011. 3. Ofotokun et al. Gend Med 2007;4:106–19. 4. Umeh et al. J Clin Pharmacol 2011;51:1665–73.

Women living with HIV: Further issues to consider

- Safe sex
- Contraception
- Conception
- Serodiscordancy
- Toxicity
- Adherence

- Cervical cytology
- Mammogram
- Non-HIV related co-morbidities and risk factors
  - B.P, Cholesterol, DM, Obesity
  - Smoking, alcohol, recreational drugs
- Later life
  - Osteoporosis, menopause, cardiovascular risk

Challenges for women living with HIV of childbearing age

- Fertility
- Pregnancy
- Contraception

Fertility

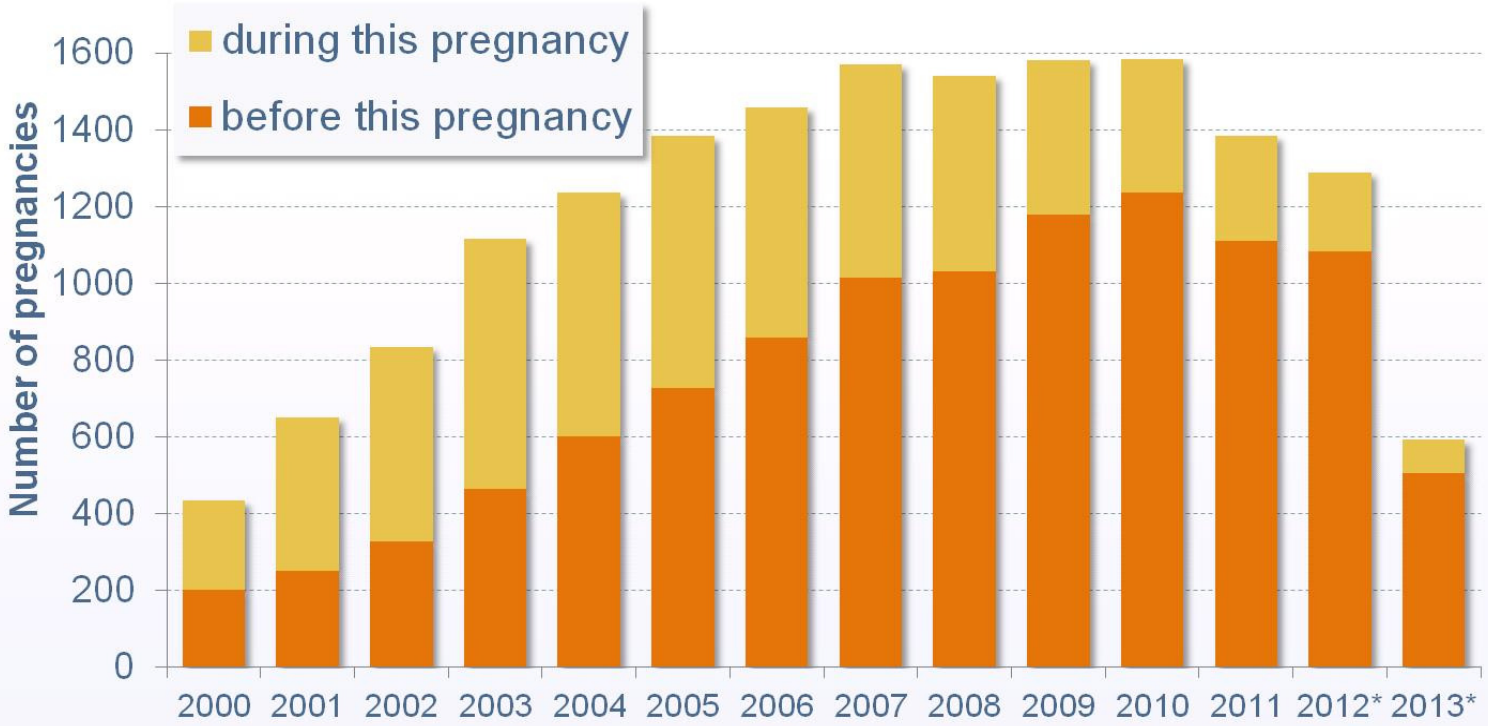
- Infertility and subfertility may occur more frequently in women with HIV[1]
- The reproductive potential of a woman with HIV may not be affected until she becomes ill due to opportunistic infection[2]
- Pregnancy rates are reduced in HIV-positive women undergoing in vitro fertilization (IVF) using their own oocytes[3]

