# Treatment of Early and Late cases – Dr Mike Youle

# New HIV cases in the WHO European Region

In 2013 there were

**80% MORE**

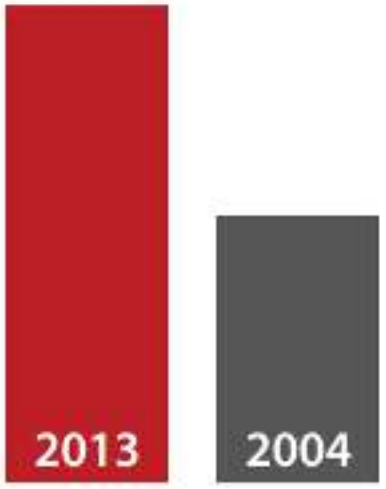
new HIV cases
compared to 2004

Average number of new HIV cases per 100 000 people:

**6.6**

**1.9**

**22.0**



# EARLY TO CARE PATIENTS

**Management of genital infections (STIs)**

**Microbicides**

**Cervical Barriers**

**Condo**

**Male cumcision**

**Behavior Counseling Testing**

**ophylaxis**

**Treating**

Other STI

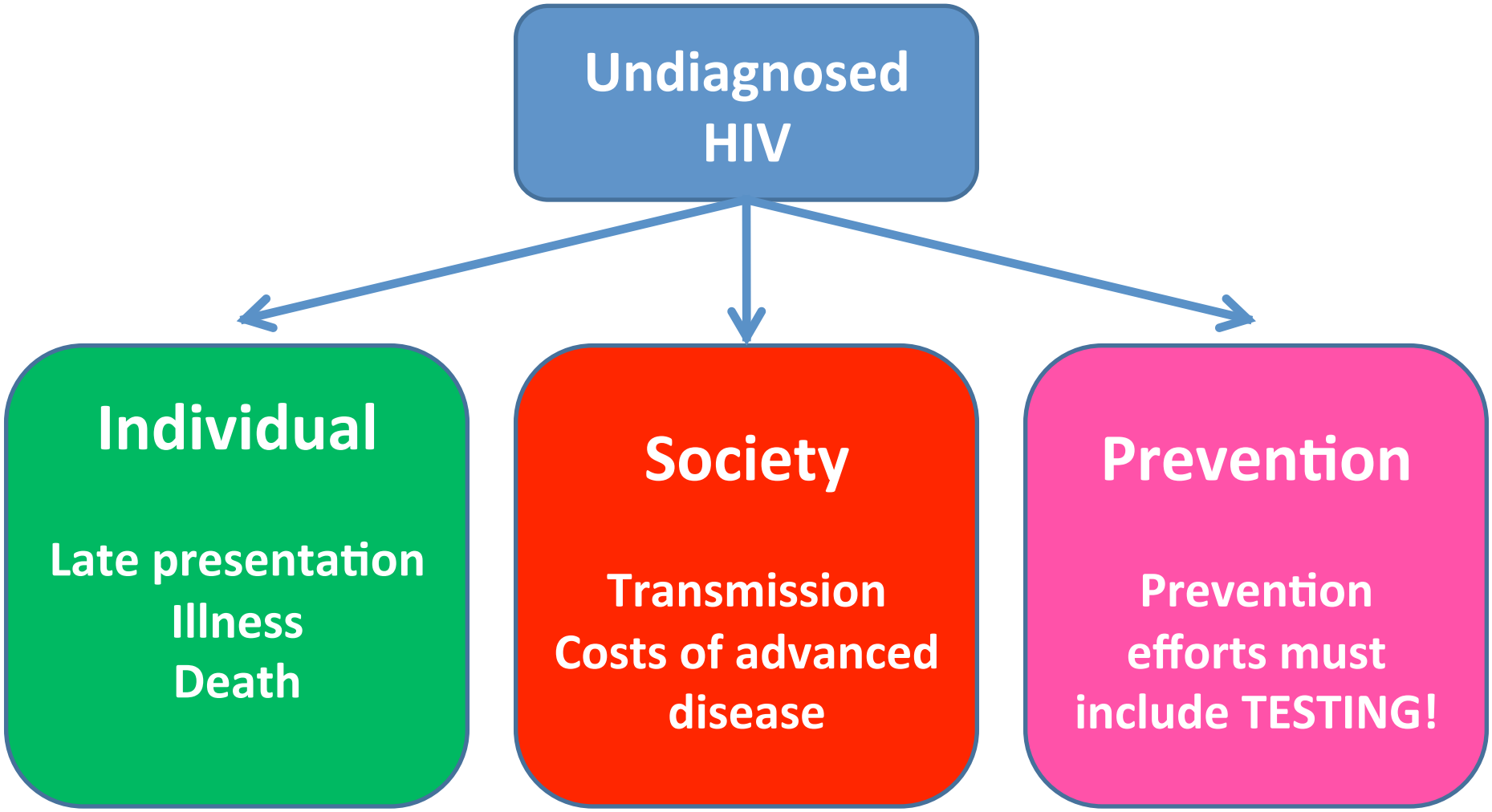
**PEP**

**PrEP**

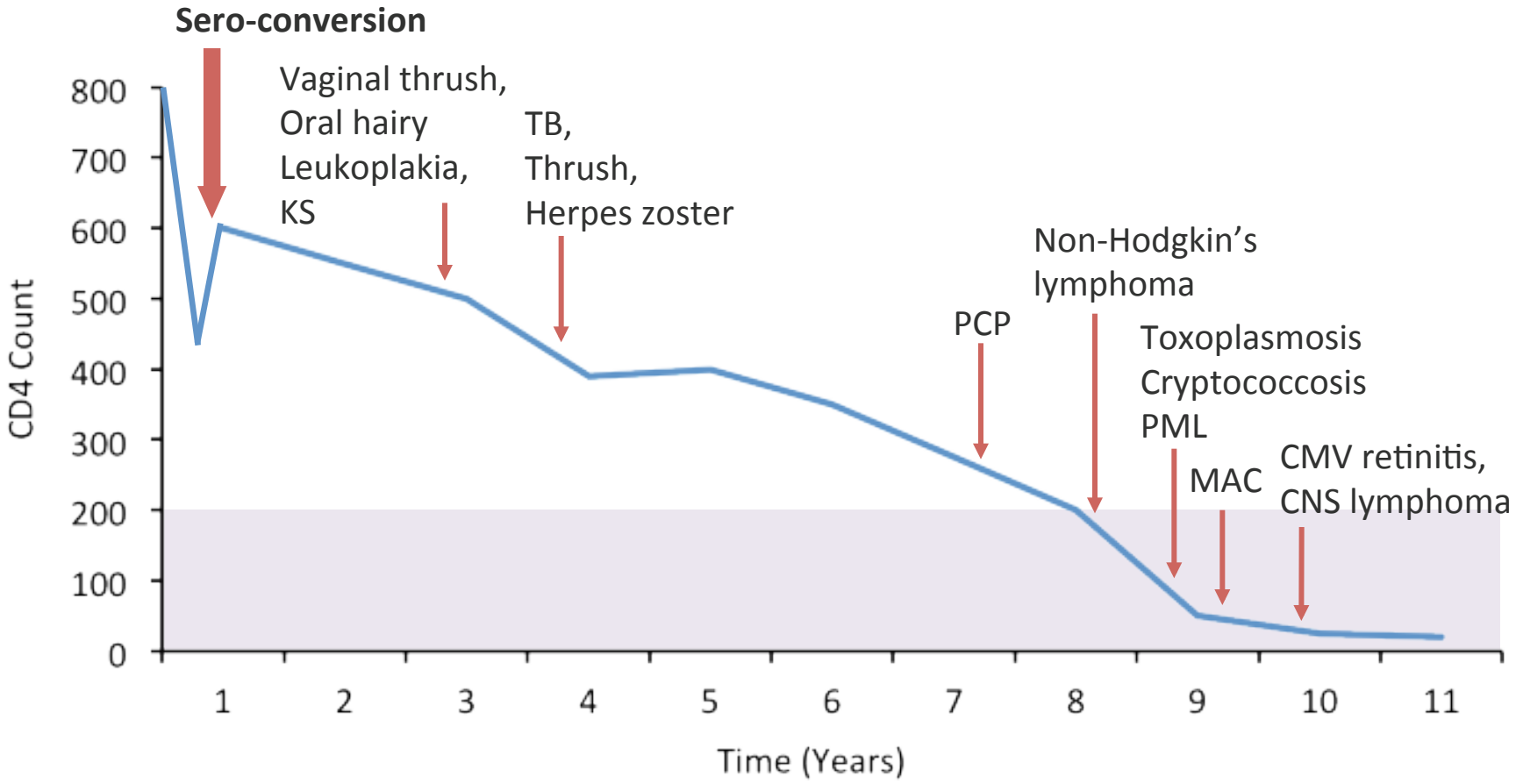
