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14-16 Δεκεμβρίου 2018
ΞΕΝΟΔΟΧΕΙΟ ROYAL OLYMPIC ΑΘΗΝΑ

HIV Infection in children: Past present and future

Carlo Giaquinto
University of Padova, Italy
PENTA , Europe

HIV in pregnancy and some ART milestones

- Globally 15.3 million women of reproductive age are living with HIV, with around 1.4 million pregnancies per year
- **1994**: trial results show efficacy of antiretroviral drug (zidovudine) in preventing VT (antenatally, intrapartum, neonatal)
- **1996**: combination ART shown to be more efficacious than monotherapy for HIV treatment
- **2013** WHO guidelines: pregnant and BF women should start life-long treatment regardless of immune status
- **2015** WHO guidelines: “Treat all” lifelong as soon as possible after diagnosis

UNAIDS 2018

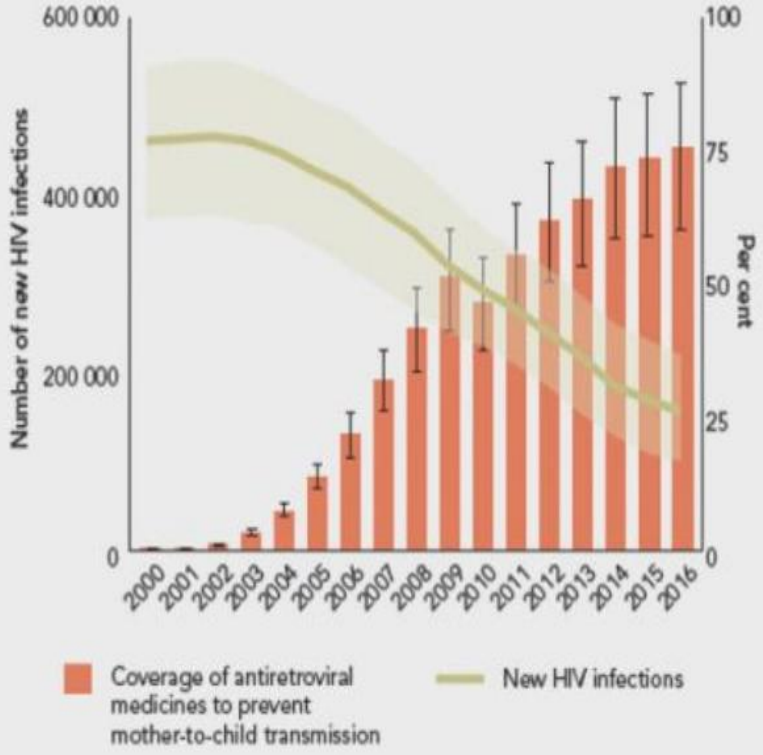


FIGURE 2.5. NEW HIV INFECTIONS AMONG CHILDREN (AGED 0–14 YEARS) AND COVERAGE OF ANTIRETROVIRAL REGIMENS TO PREVENT MOTHER-TO-CHILD TRANSMISSION, GLOBAL, 2000–2016

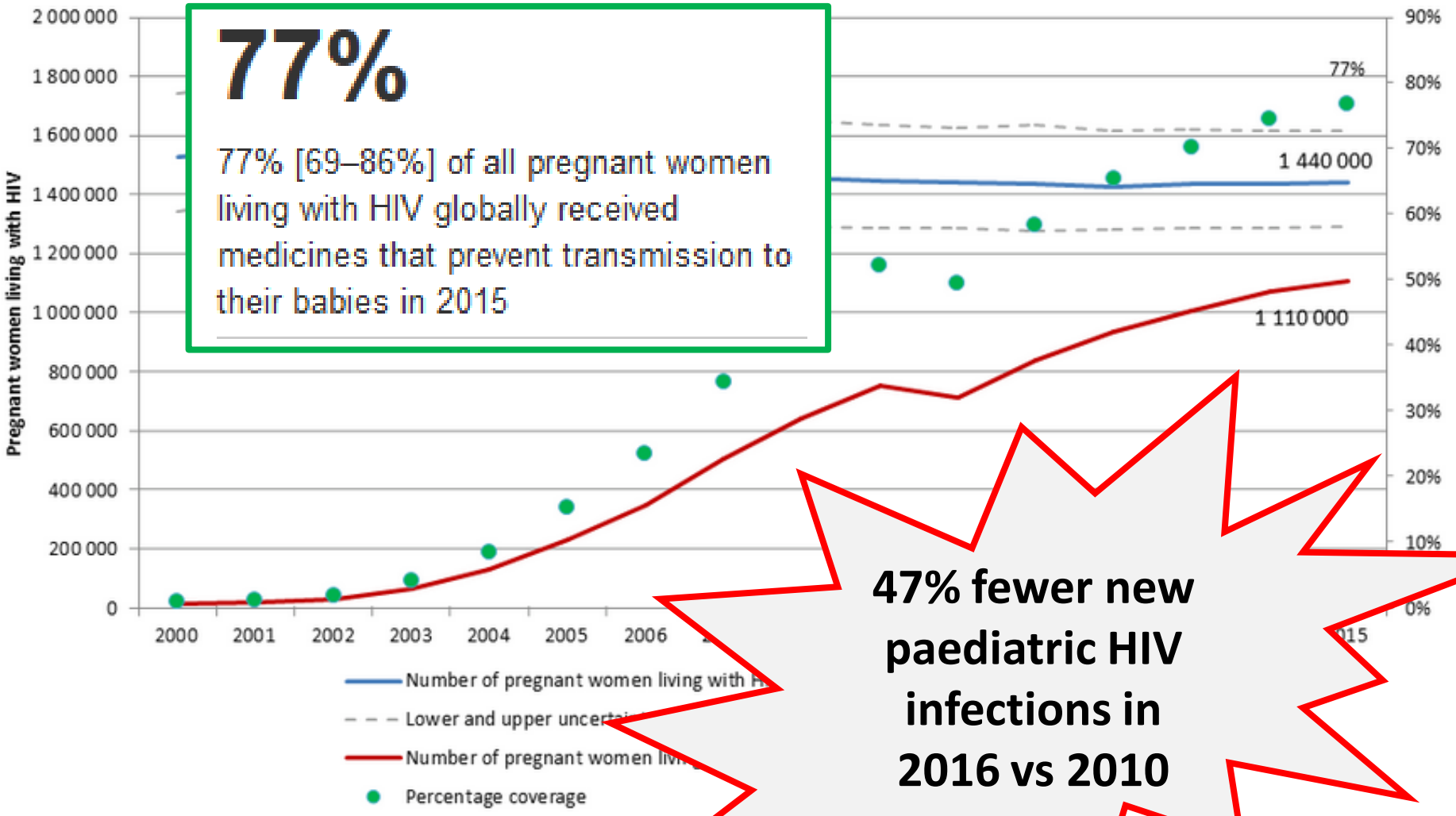
Source: UNAIDS 2017 estimates.

Perinatal HIV Infection – Current State

- 2 million perinatal HIV infections prevented
- Worldwide, 160,00 new infections in children < 15 years of age in 2016 – 400 new infections daily
- Estimated that 69 (60-83) infants born with HIV infection in US in 2013

http://www.unaids.org/en/resources/fact-sheet; Taylor A et al, JAMA Pediatr 171:435, 2017; Sohn A, Hazra R J Int AIDS Soc 16:18555, 2013; US Children's Fund, 7th Stocktaking Report. www.childrenandaids.org

Number of pregnant women living with HIV and number and percentage of them receiving ARV medicines for PMTCT, 2000-2015



Sources: Global AIDS Response Progress Reporting (UNAIDS/UN

Based on the use of different ARV medicines according to recommendations t e changed over time. Notably, single-dose nevirapine is included in the data for 2000-2009.

HIV prevalence in pregnant women in Europe

- Limited data available – largely extrapolated from antenatal HIV testing data
- Russia has the highest antenatal HIV prevalence at approx. 1% nationally
  - 9 regions have prevalence >1%, including Samara region – 2.2%, Sverdlovsk region -1.8%, St Petersburg region –1.7%
- Prevalence in Ukraine decreased from a high of 1.0% in 2010 to around 0.8% currently
- In Western Europe, prevalence <0.5%
  - Higher in migrant women from areas of high HIV prevalence, although generally prevalence in these groups is much lower than in their countries of origin

Sources: Dr I Latysheva; and Stellit Public Health Centre; Dr N Nizova Ukraine CDC

Vertical HIV transmission rates elsewhere in Europe

European Pregnancy & Paediatric HIV Cohort Collaboration

- Among women starting on ART in pregnancy in 2008-14
  - **VTR: 1.11%**
- Among all women in EU-based cohorts
  - **VTR: 0.7%** in 2012

French Perinatal Cohort, 2005-2015

- Among women on ART at conception (on LPV/r, ATZ/r, DRV/r or RAL), **VTR: <0.2%**

Russian Federation

- **VTR: 1.95%** (2016) and **1.7%** (2017, provisional data)

EPPICC IWHOD 2016, Sibiude et al CROI 2018, Favarato et al 2016, Latysheva 2018

How have countries achieved these low MTCT rates?