- However:
- Increasing numbers of HIV positive women conceiving on HAART and having more than one pregnancy[4]
  - Improved long term survival
  - More ART drugs and options for HIV positive patients
  - More drug options for HIV positive pregnant women

1. Semprini et al. Women's Health 2008;4:369-82. 2.Ethics committee of the American Society for Reproductive Medicine. Fert Ster 2010;94:11–5. 3. Coll et al. AIDS 2006;20:121–3. 4. National Study of HIV in Pregnancy and Childhood

Timing of maternal HIV diagnosis

UK & Ireland 1998-2013



UK & Ireland pregnancies (all outcomes) reported to NSHPC by June 2013**

MRC Centre of Epidemiology for Child Health

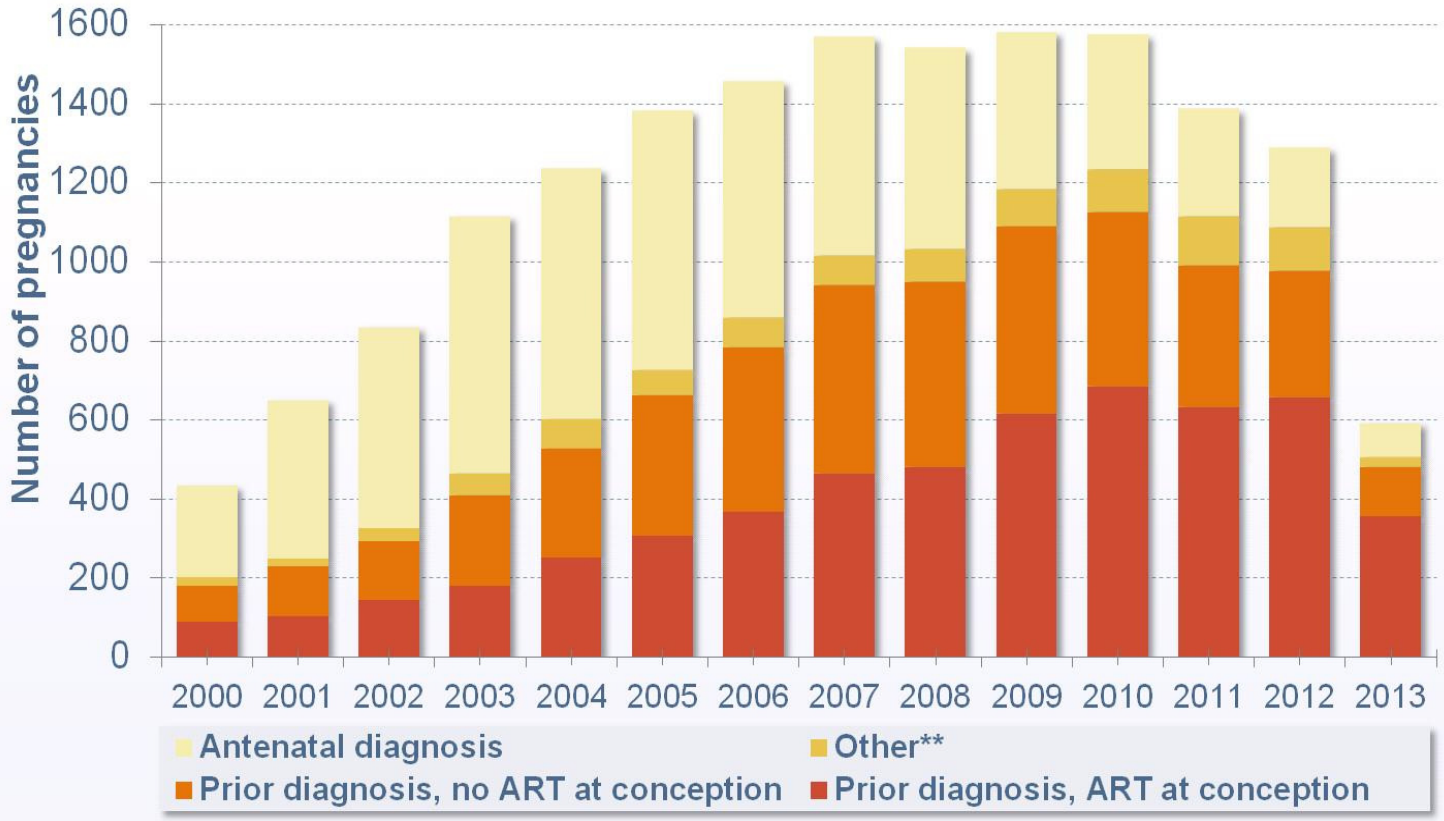
* latest years subject to reporting delay

