

Factors associated with Mother-to-Child transmission of HIV-1 in Romania: is postnatal HIV infection still a risk?

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Case study

18-year-old woman admitted in our hospital together with her 19-months-old boy

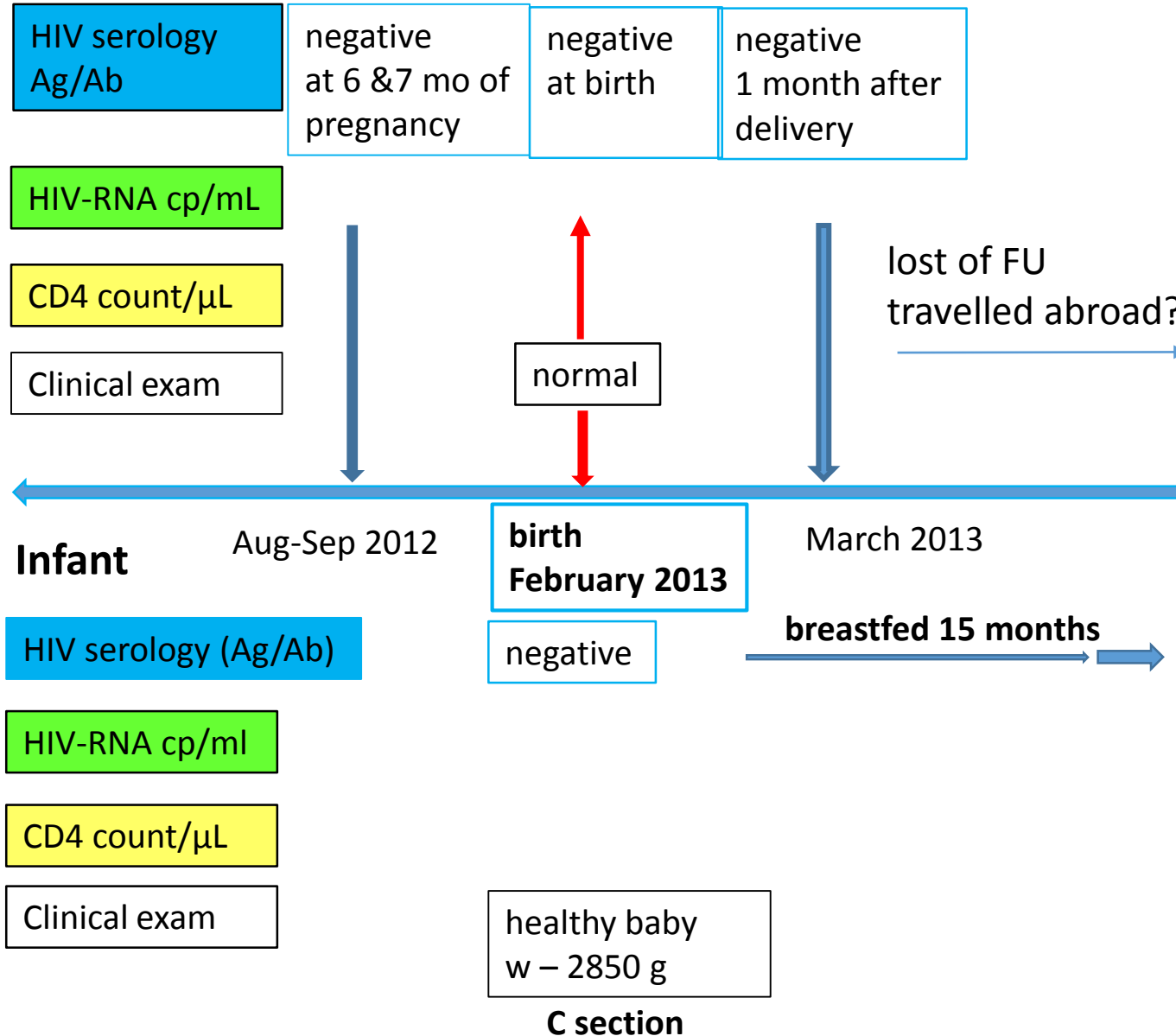
- no relevant past medical history
- unemployed
- low level of education (some primary)
- declared a single sexual partner
- tested HIV positive (one month before) in a county hospital
- HIV negative during pregnancy (2 tests) and at delivery (16 year-old)
- HCV, HBsAg, syphilis negative
- infant tested at birth (February 2012) - HIV negative

Family history

- partner 25 year-old
 - HIV positive (diagnosed in July 2011 in France)
 - former 6-year relation with a HIV positive woman (from the cohort of parenterally infected children)
 - tested HIV negative in 2009 and 2010
 - smoker, using occasionally recreational drugs (not injectable drugs)
 - treated in France with TDF + FTC + EFV
 - returned to Romania begin of 2013, stopped treatment, lost to FU
 - continues to have unprotected sex with his 16 year-old girlfriend
 - HIV positive sister