Ascertainment of maternal HIV status:

- High antenatal care coverage and very high rates of HIV antenatal screening; increasing testing coverage outside pregnancy

Key factors relating to ART:

- High proportion of women on suppressive regimens at conception
- Earlier use of cART in pregnancy for women not on treatment at conception
- Most pregnant women receive cART and obtain optimal control of viral replication before delivery

French Perinatal Study: VT rates

- 8075 mother-infant pairs, 2000-2011
  - On ART, live births
- MTCT=0.7% overall
- 33% mother-infant pairs (n=2651) were:
  - On ART from conception and throughout pregnancy
  - Delivered with maternal VL <50 copies/ml
    - **No vertical transmission** (95% CL = 0.1%)
- MTCT rate regardless of maternal VL:

  Mother on ART pre-conception: 0.2%

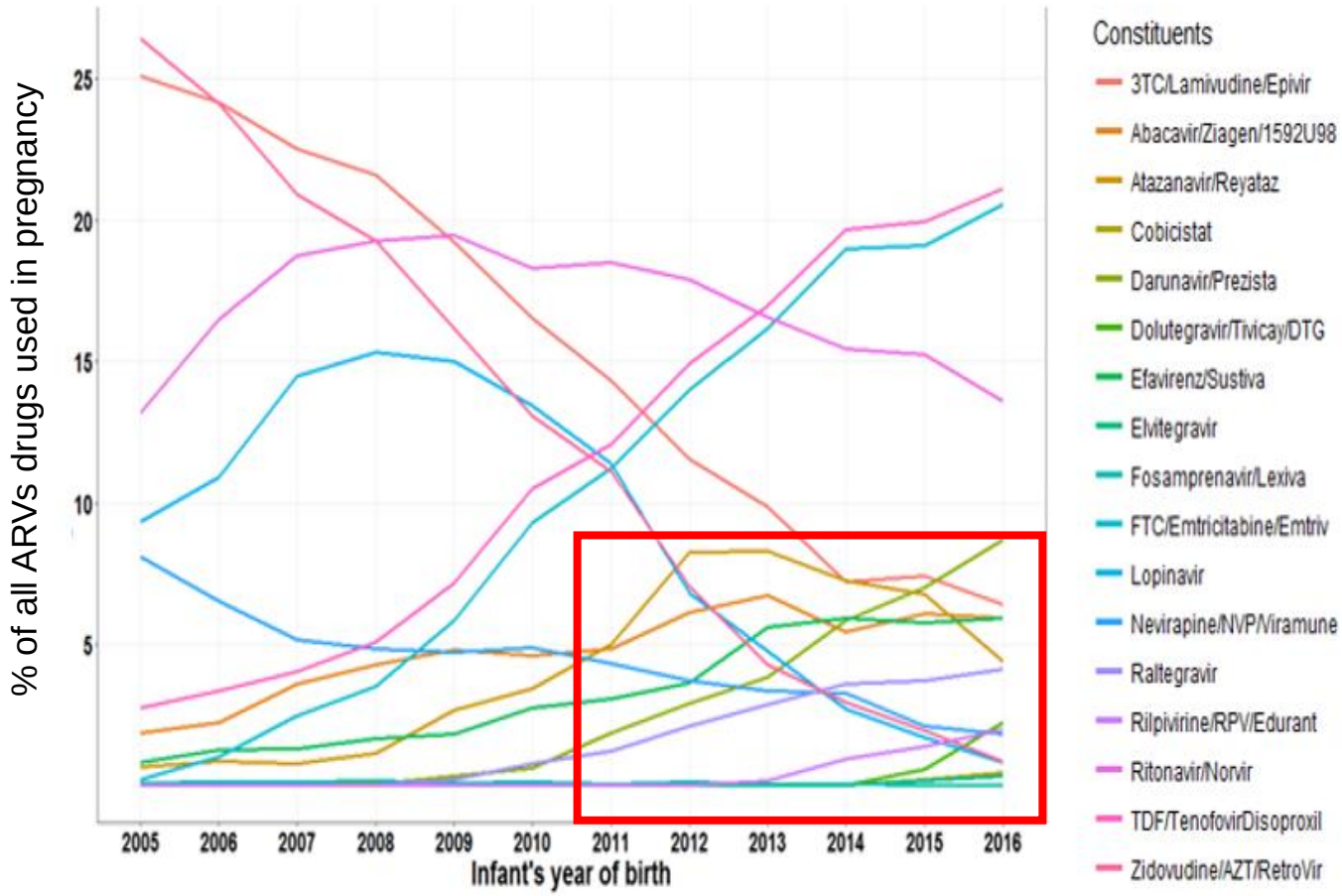
  Started ART in 1st trimester: 0.4%

  Started ART in 2nd trimester: 0.9%

  Started ART in 3rd trimester: 2.2%

Mandelbrot et al CID 2015

UK data: overall trends in ARV use in pregnancy, 2005-2016



Decreasing proportion of ZDV/3TC LPV/r Nevirapine

Increasing use of newer drugs, more diverse regimens in pregnancy

Rasi et al BHIVA 2018

Pregnancy and new drugs

- More data needed on PK and safety of **newly authorized antiretroviral drugs**
  - Particularly important as increasing numbers of women of reproductive age needing 2nd-line regimens globally
- Summary of product characteristics of new drugs are mostly based on preclinical findings
  - Limited data on human pregnancy
  - Many recommend avoiding use in pregnancy
- But at least half of pregnancies are unplanned!
- Dolutegravir safety signal has focussed more attention on this issue

Bailey et al Lancet HIV 2018

Dolutegravir in pregnancy

- DTG, an integrase strand transfer inhibitor, authorized in 2014 (DTG - Tivicay, ABC+3TC+DTG - Triumeq)
- **WHO**: in 2016, DTG recommended for 1st line ART in non-pregnant adults
  - highly effective, low toxicity and high genetic barrier to resistance, few drug-drug interactions
- **Botswana** - DTG-based ART rolled-out to all HIV+ adults including pregnant women
- Safety signal from a preliminary unscheduled analysis in the Tsepamo Study in Botswana in May 2018
  - 4 neural tube defects (NTDs) among 426 women conceiving on DTG
  - Rate of 0.94% (95% CI 0.37, 2.4) vs 0.12% (95% CI 0.07, 0.21) in infants exposed to other ARVs from conception
- Other studies (smaller numbers) showed no initial teratogenicity concerns

Zash et al 2018, Hill et al 2018

Despite huge successes, vertical transmissions do still occur….

Understanding circumstances around such cases can help us **identify missed opportunities** to prevent new infant infections and to **strengthen our systems** and / or make them as **equitable** as possible

Vertical transmissions despite interventions: EPPICC, 2002-15

- 323 infected infants with exposure to any ARVs (AN, IP or NP) from 9 cohorts in 14 countries
- **53% born in Western/Central Europe and 47% in Eastern Europe**
- 35% of mothers had been diagnosed before pregnancy
  - Only 13% conceived on ART and 38% had no antenatal ART
- 65% of mothers were diagnosed in pregnancy/at delivery
  - **Late diagnosis** and **late start or no ART** were common
- 23% infected infants were born **preterm**
  - Truncates duration of antenatal ART
- 21% born to mothers with an **injecting drug use history**

Natural history of vertically acquired HIV

- **~20% - rapid progressors**
  - early severe disease, OIs (esp PCP), encephalopathy, AIDS, death
- **~75% - slow progressors**
  - 3-5% progressing each year to AIDS/death
  - 50% survived to 10 yrs
  - Many free of clinical symptoms for long periods despite no ART
- **<1% - long term non-progressors**

1983

Tovo et al Lancet 1992, ECS Pediatrics 1994, Mayaux et al JAMA 1996, French & ECS JAIDS 1997, Pliner et al AIDS 1998