**ART**

**You cannot prevent if HIV is not diagnosed!!**

# Implications of undiagnosed HIV



# Untreated HIV infection




CMV, cytomegalovirus; CNS, central nervous system; KS, Kaposi's sarcoma; MAC, *Mycobacterium avium* complex; PCP, pneumocystis jiroveci pneumonia (formerly known as pneumocystis carinii pneumonia); PML, progressive multifocal leukoencephalopathy; TB, tuberculosis

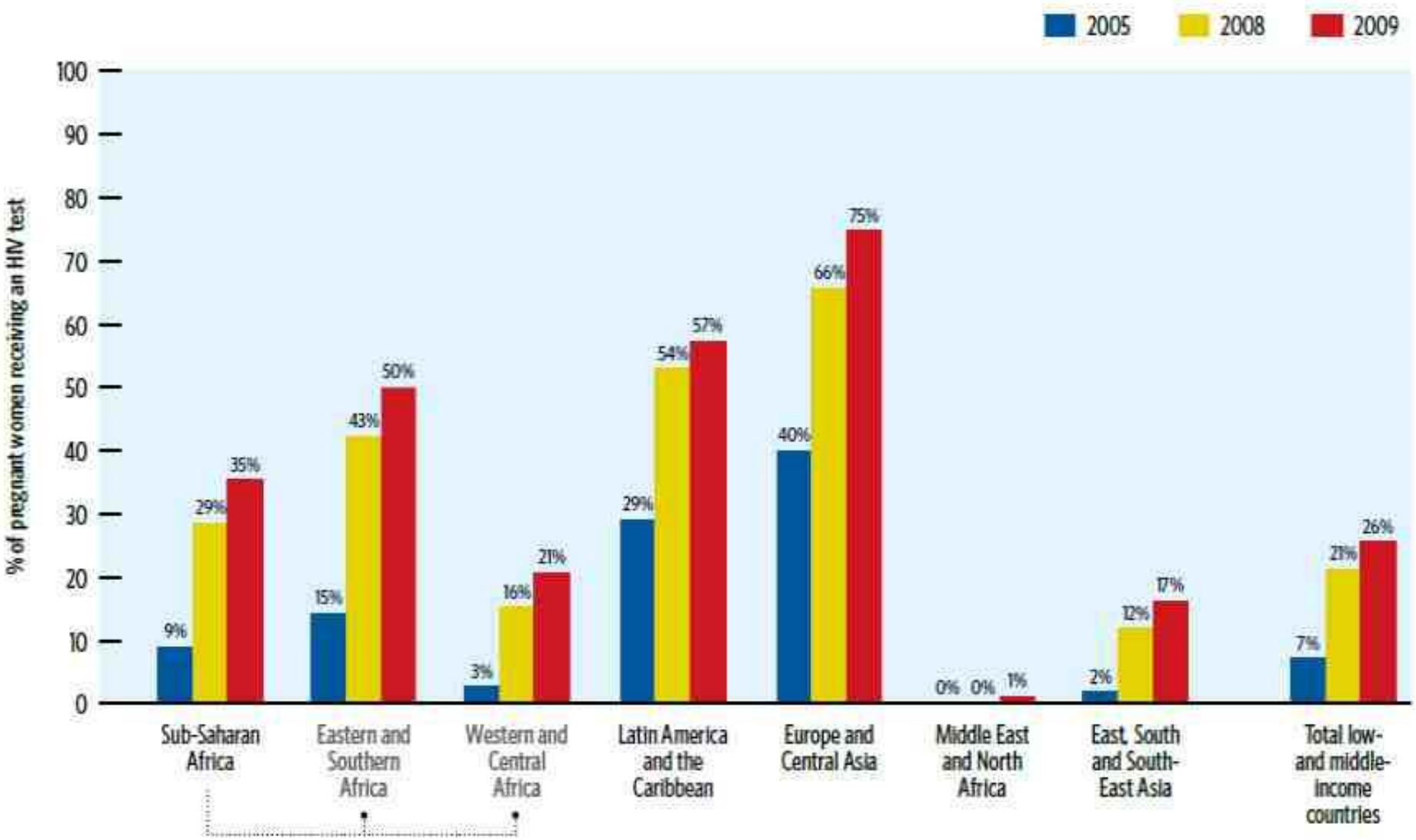
Adapted from: Jung, Paauw. *J Gen Intern Med* 1998;**13**:131–6 and Pantaleo *et al. New Engl J Med* 1993;**328**:327–35