** includes data from all NSHPC reporting sources

National Study of HIV in Pregnancy and Childhood
NSHPC

Timing of diagnosis & ART at conception

UK & Ireland 2000-2013



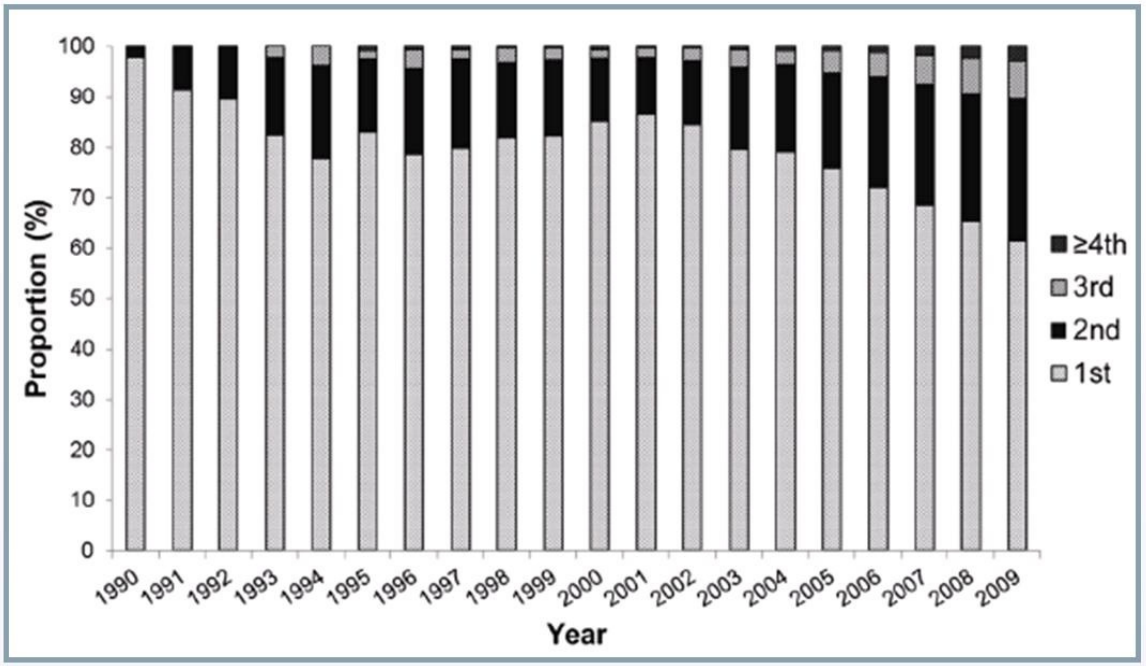
MRC Centre of Epidemiology for Child Health

* All pregnancies reported by June 2013, regardless of outcome
** Other category consists of pregnancies lacking information on precise timing of diagnosis and/or ART use

National Study of HIV in Pregnancy and Childhood NSHPC

Incidence, patterns and predictors of repeat pregnancy among HIV-infected women

UK & Ireland 1990-2009



Proportion of repeat pregnancies*:

1997	20.3%
2009	38.6%

* % of pregnancies in women who had at least one previous pregnancy reported since HIV diagnosis

Proportion of first and subsequent pregnancies by year 1990-2009

MRC Centre of Epidemiology for Child Health

Adapted from C French *et al*.
J Acquir Immune Defic Syndr 2012;59:287-293

National Study of HIV in Pregnancy and Childhood
NSHPC

Conception

Issues to consider and discuss:

- Health before conception
- Identify risk factors for adverse maternal and fetal outcomes
- Prevent mother to child transmission (MTCT)
- Prevent transmission to partner
- Pregnancy planning for discordant couples

Serodiscordancy

- Male circumcision can decrease risk of male infection[1,2]
- Initiating ART immediately associated with 96% relative reduction in HIV transmission to uninfected partner when compared with delayed treatment[3]
- Viral Load (VL) chief predictor of heterosexual HIV-1 transmission[4]
- In absence of other STIs transmission rare if VL <400copies/ml[5]
- Swiss consensus statement (2008): "An HIV-infected person on ART with completely suppressed viraemia (undetectable VL for atleast 6 months) and no other sexually transmitted infections has an extremely low risk (<1:100,000) of HIV transmission even without a condom"[6]

1.Baeten JM, et al. J Infect Dis. 2005;191: 546–53; 2. Quinn TC, et al. N Engl J Med. 2000;342:921–29. 3. Cohen et al. NEJM. 2011;365:493–505. 4. Quinn TC, et al. N Engl J Med. 2000;342:921–2; 5. Attia S, et al. AIDS 2009;23:1397–40;. 6. Vernazza P, et al. Bull Med Suisses 2008;89:165–69.

Conceiving with HIV diagnosis

In all scenarios, should be consistent condom

use and ARV treatment with undetectable VL

- HIV positive female + HIV negative male= female self insemination[1]
- HIV negative female + HIV positive male= sperm washing / adoption / donor sperm[1]
- HIV positive female and HIV positive male= no condoms during ovulation to maximize chances of conception[1]
- ? Pre-exposure prophylaxis (PrEP)

1. BHIVA: UK guidelines for the management of the sexual and reproductive health of people living with HIV infection (2008)

Pre-exposure prophylaxis (PrEP)

- One of 4 HIV transmission prevention methods
- Others: male circumcision, PEPSE, early treatment of positive partner
- RCTs have shown that daily oral Truvada is effective in MSM[1], predominantly heterosexual serodiscordant couples[2] and young heterosexual adults[3]
- PrEP approved for use by FDA in the USA in 2012
- CDC interim guidance for use in MSM and heterosexual adults
- **Including HIV negative women whose partners are HIV positive during conception**

1. Grant RM, Lama JR, Anderson PL, et al. Pre-exposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010;363:2587–99 2. http://depts.washington.edu/uwicrc/research/studies/files/PrEP_PressRelease-UW_13Jul2011.pdf

3. http://www.cdc.gov/nchhstp/newsroom/PrEPHeterosexuals.html

CDC Interim Guidance on PreP use in USA

Before initiating PrEP:

- Exclude HIV infection
- In female: determine if planning pregnancy, is pregnant or breastfeeding
- Establish ongoing high risk of HIV acquisition
- Determine whether partner receiving ART
- Creatinine clearance > 60ml/min
- Screen for and vaccinated against Hep B
- In female: explain that safety in pregnancy not fully assessed but no harm reported
- Do not prescribe if breastfeeding

PrEP regimen:

- Truvada one tablet once daily

Follow up

- Every 2-3 months with HIV and pregnancy tests
- Assess adherence
- Assess risk behaviours; STI screening every 6 months; condom use
- Monitor renal function

The British HIV Association/British Association for Sexual Health and HIV Position Statement on pre-exposure prophylaxis in the UK (2012)

- Recommended only for use in clinical research studies
- Further evidence relevant to UK setting required
- Issues to consider: cost, feasability, drug resistance, toxicity, less condom use, pressure from partners or peers
- PrEP should be cost effective, universally accessible and part of combination prevention package
- Already strong evidence for condoms and early treatment of positive partners