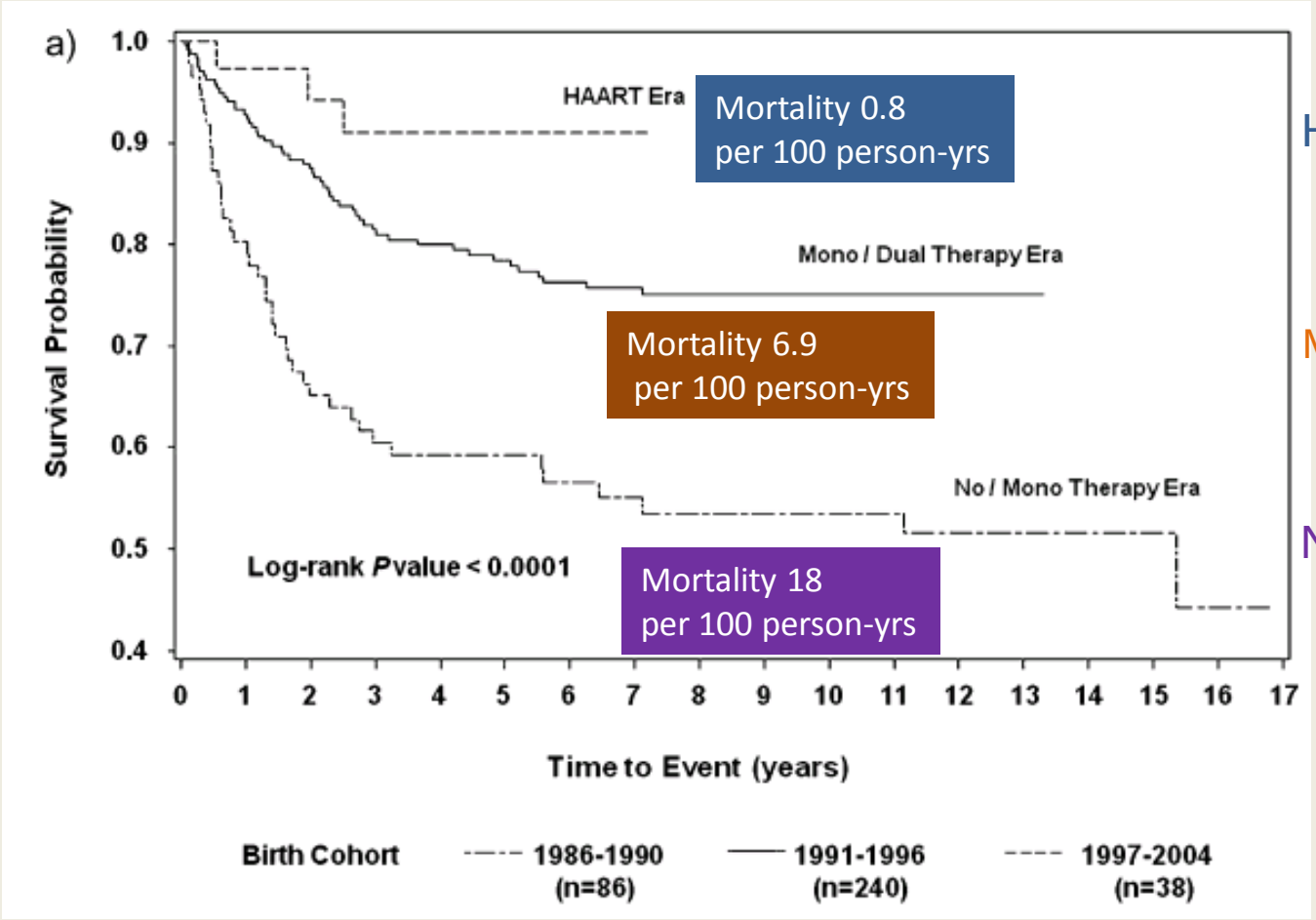
Antiretroviral therapy

"In the late 1980s part of my routine, as the director of a pediatric human immunodeficiency virus (HIV)/AIDS clinic, was to attend funerals of my patients, children who succumbed to this disease. Now I am attending their graduations from high school and some of my patients are going to college."

Yogev R. JAMA 2005; 293: 2272-5.

Mortality Trends in the US Perinatal AIDS Collaborative Transmission Study (1986–2004)

Kaplan-Meier survival analysis by birth cohort, n=364



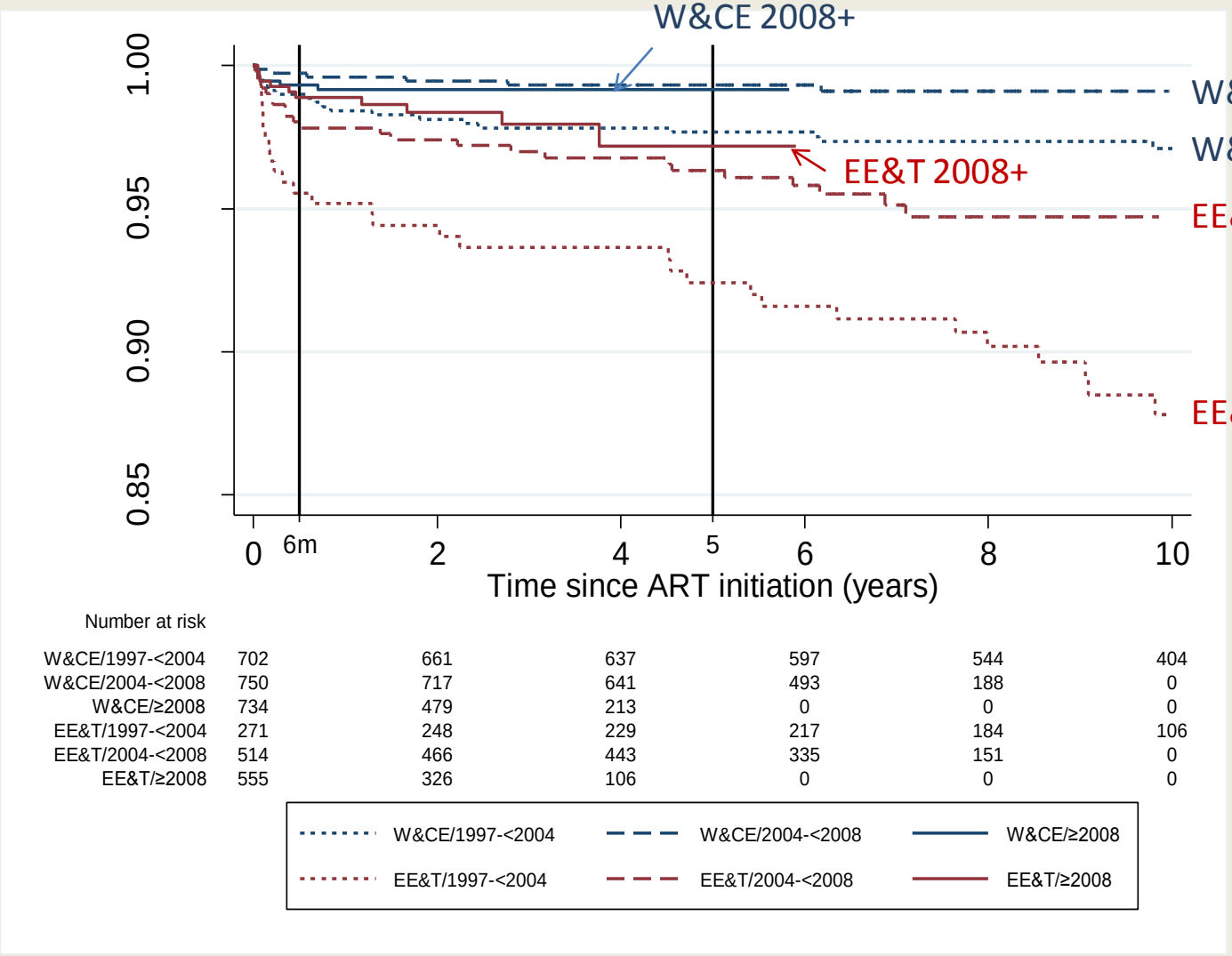
HAART 1997+

Mono / dual 1991-1996

No /mono 1986-1990

Kapogiannis et al, CID 2011, 53: 1024-1034

Time from cART initiation to death by calendar period of ART initiation and country group