# Getting better….& worse: incidence

- In 33 countries HIV incidence has fallen by **>25%** between 2001 & 2009:
  - 22/33 in sub-Saharan Africa
  - Biggest epidemics (Ethiopia, Nigeria, S Africa, Zambia, & Zimbabwe) stabe or declining
- **BUT** in seven countries HIV incidence increased by **>25%** between 2001 & 2009:
  - 5/7 in Eastern Europe and Central Asia

UNAIDS 2010 Global report

# % pregnant women having an HIV test by region: 2005, 2008, 2009



# Overcoming barriers

- Normalising HIV testing
- Specialist ‘counselling’ not required
- Testing ‘anonymously’
- Point of care testing
- Testing outside ‘traditional’ settings
- EDUCATING HEALTH CARE WORKERS!!!

# British Guidelines

- **Everyone attending particular services:**
  - Sexual health, antenatal & termination clinics
  - Drug dependency programmes
  - TB, hepatitis B/C & lymphoma services
- **If local prevalence >2 per 1000, test:**
  - All men and women registering in primary care
  - All general medical admissions
- **All individuals with 'indicator diseases'**

# UK

- UK target for antenatal testing = **95%**
- 2011 uptake **97%**
- What is the risk of mother to child transmission without treatment?
- What is the risk of mother to child transmission with effective treatment?

# HIV in Europe: Indicator Diseases

- Sexually Transmitted Diseases
- Malignant Lymphoma
- Cervical or anal dysplasia or cancer
- Herpes Zoster
- Hepatitis B or C virus infection
- Ongoing mononucleosis-like illness
- Leukocytopenia or thrombocytopenia
- Seborrheic dermatitis / exanthema

http://www.hiveurope.eu/Project3IndicatorDiseases/tabid/72/Default.aspx

*We'll be doing some blood tests and one of those will be a test for HIV….*

# LATE TO CARE PATIENTS

# Undiagnosed HIV

- Where we have data up to 1/3 cases of HIV **UNDIAGNOSED**

# Late diagnosis

- Up to 40% of new diagnoses in **Europe**
- Common characteristics:
  - Migrant status
  - Older age
  - Heterosexual status
  - Male gender

# Late presentation of HIV infection: A consensus definition

Two definitions were agreed upon, as follows.

- *Late presentation:* Persons presenting for care with a CD4 count below 350 cells/μL or presenting with an AIDS-defining event, regardless of the CD4 cell count.
- *Presentation with advanced HIV disease:* Persons presenting for care with a CD4 count below 200 cells/μL or presenting with an AIDS-defining event, regardless of the CD4 cell count.

**Currently, should we consider 500 CD4+ cell counts/mm$^3$?**

Antinori A, et al. for the European Late Presenter Consensus working group HIV Medicine 2011;12:61–4

# LTC patient profile: Epidemiology

**Europe:** 51.7% of individuals presented LTC in 2010/11 vs. 57.3% in 2000

- COHERE study of 84,524 HIV-infected people from 35 European countries where 53.8% were late presenters (CD4+ cell count: <350 cells/$mm^3$)
- A high rate of late presentation to care has remained unchanged for several years

**North America:** 54% of individuals presented LTC in 2007 vs. 62% in 1997 (CD4+ cell count <350 cells/$mm^3$)

- 35–45% of newly diagnosed individuals have AIDS within a year of diagnosis

**Asia:** 36.6% of individuals across 13 countries presented LTC in 2011 vs. 79.1% in 2007 (CD4+ cell count <200 cells/$mm^3$)