BHIVA: Recommendations for treatment of HIV-positive pregnant women (2012)

Scenario	Recommendation[1]
Conceiving on HAART	Continue HAART even if contains efavirenz or does not contain zidovudine
Naïve to HAART – mother needs ART for herself	Commence treatment as soon as possible
Naïve to HAART – mother does not need HAART for herself	Commence temporary HAART at start of second trimester if the baseline VL is >30K (Consider starting earlier if VL >100,000). All women should have commenced HAART by 24 weeks
Late-presenting woman not on treatment	If after 28 weeks, commence HAART without delay
Maternal viral load uncontrolled on HAART and baby likely to be delivered prematurely	**Consider intensification with therapies such as double dose TDF, RAL or single-dose NVP**

1. de Ruiter, et al. BHIVA Guidelines for the management of HIV infection in pregnant women 2012. Available from: http://www.bhiva.org/documents/Guidelines/Treatment/2012/120430PregnancyGuidelines.pdf

Women, HIV and Pregnancy in the UK

- Due to the success of the introduction of the universal offer of antenatal screening and improved long term survival in HIV infection:
  - Significant decline in MTCT transmission rates in UK (1.3% in 2000-2006; 0.5% in 2007-2011)[1]
  - Of all children born to HIV-infected women in the UK between 2005 and 2011, an estimated 2% became infected with HIV. However, the transmission rate of HIV among children born to women with diagnosed HIV infection was under 1%[2]
  - Increasing numbers of HIV positive women having more than one pregnancy[1]
  - Increasing numbers of HIV positive women conceiving on HAART[1]

1. National Study of HIV in Pregnancy and Childhood 2. Tookey P. Obstetric and paediatric HIV surveillance data from the UK and Ireland. NSHPC 2013. MRC Centre of Epidemiology for Child health, UCL institute of Child Health London. Available from: URL www.ucl.ac.uk/nshpc

Women, HIV and Pregnancy in the UK

- By the end of 2012, ~98,400 people were living with HIV in the UK with ~21,900 (22%) unaware of infection[1]
- ~ 31% diagnoses were in women[1]

- In 2012, 675,800 pregnant women were screened for HIV in England, comprising an uptake rate of 98% [2]

- Of these, 1,310/675,800 (0.19%)were positive and one in 2,500 (0.04%) were newly diagnosed[2]

1. Public Health England. Available at https://www.gov.uk/government/organisations/public-health-england
2. Tookey P. Obstetric and paediatric HIV surveillance data from the UK and Ireland. NSHPC 2013. MRC Centre of Epidemiology for Child health, UCL institute of Child Health London. Available from: URL www.ucl.ac.uk/nshpc

Antiretroviral Pregnancy Register (APR)

- Prospective database providing best data on teratogenicity and 1st trimester ART exposure

- Records rates of congenital birth defects in 1st trimester exposure to ART compared to background rates and 2nd and 3rd trimester exposure

- Records show no **No** increased risk with Zidovudine, Lamivudine, Ritonavir, Abacavir, Tenofovir, Emtrcitabine, Lopinavir, Atazanavir, Nevirapine, Efavirenz

Management of UK HIV Positive Pregnant Women

- The risk of MTCT in appropriately managed pregnancies continues to be low in UK and Ireland
- Transmission rates of <1% [1] due to:
  - Effective ART
  - Appropriate management of delivery
  - Avoidance of breastfeeding

- A study of 2,561 women with HIV showed that *in utero* HIV transmission was associated with:[2]
  - Recent HIV infection (p=0.006)
  - Viral load at delivery (p<0.0001)
  - Younger age (p=0.02)

- Cohort data from UK and Europe have shown MTCT rates of < 0.5% in women with plasma VL<50 HIV RNA copies/ml taking HAART irrespective of mode of delivery[3]

1. National Study of HIV in Pregnancy and 2. Taha, et al. AIDS 2011:25;1357–64 Childhood 3. BHIVA guidelines for the management of HIV infection in pregnant women 2012