Number at risk

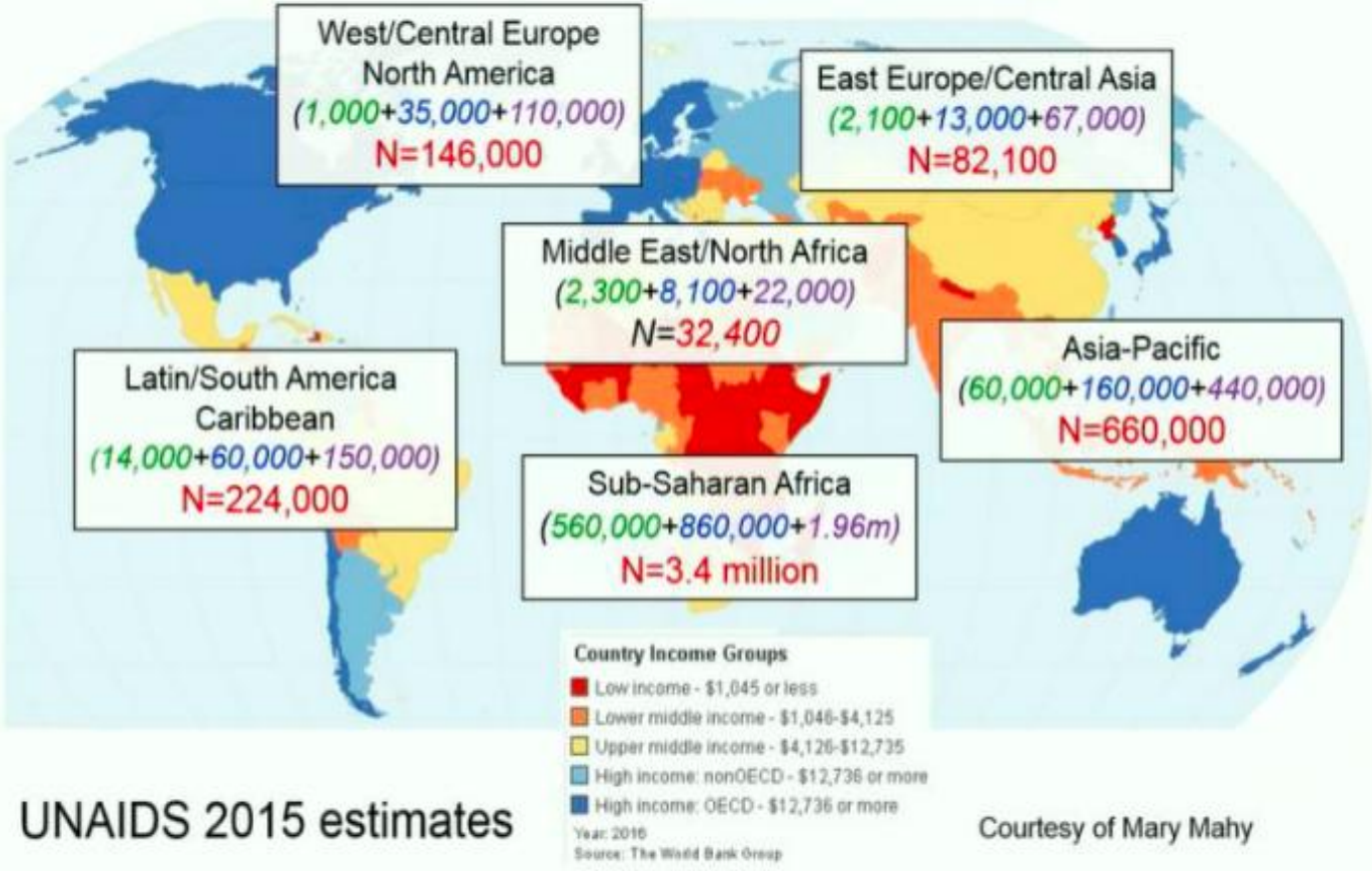
W&CE/1997-<2004	702	661	637	597	544	404
W&CE/2004-<2008	750	717	641	493	188	0
W&CE/≥2008	734	479	213	0	0	0
EE&T/1997-<2004	271	248	229	217	184	106
EE&T/2004-<2008	514	466	443	335	151	0
EE&T/≥2008	555	326	106	0	0	0

Judd A *et al.* 21st International AIDS Conference, Durban, South Africa, 2016

Adolescents and youth *living* with HIV, 2015

N=640,000 (10-14) + 1,100,000 (15-19) + 2,800,000 (20-24)