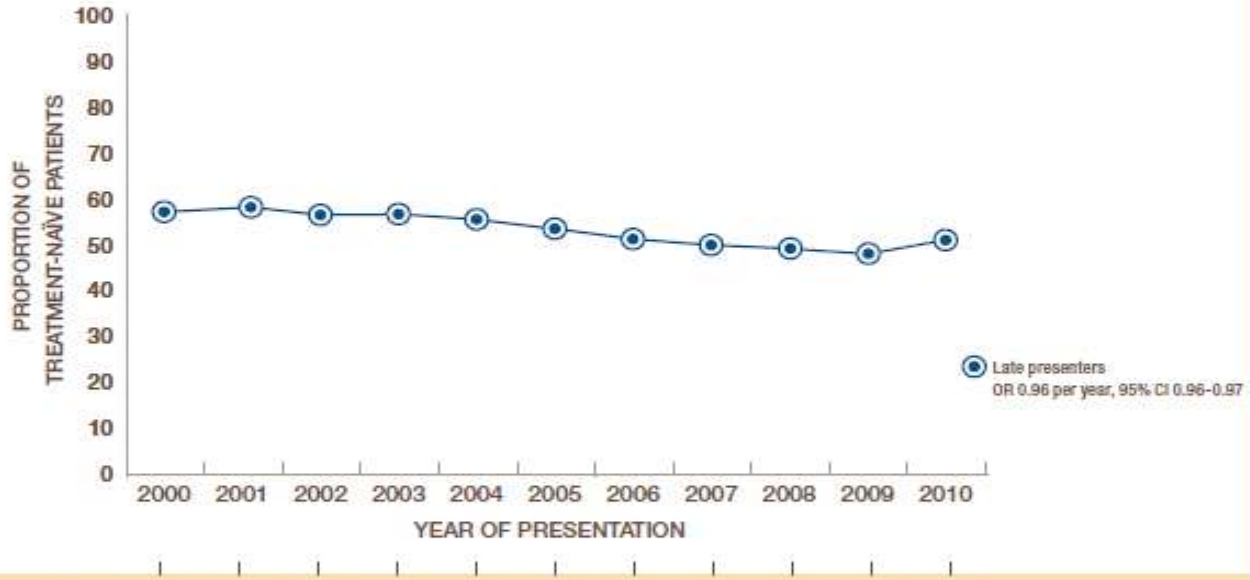
**Latin America:** 61% of individuals in Mexico City presented LTC in 2001–2008 (CD4+ cell count of <200 cells/$mm^3$ or AIDS defining event)

Antinori A, et al. HIV Med 2011;12:61–4; Althoff KN, et al. Clin Infect Dis 2010;50:1512–20; Gardner EM, et al. Clin Infect Dis 2011;52:793–800; Kiertiburanakul S, et al. J AIDS 2014;7:18804; Mocroft A, et al. PLoSONE 2013;10:e1001510; Crabtree-Ramírez B, et al. Salus Pub de Mexico 2012;X:506–14

# Treatment for Late-to-care Patients

**Despite the many advances made in HIV, over 50% of patients present late**
**to care across the Europe**

## Proportion of individuals presenting late by year of presentation[35]



# What are the consequences of starting late?

## Short Term

**Lower CD4 recovery**
**Higher incidence of ADIs**

**Higher risk of mortality in the 1st year**
ART CC and ART LINC, Lancet 2006;367: 817–24

**Reduced chance of viral suppression**
Waters L, HIV Med 2011;12:289–98

**Increased risk of hospitalization**
Sabin CA, AIDS 2004;18:2145–51

**More potential drug-drug interaction**
Rockstroh JK, Antivir Ther 2010;15 (S1):25–30

**More likely to have IRIS**
Barber D, Nature Rev 2011;10:150

## Long Term

**Increased risk of non-AIDS events**
Reekie, AIDS 2011;25:2259–68

**Increased risk of neurocognitive impairment**
Ellis RJ, AIDS 2011;25:1747–51

**Potentially increased risk of HIV transmission**
Cohen MS, N Engl J Med. 2011;365:493-505

**Higher direct cost of care**

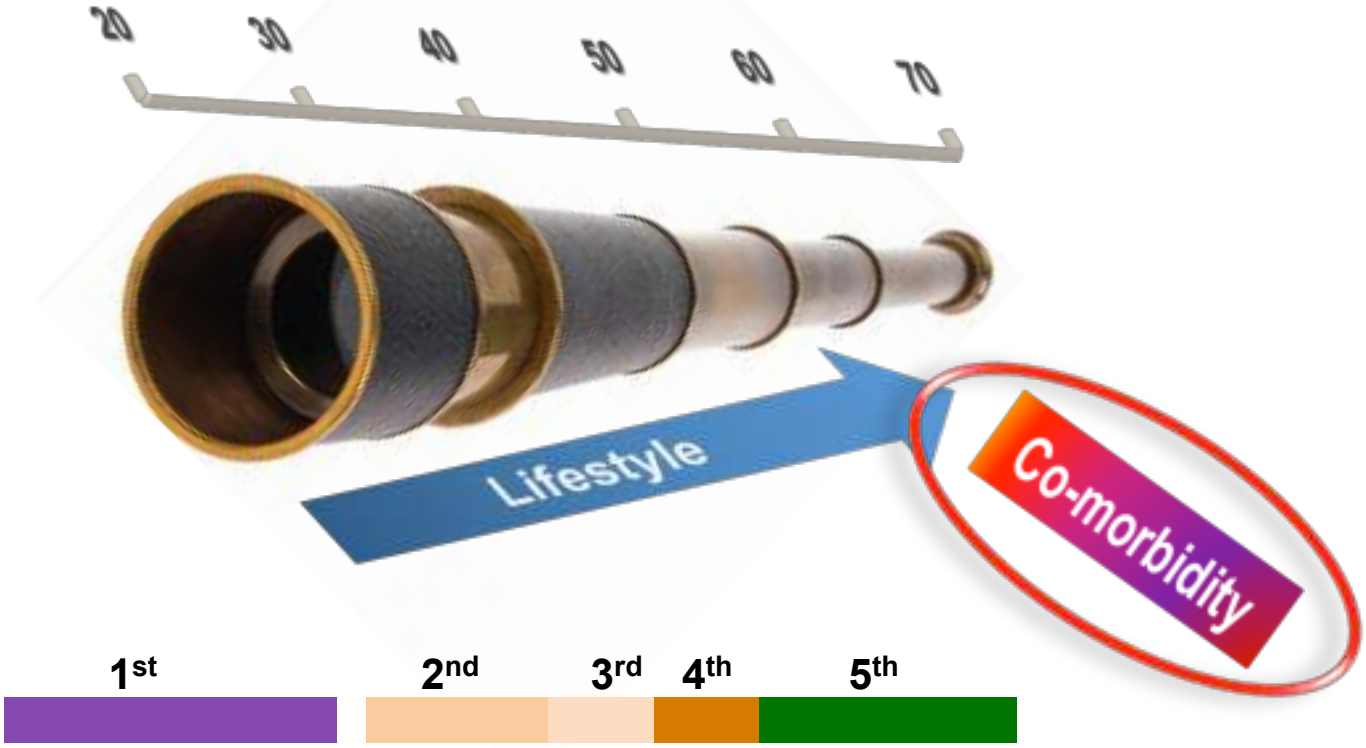
Waters and Sabin, Expert Rev Anti Infect Ther. 2011;9:877–89