Mode of delivery

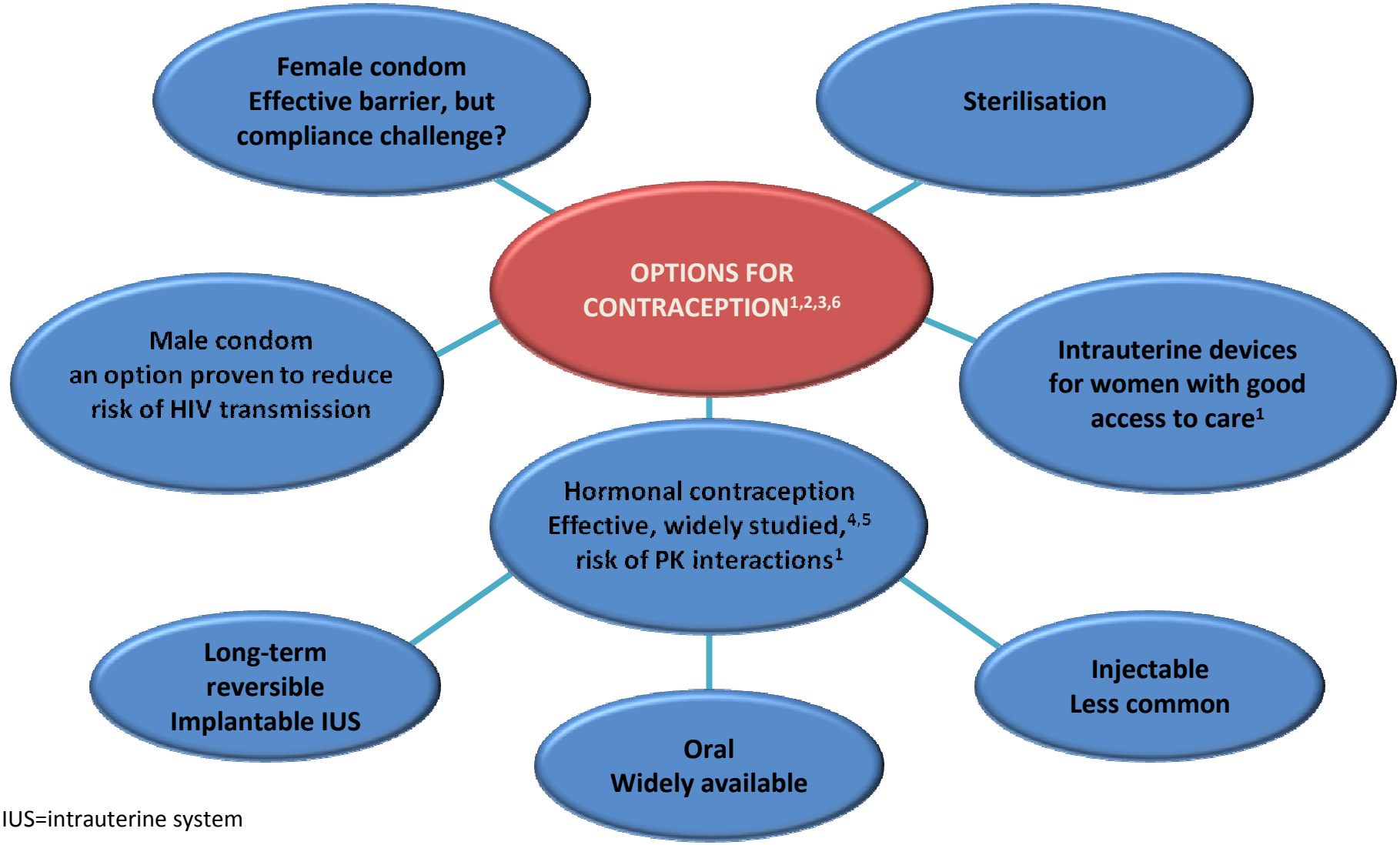
Published cohort data from UK and Europe show MTCT rates of <0.5% in VL < 50 HIV RNA copies/mL if taking HAART irrespective of mode of delivery[1]