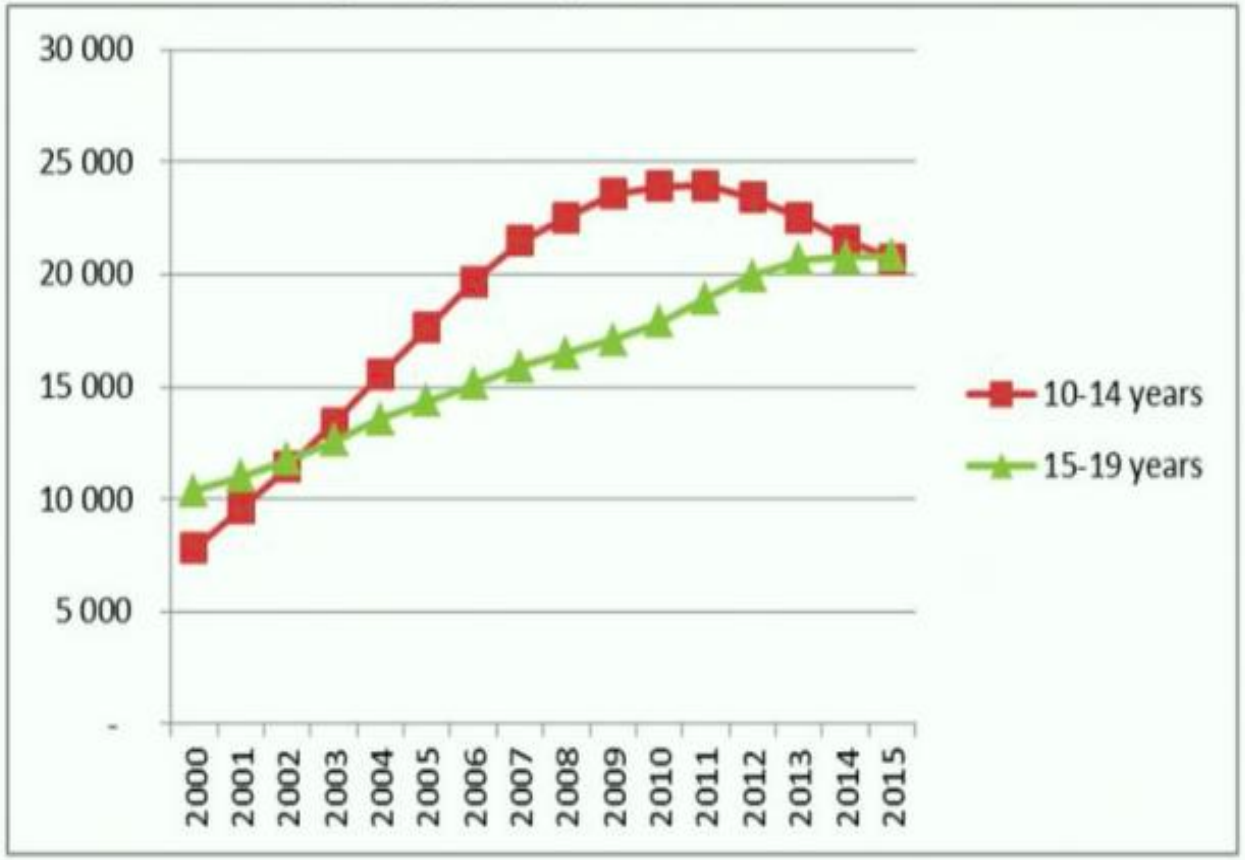
Total: 4.5 million



UNAIDS 2015 estimates

Courtesy of Mary Mahy

Estimated number of AIDS deaths by age group 2000-2015

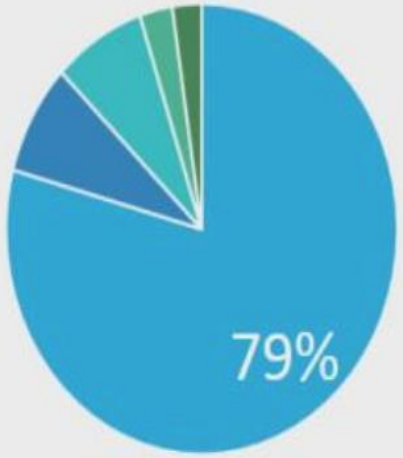


UNAIDS 2016 – courtesy of Mary Mahy

CIPHER

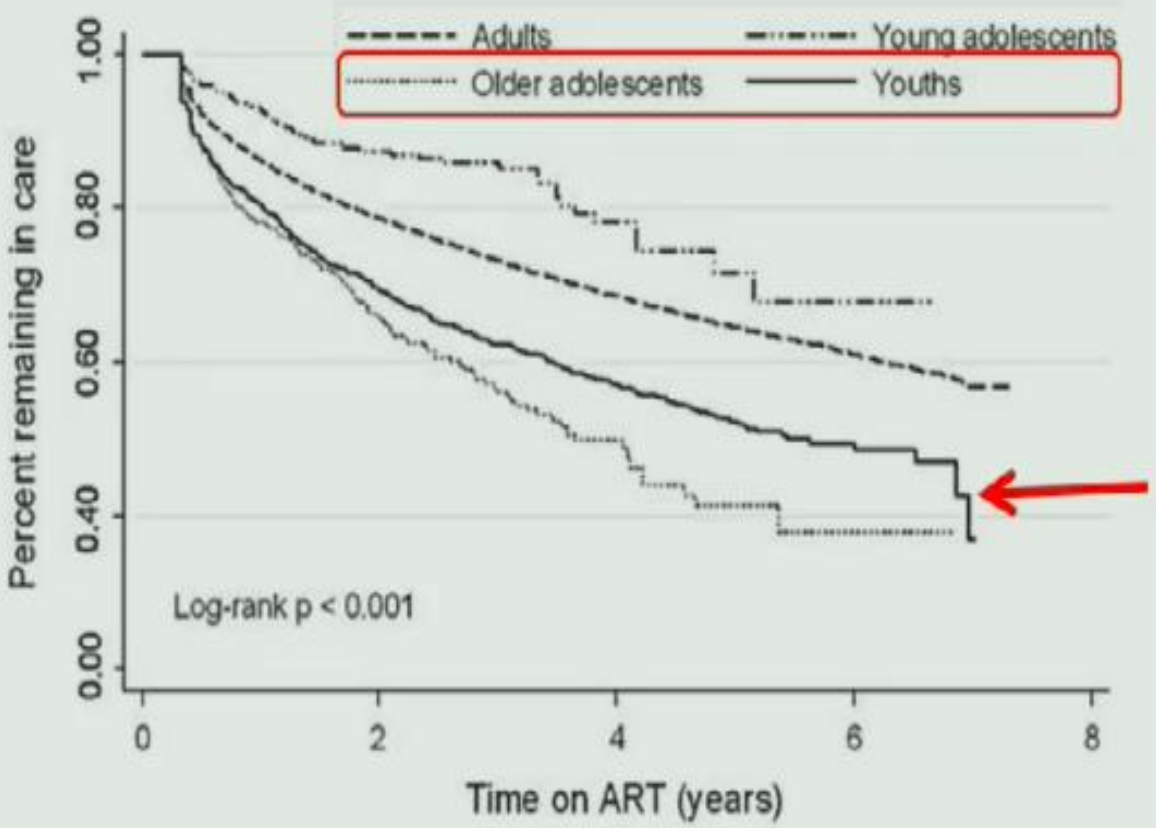
(Collaborative Initiative for Paediatric HIV Education and Research Cohort Collaboration)

- 38,187 adolescents with HIV included in cohort between 1982 and 2014
- Median age starting ART (0.9 vs. 7.9 years), youngest in North America and oldest in Sub-Saharan Africa
- 88% had received ART
- Only 38% had any viral load recorded at any time
- 72% were suppressed at last viral load measurement



Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration, PlosMed, 2018, in press

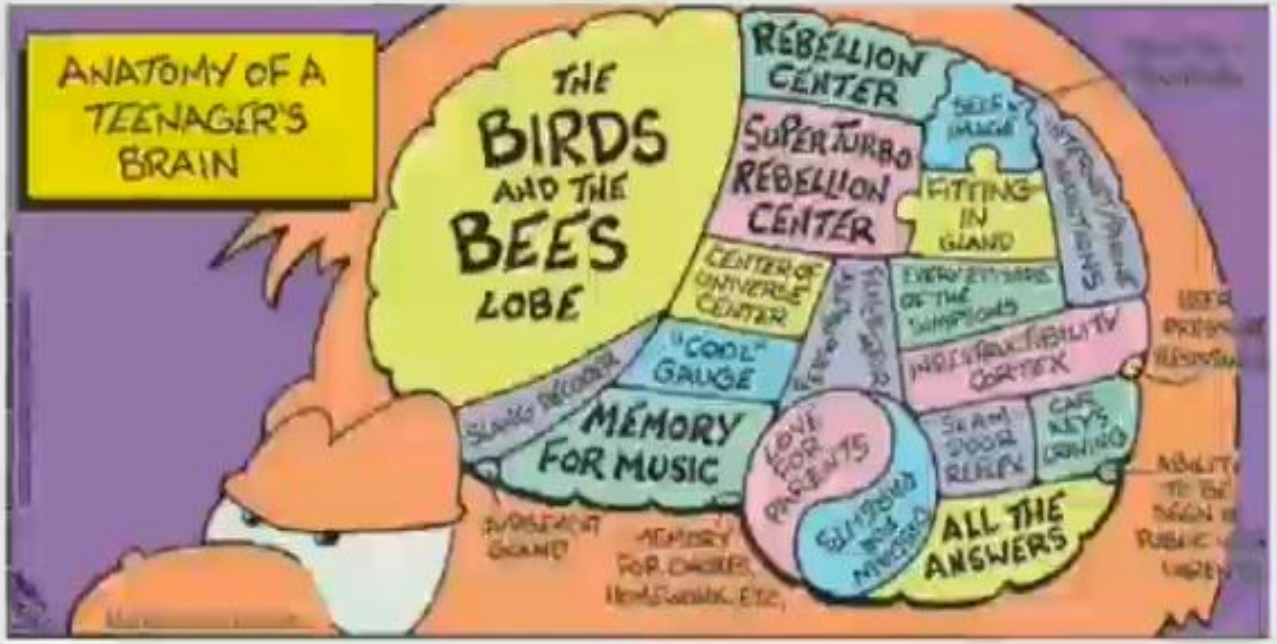
LTFU among 42,427 rural and urban patients on ART South Africa



Evans *et al.* AIDS Res Hum Retro 2013

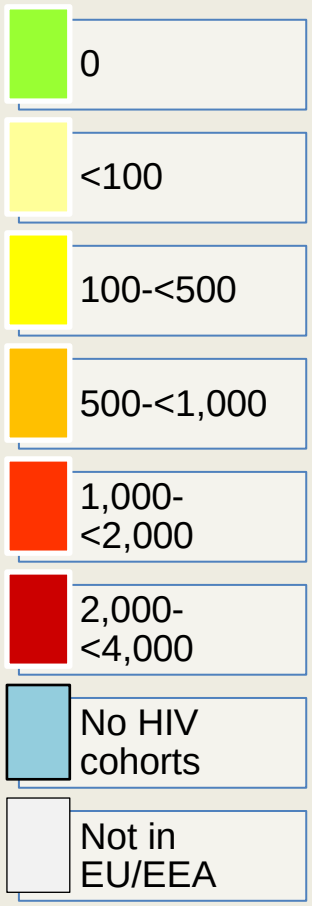
Why could 90:90:90 be so impossible for adolescents and young people?

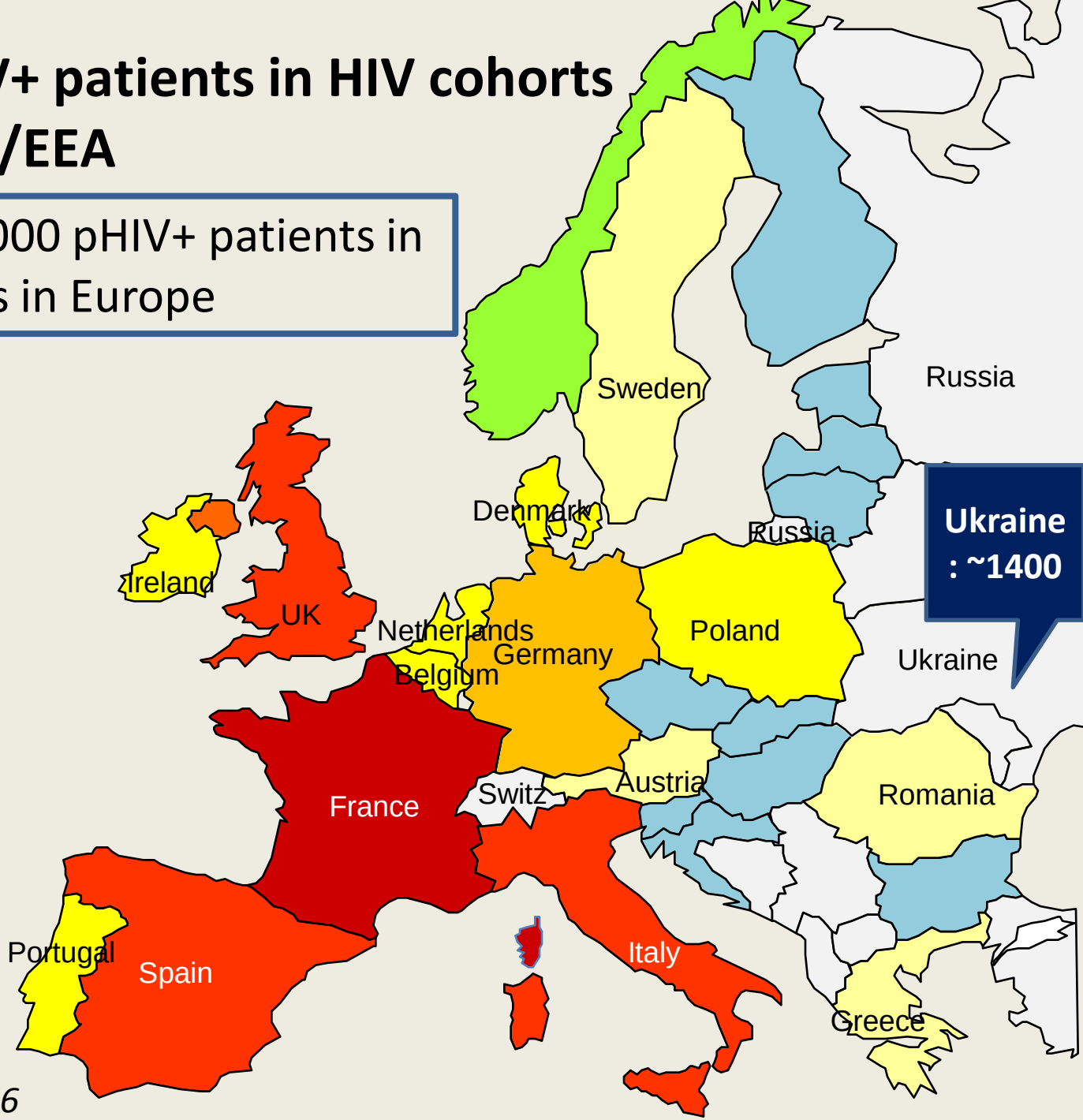
- Transitions: Developmental, Health care, Responsibility
- Finances, Employment, Housing, Education
- Gender identity, Peer pressure
- Drugs, Sexuality
- Disclosure
- Co-morbidities or effects of lifelong Rx
- Mental health & neurocognitive comorbidities
  - Andiman 2011, Lowick 2012, Kamau 2012, Puthanakit 2010