# LONG-TERM MANAGEMENT OF HIV TREATMENT

# To Begin

- HIV treatment is a marathon
- Treatment options may be limited despite new advances
- First treatment should be carefully picked
- **Efficacy** and **resistance** issues are two important factors for a sustainable success in HIV treatment

# Antiretroviral stewardship



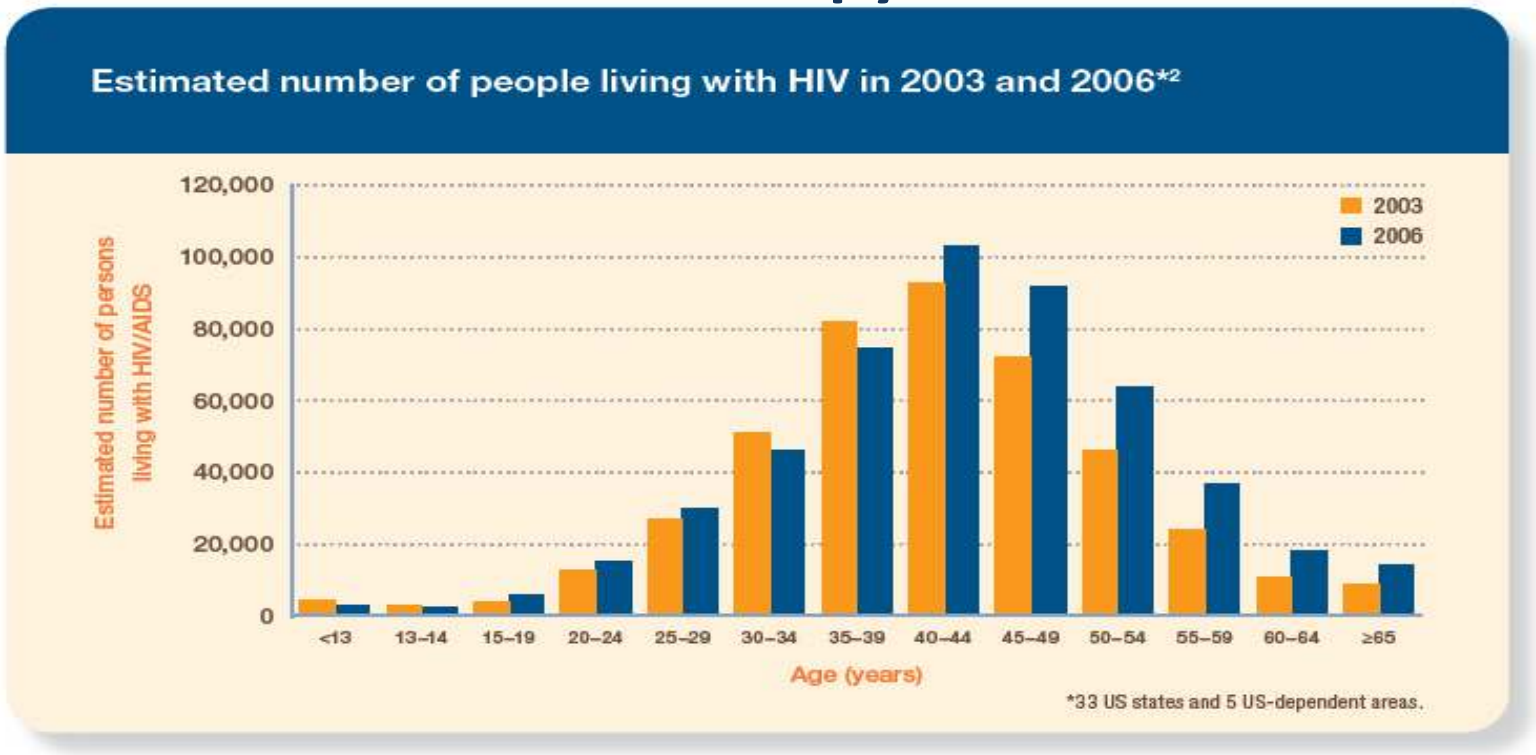

## Plan now

- What to give?
- When to start?
- How to manage?

## For then

- Minimise resistance
- Minimise toxicity
- Normalise immunity

# HIV is a chronic disease requiring lifelong suppressive therapy




- Although mortality rates have not been reduced to those of the general population, most young HIV-infected persons undergoing treatment have estimated survivals of at least 35 years after diagnosis, according to a 10-year population based cohort stufy in Denmark.