- Pregnant HIV positive women taking HAART in UK and Ireland 2000-2006[2]
  - No difference in MTCT rate whether planned CS (0.7%) or planned vaginal delivery (0.7%)
  - Median VL on HAART <50 HIV RNA copies/mL

- ANRS French Perinatal cohort[3]
  - 5271 women delivering between 1997-2004- 48% on HAART
  - In VL < 400 copies/mL no significant difference in MTCT rates in ECS group (0.4%) compared with vaginal delivery group (0.5%)
- ECS data[4]
  - 5238 women delivering between 1985 and December
  - In 960 delivering with VL < 50 HIV RNA copies/mL, elective CS associated with 80% decreased risk of MTCT (AOR 0.2; 95% CI 0.05-0.65) adjusting for HAART and prematurity
  - Only 2 transmissions among 599 women delivering with VL < 50 HIV RNA copies/mL (MTCT 0.4%)

1.De Ruiter, et al. BHIVA Guidelines for the management of HIV infection in pregnant women 2012.Availablefrom:http://www.bhiva.org/documents/Guidelines/Treatment/2012/120430PregnancyGuidelines.pdf2. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. AIDS 2008: 22: 973-981 3. Warszawaski J, Tubiana R, Le Chenade J et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. AIDS 2008; 22: 289-299 4. Boer K, England K, Godfried MH, Thorne C. Mode of delivery in HIV infected pregnant women and prevention of mother-to –child transmission: changing practices in Western Europe. HIV Med 2010; 11: 368-378

Contraception



IUS=intrauterine system

1. Heikinheimo O, et al. Hum Reprod Update 2009;15:165–76; 2. Cates W. JAIDS 2005;38 Suppl 1:S8–10; 3. Mitchell HS, et al. Sex Transm Infect. 2004;80:167–73; 4. Cejtin HE, et al. AIDS 2003;17:1702–4; 5. Richardson BA, et al. AIDS 2007;21:749–53; 6. Waters L, et al. J Fam Plann Reprod Health Care 2006;32:10–4.

BHIVA guidelines recommendations

- Consistent condom use and additional contraception method
- If not on ART, all available contraceptive methods are suitable but N-9 spermicide should be avoided

- COC, POP and etonogestrel implant may be less effective in those on HAART – due to **induction of liver enzymes**
- Role for COC, POP, Implant in conjunction with an additional method
- DMPA, LNG-IUS and Cu-IUD not known to be affected by liver enzyme inducers, and effective options with HAART

- Cu-IUD is recommended method of emergency contraception for women on HAART.
- If POEC is used, a doubling of the standard dose to 3 mg stat (immediately) is recommended

COC=combined oral contraceptive pill; POP=progestogen-only pill; DMPA=depot medroxyprogesterone acetate; LNG-IUS=levonorgestrel intrauterine system; Cu-IUD=copper-bearing intrauterine device; POEC=progestogen-only emergency contraception

Fakoya et al. HIV Medicine 2008:9:681–720.

Women, HIV and later life

- Risk factors associated with ageing, HIV and ARV drugs

- Overlapping risk factors:
  - Cardiovascular
  - Bone
  - Renal

- HIV positive women more likely to have earlier menopause compared to HIV negative

- Important to ensure that HIV positive women are included in national screening programmes- cervical, bowel, breast etc

Hot Topics

1. PrEP
2. ? Cure for HIV infection
   - USA 2013: child who had acquired HIV from mother was given ARV as soon as diagnosis made. HIV negative despite only taking treatment for a few months
   - Believed that early treatment stopped formation of hard to treat viral reservoirs
   - UK: CHERUB Collaboration (Collaborative HIV Eradication of Viral Reservoirs: UK BRC)
   - New approach to HIV therapeutics in UK
   - Biomedical research in to cure

Summary

- Worldwide ~ 50% of HIV infected are women
- UK ~ 30%
- Improved long term survival
- Increasing drug options
- Increasing numbers of women having more than one child and conceiving on HAART
- Very low MTCT rates in UK
- Women ageing with HIV: overlapping risk factors of ageing, HIV and ARV drugs
- Important to screen and manage appropriately