Number of PHIV+ patients in HIV cohorts in countries, EU/EEA

Estimate: up to 8,000 pHIV+ patients in EuroCoord cohorts in Europe





Judd, Eurosurveillance 2016

Adolescents MSM at higher risk of HIV infection

Table 1. Characteristics of adolescent MSM (13–19 years) who received a Centers for Disease Control and Prevention-funded HIV test at a nonhealthcare facility, 2015[a].

	HIV test events		Persons with newly diagnosed HIV infection		Linkage[b] to HIV medical care within 90 days
	N	%	*N* (%)	OR[c] (95%)	*N* (%)
Race/ethnicity					
White	1824	27	17 (0.9)	Referent	15 (88.2)
Black/African-American	2410	36	76 (3.2)	3.97 (2.16–7.29)*	45 (59.2)
Hispanic or Latino	1935	29	24 (1.2)	1.77 (0.89–3.55)	17 (70.8)
Others[d]	563	8	4 (0.7)	0.72 (0.20–2.55)	4 (100.0)
Region[e]					
Northeast	1003	15	14 (1.4)	0.46 (0.22–0.98)**	9 (64.3)
Midwest	1330	20	11 (0.8)	0.27 (0.14–0.53)*	8 (72.7)
South	2737	41	76 (2.8)	Referent	50 (65.8)
West	1615	24	20 (1.2)	0.73 (0.42–1.27)	14 (70.0)
Reported HIV-related risk behaviors[f]					
Yes	5103	85	97 (1.9)	2.05 (0.99–4.26)	67 (69.1)
No	876	15	8 (0.9)	Referent	3 (37.5)
Total tests provided to adolescent MSM	6848		121 (1.8)		81 (66.9)
Total tests provided in nonhealthcare facilities	703 890		4860 (0.7)		3157 (65.0)

Marano MR. AIDS 2017; 31: S261-5.

First cohorts of PHIV survivors reaching adulthood: psychosocial issues plus biological factors

Different to younger PHIV

- Historical sub-optimal treatment
- Older ages at ART initiation
- History of severe HIV disease
- Comorbidities
- Parental sickness /death
- In EE, parental drug use and institutionalisation

Other issues in adolescence

- Stigma, disclosure to friends /sex partners
- Adherence (estimated at 62% among adolescents in Europe vs. 80% of adults, *Kim AIDS 2014*)
- Mental health
- Education /employment
- Navigating health systems
- Risk behaviours

ARV resistance among HIV-positive young people

Country /region	Population	Proportion with ARV resistance
UK	644 YP transferring to adult care in 1996-2014	82% resistance to ≥1 drug class; 56% to 2 classes; 12% triple class resistance
Spain	63 patients before transfer to adult care in 1993-2010, median age 14.7 years	17% had triple class resistance Resistance prevalence was 51% for PI, 77% for NRTI, 37% for NNRTI
Europe	806 PHIV aged <20 at ART start, 5166 BHIV aged 15-29 at ART start	9.6% of PHIV had triple class failure 5 years after ART start, vs. 4.7% of BHIV. Highest risk in PHIV starting ART at 10-14 years (c.30% at 5 years)
US	234 YP; median age 15 years. Mean duration of cART: 10.2 years.	75% had intermediate /high level resistance to ≥1 ARV. 18% had triple class resistance
Canada	45 young people transferred to adult care between 1999 and 2011, median age 18.1 years, 32 were PHIV	28/38 patients had drug resistance to ≥1 ARV. 12/38 (32%) had triple class resistance

Collins, CID 2017; De Mulder, PLoS ONE 2012; Judd for PLATO II COHERE, HIV Med 2016; Van Dyke, CID 2016; Van der Linden, J Ped Infect Dis 2012

Cardiac abnormalities in perinatally-infected HIV+ South African adolescents on ART

CROI 2018
Abstract # 702

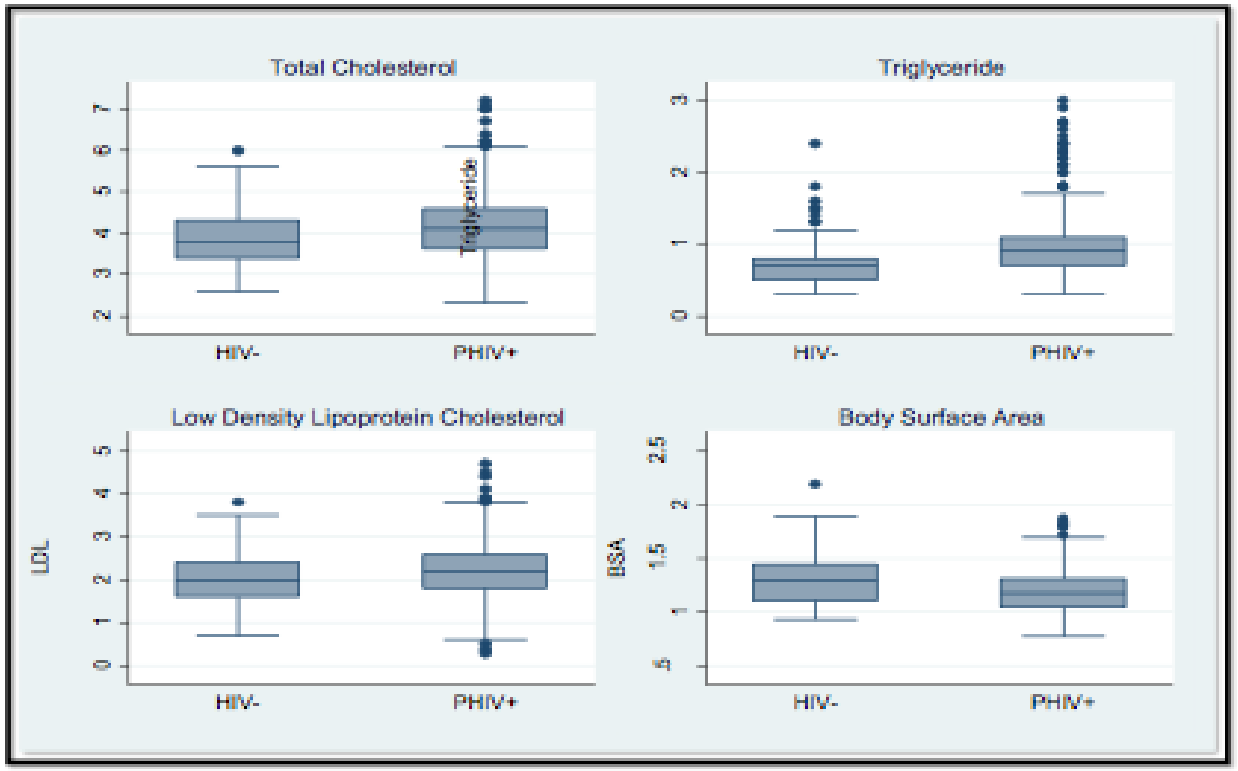
Sana Mahtab[1], John Lawrenson[2,3], Norme Jamieson Luff[1], Nana Akua Asafu-Agyei[1], Liesl Zülke[2], Landon Myer[4], Heather Zar[1]

(1) Department of Paediatrics & Child Health, Red Cross War Memorial Children's Hospital and SA-MRC Unit on Child & Adolescent Health, University of Cape Town, South Africa (2) Department of Paediatric Cardiology, Red Cross War Memorial Children's Hospital and University of Cape Town, South Africa (3) Department of Paediatrics and Child Health, Stellenbosch University, South Africa (4) Division of Epidemiology & Biostatistics and Centre for Infectious Diseases Epidemiology & Research, University of Cape Town, South Africa