# HIV patients are living longer

**50** years of therapy

A person in the Us or Canada strating on ARV therapy at the age of can expect to live about 50 additional years*

**25** switches

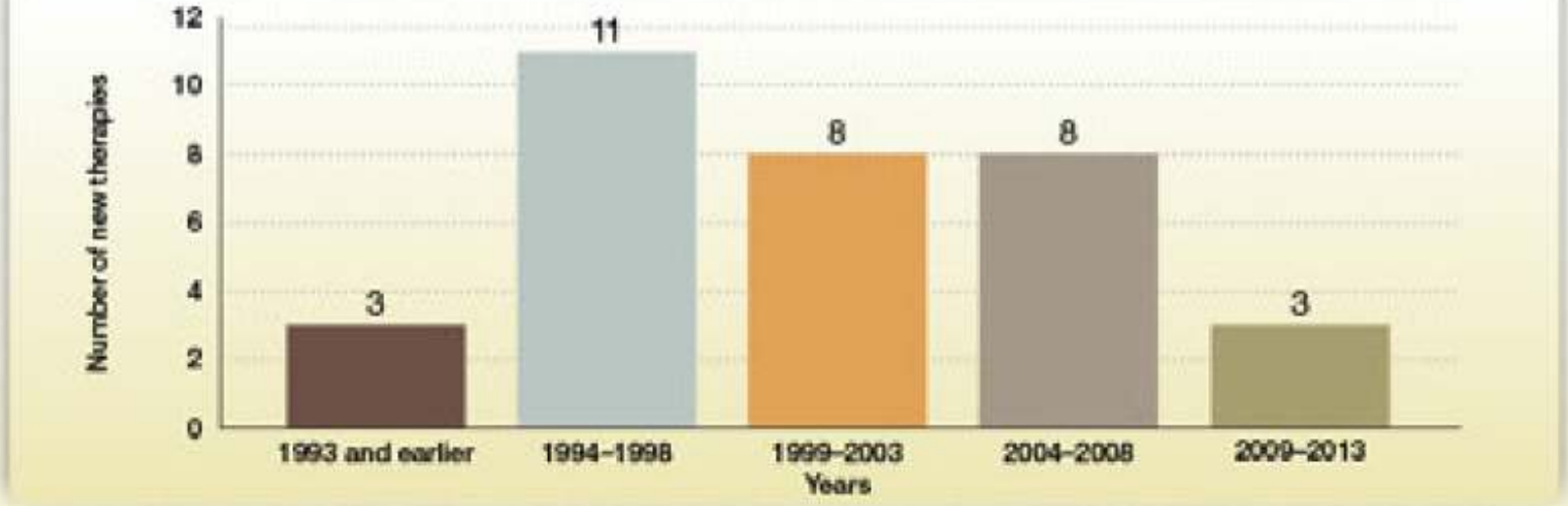
Patients can be on as many as 25 different therapies over the course of their lifetime

Some patients may exhaust their available HIV therapies, leaving them without future treatment options.

*Based on multiple cohort studies in Europe and North America.

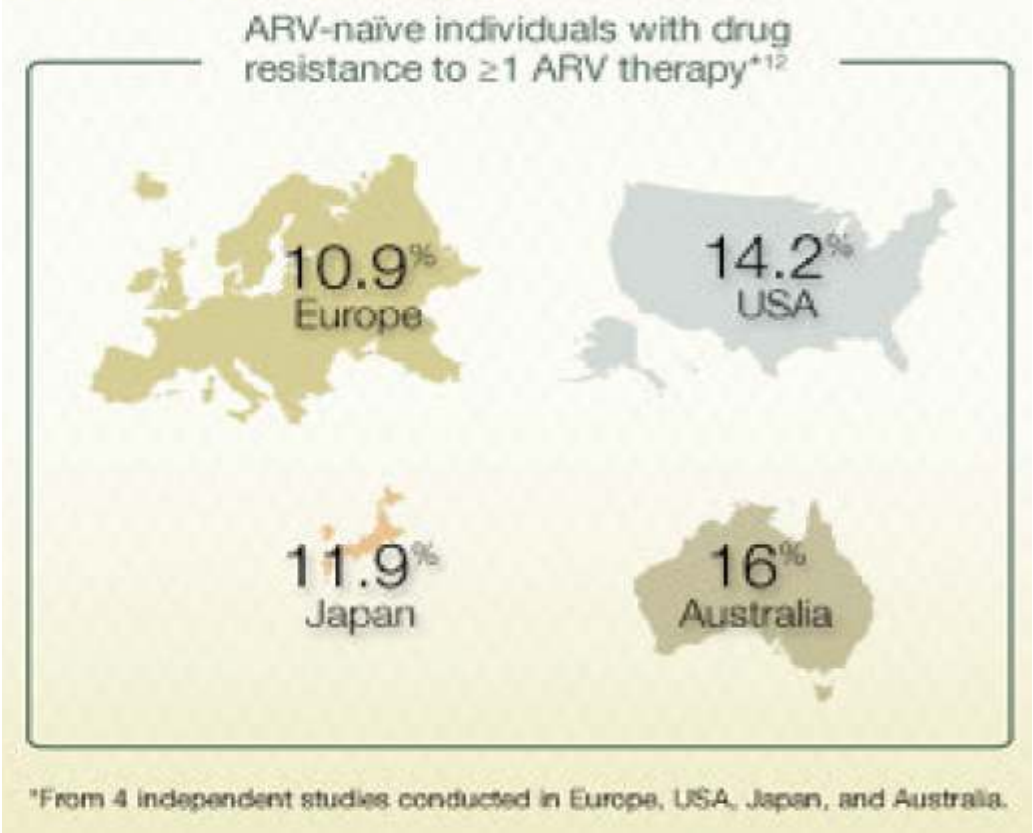
# HIV therapy pipeline is shrinking – lots of 'me too drugs'

While the search continues for ARVs that improve tolerability, reduce toxicity, and exploit new targets, the number of potential new therapies is dwindling.[9]



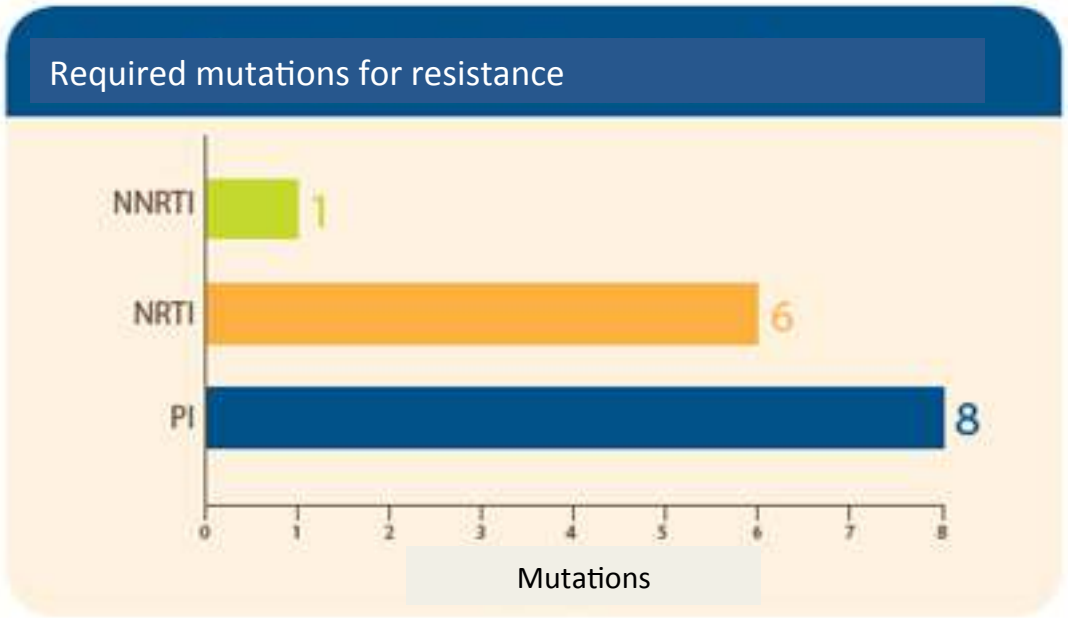
# Transmitted drug resistance is increasing

- Many newly infected patients are at least partially resistant to one or more ARV therapies
- 10% - 17% of treatment-naive patients with HIV have resistance to at least 1 ARV therapy in Europe, USA, Japan and Australia
- In Turkey, transmitted drug resistance mutations is 6.5* - 6.7%**




*Korten V, HIVTR study, 2011-2012 cohort report
**Sayan M et al, J Int AIDS Soc. 2014 Nov 2;17(4 Suppl 3)

# PI’s have higher resistance barrier in ART groups




- **Integrase Inhibitors have lower resistance barrier than most of PIs and NRTIs**
- **Raltegravir and elvıtegravır requıre 2 mutations for causes high level resistance to**

# Less resistance at virological failure with Kaletra than efavirenz: ACTG 5142

## Preliminary 96-week resistance results in treatment-naive patients

| | LPV/r + 2 NRTIs (n = 253) | EFV + 2 NRTIs (n = 250) | LPV/r + EFV (n = 250) |
|---|---|---|---|
| Observed VF*, n | 94 | 60 | 73 |
| Genotypic assays, n | 52 | 33 | 39 |
| NRTI mutations, n (%)<br>M184I/V, n<br>K65R, n | 8 (15)<br>7<br>0 | **11 (33)**<br>**8**<br>**3** | 4 (10)<br>1<br>0 |
| NNRTI mutations, n<br>K103N, n | 2 (4)<br>0 | **16 (48)**<br>**9** | **27 (69)**<br>**21** |
| Major PI mutations†, n | 0 | 0 | 2 |
| Mutations in two classes, n | 2 | **10** | 2 |

* Defined as early: lack of suppression by 1 $\log_{10}$ or rebound before Week 32, or late: failure to suppress to < 200 copies/ml or rebound after Week 32.

† 30N, 32I, 33F, 46I, 47A/V, 48V, 50L/V, 82A/F/L/S/T, 84V, 90M.

Riddler S, *et al. XVI IAC* 2006; Abstract THLB0204

# Case-SP

- A 57 years old man presented to the emergency department with progressive difficulty in **swallowing** over the last 4 weeks.

- He is **hypertensive** and has diet controlled **diabetes** and **asthma**
- He had seen his family practitioner who saw oral thrush and thought it was related to his diabetes/ inhalers and gave him amphotericin lozenges

- He had been diagnosed with HIV **a year** before but had not attended any clinics as he “felt well”

# Case-SP

- He had extensive oral thrush and had severe dysphagia
- BP 145/90 mmHg
- He was admitted and treated with fluconazole

- Social History
  - Lives alone is MSM
  - Smokes 15 a day
  - Alcohol 20 units a week, no recreational drugs
- Drugs
  - Salbutamol inhaler
  - Fluticasone Inhaler
  - Amlodopine
  - St Johns Wort for depression

# Case-SP

- **Labs**
- STD screen negative
- FBC,U and Es, LFTs Normal ,
- Cr CL 69 mls/min, Urine protein +no glucose
- CD4 33 cells/uL
- VL 365000 copies/ml
- Hep B immune
- Hep C negative
- Resistance test and HLA B5701 awaited