Result

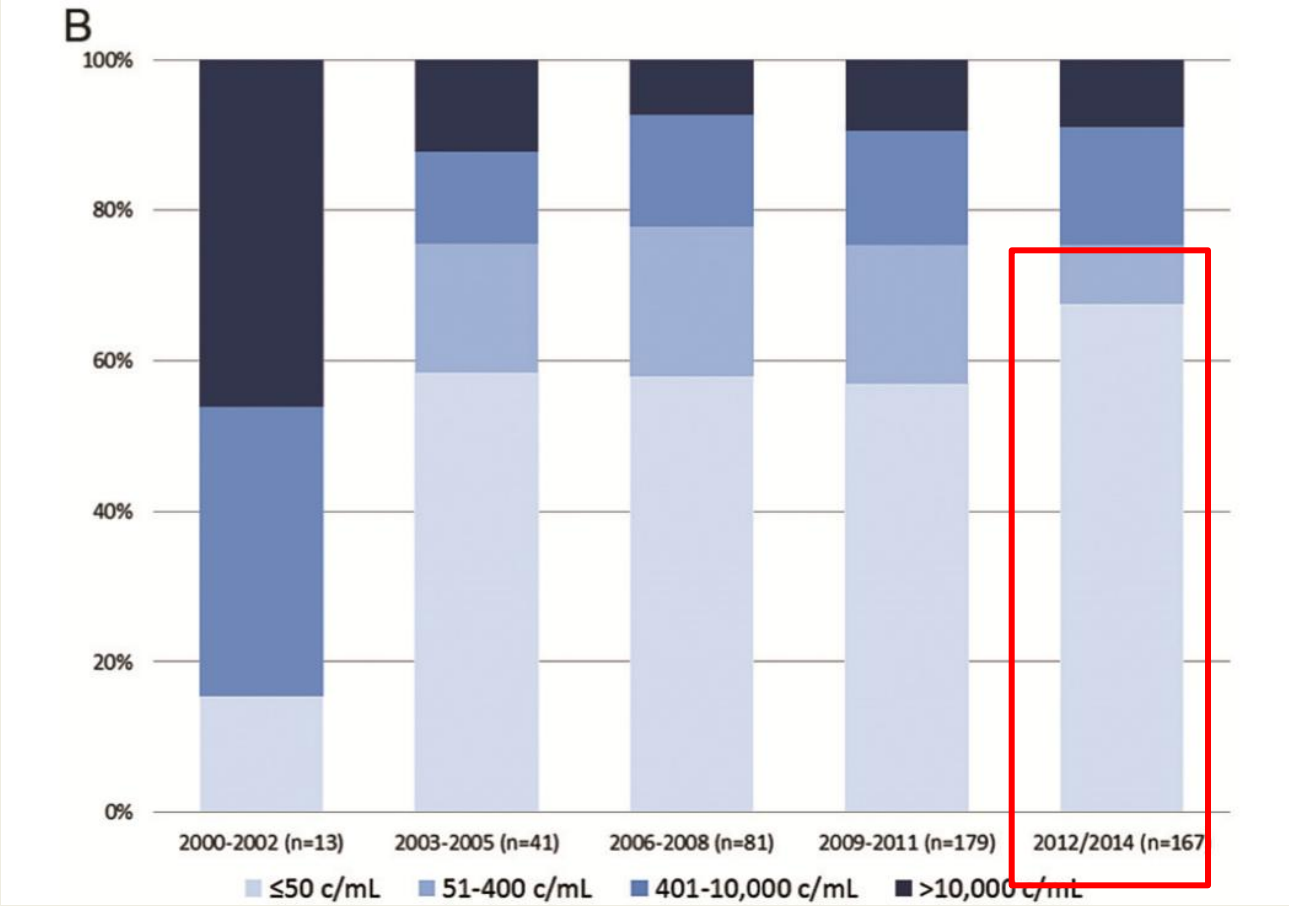
- Overall 474 PHIV+ (median age, 12 years; 51% male; mean age at ART initiation 5 years; SD, 3.5) and 109 controls (median age, 12 years; 45% male) were included.
- Mean duration on ART was 7.0 years (SD, 3.0) with 37% initiating <2 years of age.
- Median TC (4.1 vs 3.8 mmol/L, p<0.001), LDL (2.2 vs 2.0 mmol/L, p=0.013), and TG (0.9 vs 0.7 mmol/L, p<0.001) were higher in PHIV+ (Figure 1).
- PHIV+ had lower mean z-scores for LV internal dimension at the end of diastole (-0.16 vs -0.49, p<0.01), LV posterior wall thickness at the end of systole (-0.45 vs -0.65, p=0.01), and RV internal dimension at end diastole (0.24 vs 0.43, p=0.01) and greater thickness of inter-ventricular septum at the end of systole (0.7 vs 0.6, p=0.04) vs controls.

Figure 1. Comparison of PHIV+ and HIV- controls on selected cardiovascular parameters



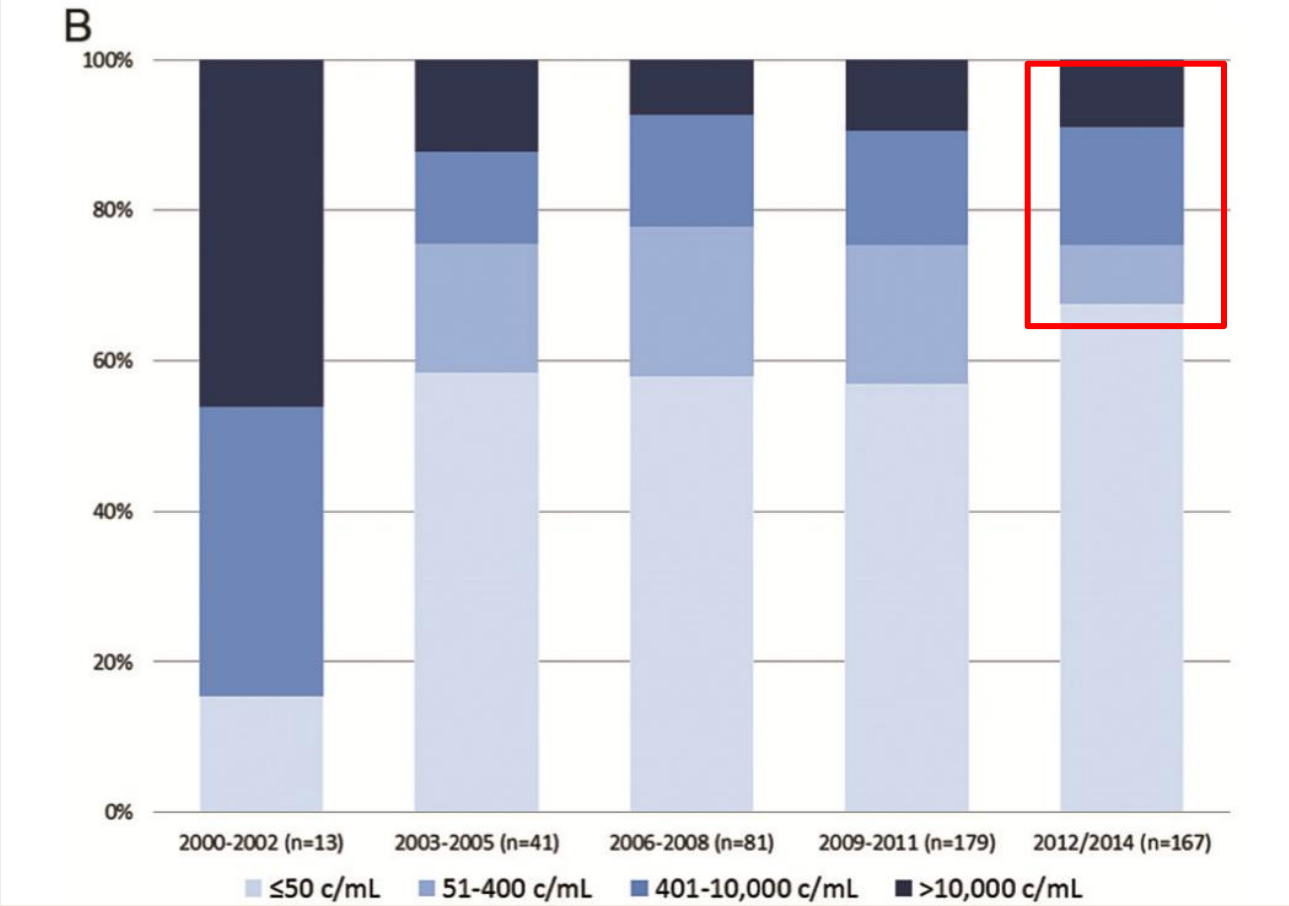
Transfer to adult care?

Increased proportion of adolescents transferred to adult care who are virologically suppressed



IJ Collins. Clin Infect Dis 2017; 68: 1005-12.

… still an un-acceptable percentage with high VL !



IJ Collins. Clin Infect Dis 2017; 68: 1005-12.

When do we transfer to adult care?

- When they are around 16 years old:
  - Inform of the possibility of being transfered.
  - Start treating them as adults:
    - See them without their parents, at least part of the visit.
    - They are responsable for their appointments
    - They call us for results

- Evaluate transition:
  - After 18 years old
  - Around 21 to 24, when they are behaviourly young adults

Second generation PMTCT

- Young PHIV+ women have a higher risk of treatment failure and multiclass drug resistance than those with BHIV
  - Long treatment histories
  - Previous exposure to obsolete and suboptimal ART
  - Adherence problems (stigma, discrimination, HIV-associated neurocognitive deficits, toxicity etc)
  - Treatment interruptions
- Other issues include problems with retention in care
- PHIV+ women are therefore a potentially high risk group for MTCT – and MTCT of resistant virus

Kenny et al 2012

Poster number # 775
Conference on Retroviruses and Opportunistic Infections
Feb 13 – Feb 17, 2017

PREGNANCIES IN WOMEN WHO ACQUIRED HIV PERINATALLY

The ANRS French Perinatal Cohort, 2006-2014

M Hleyel[1], C Dollfus[2], R Tubiana[3,4], C Rouzioux[5], P Frange [5], S Blanche[5] , J Le Chenadec [1], A Faye[6,7], L Mandelbrot[1,7,8] , J Warszawski [1,9,10] and The French Perinatal Cohort (ANRS-EPF CO1/CO11) [11]

[1] CESP INSERM U1018, Le Kremlin-Bicêtre; [2]AP-HP Hôpital Trousseau, Paris; [3] Sorbonne Universités, UPMC, Paris; [4]INSERM IPLESP UMRS 1136, Paris; [5]AP-HP Hôpital Necker, Paris ; [6]AP-HP Hôpital R. Debré, Paris; [7]Univ Paris Diderot ; [8]AP-HP Hôpital L. Mourier, Colombes ; [9]Univ Paris Sud, Le Kremlin-Bicêtre; [10]AP-HP Hôpital Bicêtre, Paris

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Fig. 1 – FLOW CHART

2201 pregnancies /1425 women
18-30 years old, delivery 2006-14

1650 pregnancies
HIV+ status known BEFORE conception

HIV perinatally acquired = PHIV

NO (Non-PHIV)
1586 pregnancies including:
470 primipara pregnancies

YES (PHIV)
64 pregnancies including:
46 primipara pregnancies

Fig. 2 – Trends over time of PHIV among pregnancies of HIV-infected women - ANRS EPF 2006-14

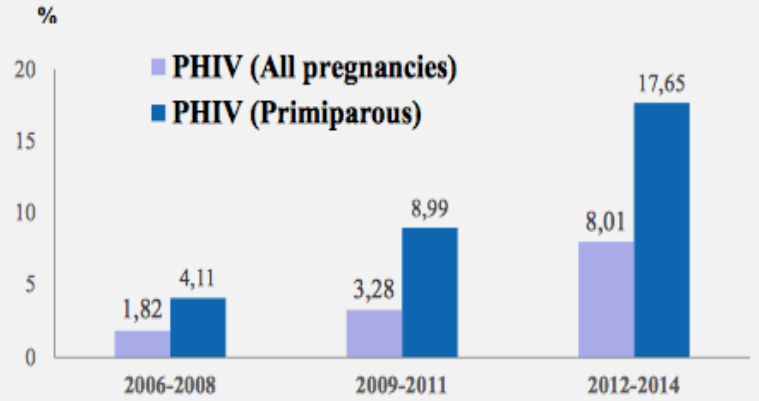
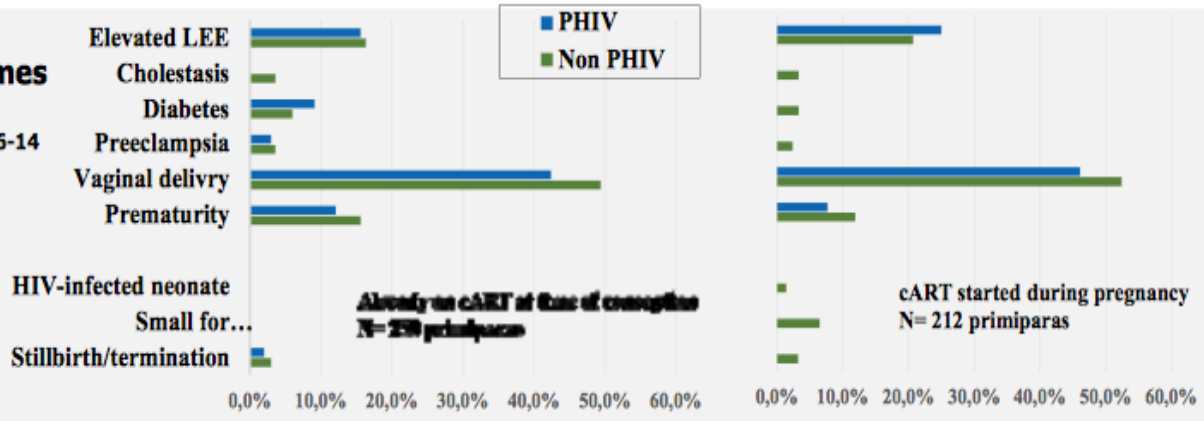


Fig. 3

Pregnancy and neonatal outcomes according to PHIV status

in primiparous 18-30 years women - ANRS EPF 2006-14



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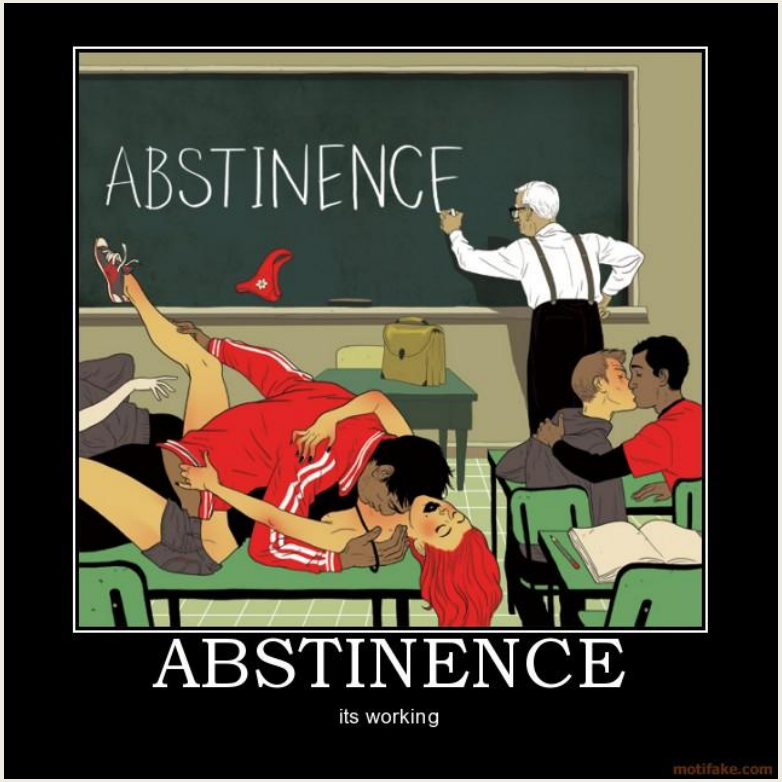
RESULTS

- **Increasing proportion of PHIV (Fig 2) among infected pregnant women aged 18-30 years** from 4.1 % to 17.7 % in primiparous women (p<0.001) over the study period.
- **Socio-demographics, compared with non-PHIV women:**
  - PHIV had similar living conditions : about half not living with a partner, 40% being jobless, and less than 10% having psychoactive substance abuse.
  - PHIV were significantly more likely to have been born in France (73.9% vs 15.9%, p<0.001),
- **Care management, compared with non-PHIV women:**
  - PHIV women were significantly more likely to to be on combined antiretroviral treatment at the time of conception (71.7% vs. 54.1%; p=0.02).
- **Obstetrical and neonatal outcomes (Fig 3), compared with non-PHIV**
  - The prevalences of obstetric complications and neonatal outcomes were very similar in the two groups. No case of MTCT occurred in the PHIV group (upper CI =0.1%), versus three cases (0.7%; CI: 0.1-1.9) in the non-PHIV group.
- **Viral load (Fig 4), compared with non-PHIV women if ART present at conception:**
  - PHIV had higher proportion of uncontrolled viral load (VL) during the first trimester (44.8% vs. 21.4%; p=0.007), as well as at delivery (26.7% vs. 10.6%; p=0.03).

    Virological failure at delivery remained more frequent in PHIV women born outside France, after adjustment for initial viral load.



Thanks for your attention

…. And to Claire Thorne, Pablo Rojo, Heather Bailey, Jeannie Collins and all of those that recognize their slides.