# You decide to start ARVs

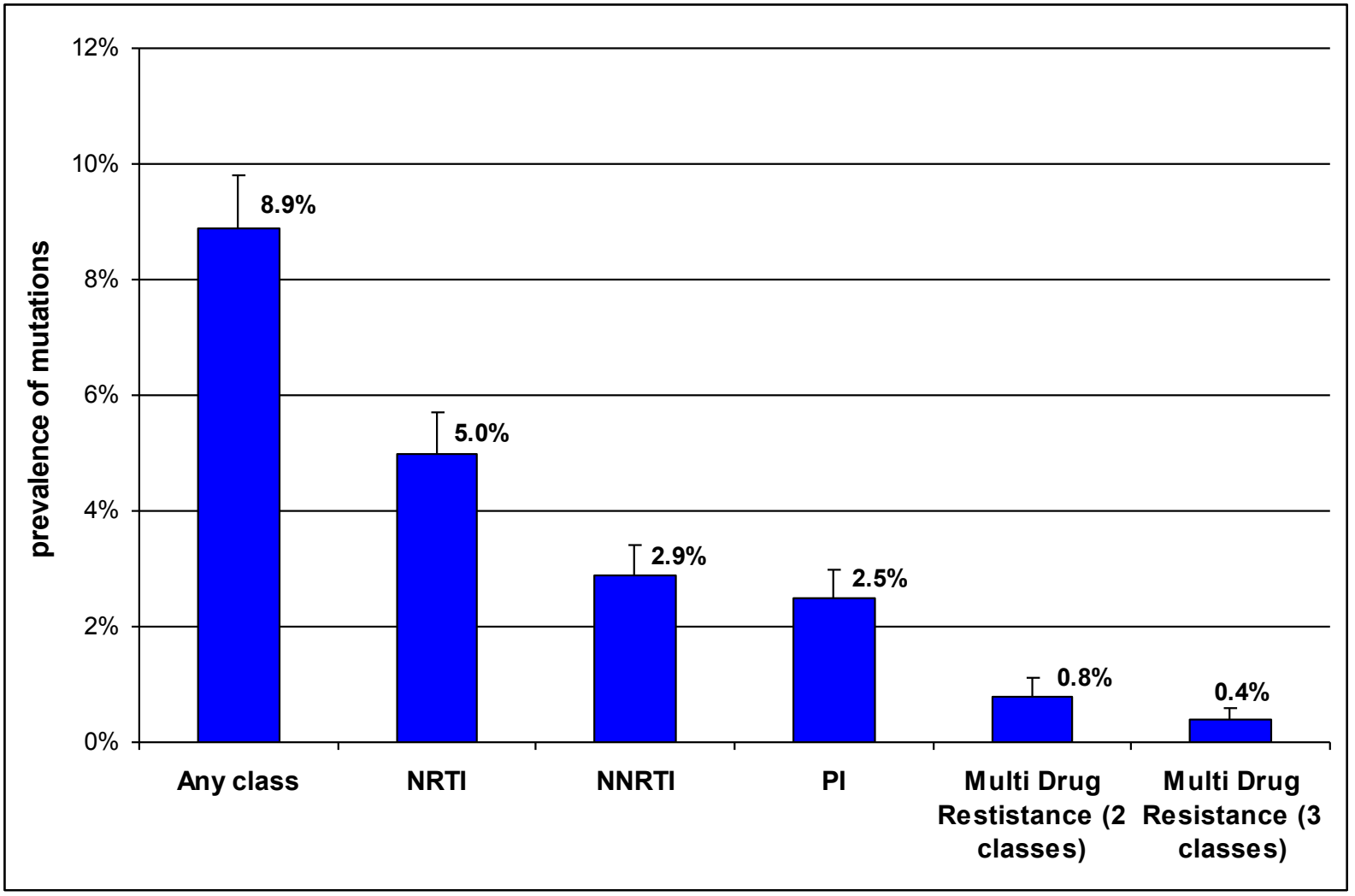
What is your choice of main agent?

- NNRTI
- PI/r
- Integrase
- other

# Difficulties in choosing-which 3rd agent?

- NNRTI-
  - may have transmitted drug resistance
- Integrase
  - may have  NRTI transmitted drug resistance
- PI/r
  - drug interactions,
  - diabetes, lipids

# NNRTI/NRTI and Prevalence of Transmitted Drug Resistance




Eacs 2011 SPREAD

# If you decide to give a boosted PI Drug Interactions

- What Drugs have significant interactions with a boosted PI?

1 St Johns Wort
2 Fluticasone
3 Amlodopine
4 None
5 all

# What NRTI back bone?

- AZT/3TC
- ABC/3TC
- TDF/FTC
- DDI/d4T
- OTHER

# Difficulties in choice of NRTI

- AZT-
  - lipodystrophy
- ABC
  - High viral load and HLA issues
  - Cardiovascular risk (smoker and diabetic and BP)
- TDF
  - Renal changes, Bone changes

# Case-SP

- He starts Kaletra + TDF/FTC

# Case AP

- 35 year old Asian women presents with
- Night sweats, weight loss and cough
- CXR - RUL **cavity** and **infiltrates**
- AAFB - **smear positive** and started on RZHE
- Had an HIV test and was positive CD4 was **35** cells/uL

# Case AP

- As her CD4 was<50 cells/uL she was offered ARVs within **2 weeks** of starting and **tolerating her TB meds**

What ARV combination would you offer her?

What is your choice of main agent?

- NNRTI-Efavirenz
- PI/r-Lopinavir/r
- Integrase-Raltegravir
- other

# Case AP

- Started Efavirenz but couldn't tolerate it
- What would you offer her?

- NNRTI-Nevirapine
- PI/r-Lopinavir/r
- Integrase-Raltegravir
- other

# Case AP

- What would you offer her?
- NNRTI- nevirapine-less efficacy ? Drug interaction
- PI/r-Lopinavir/r major interaction with rifampicin so switch to rifabutin,
- Integrase-Raltegravir 400 or 800mg bd
- Other-4 nucleosides

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