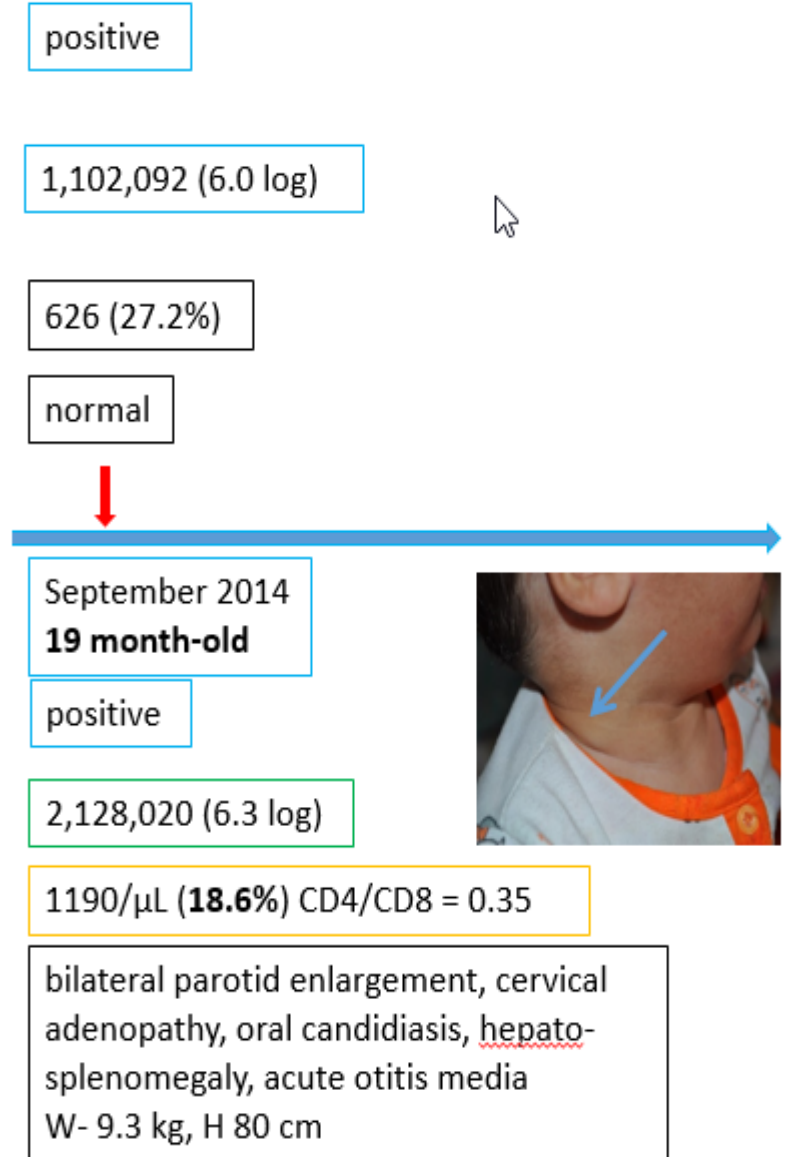
Case history

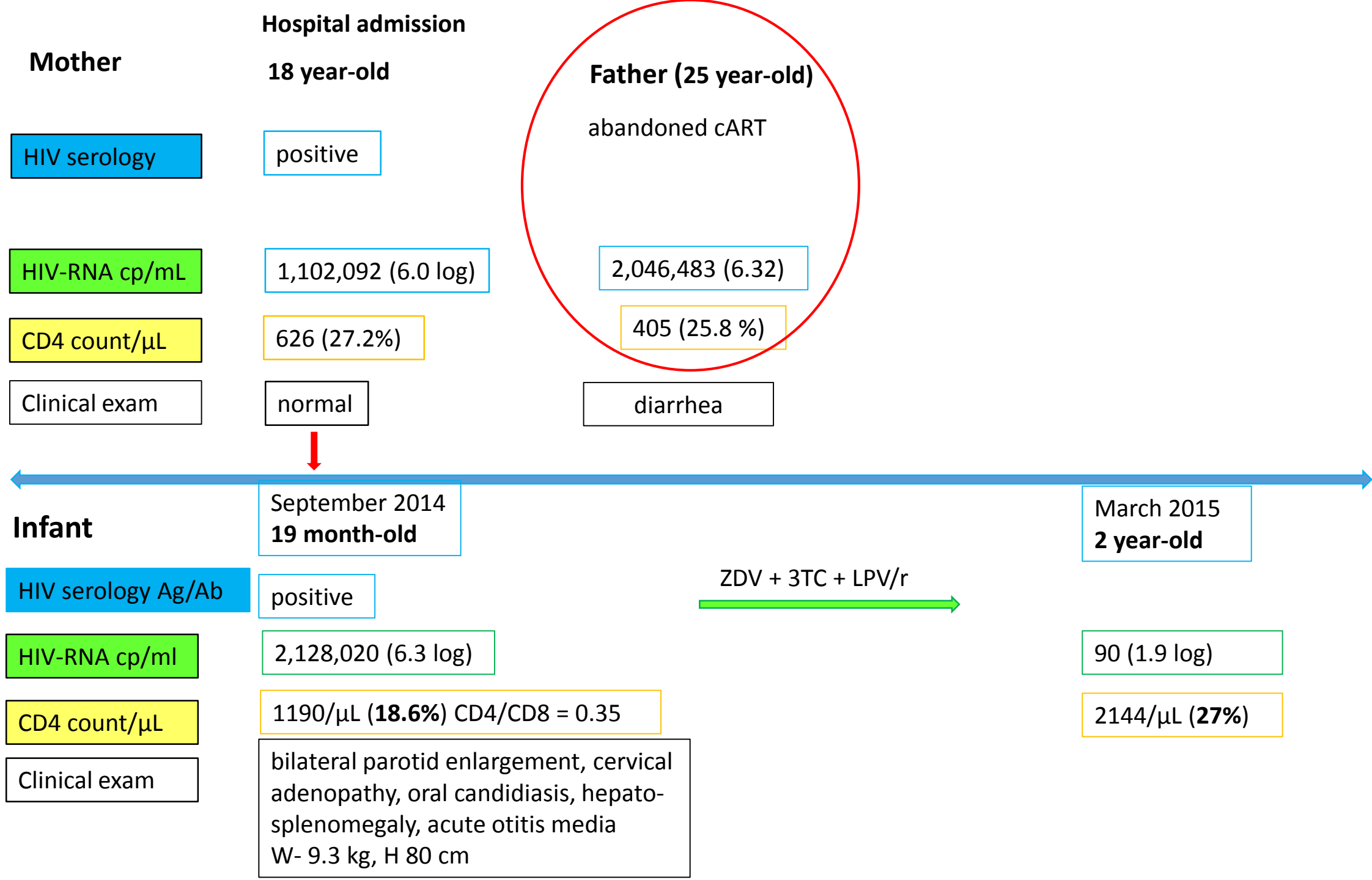
Pregnant at 16 years



Hospital admission

18 year-old





Acute HIV infection during breastfeeding ?!

Mother: tested HIV negative at birth and positive after 18 months

Infant: HIV testing negative at birth and positive when he was 19 month- old and symptomatic (breastfed for 15 months)

Father (probably the source of infection, no viral sequencing to confirm): HIV positive, stopped cART treatment and continued to have unprotected sex with the mother during breastfeeding period)

Mother developed most probably an acute infection during the breastfeeding period and the child acquired HIV postnatally.

Risk of HIV transmission during breastfeeding

- The rate of MTCT is estimated to be 5% to 10% during pregnancy, 10% to 15% during labor, and 15% to 20% during prolonged breastfeeding when strategies to reduce HIV transmission are not adopted.
- The estimated risk of breastfeeding transmission among women with acquisition of HIV-1 infection after delivery was 27% - 36.7% (Palasanthiran P, J Infect Dis 1993, Liang K J Infect Dis 2009, Humphrey JA BMJ 2010)
- There are few reports of HIV transmission during breastfeeding in developed countries (Blumental S et al, Pediatrics,2014;134:875-79)

Factors associated with transmission of HIV during breastfeeding

Maternal

Younger maternal age, lower parity

Maternal seroconversion during lactation

RNA HIV in breast milk

RNA HIV in plasma

Local immune factors in breast milk: breast milk IgA and secretory IgA responses against HIV-1 envelope proteins associated with reduced risk of postnatal HIV-1 transmission (Pollara J et al J Virol 2015 Oct 1;89(19):9952-61)

Breast lesions or inflammation (mastitis, cracked nipples) associated with increased VL in milk

Duration of breastfeeding

CMV infection - breast milk CMV DNA level correlated positively with breast milk HIV-1 RNA level

(Chang TS BAN Study team) AIDS 2015 24;29(7):831-6, Viljoen J et al AIDS 2015, 14;29(2) 145-53)

Maternal nutritional status

Infant

Factors associated with the immune system

Genetic factors (HLA concordance with mother)

Patterns of feeding: **mixed** breastfeeding: risk of gastrointestinal infection with mucosal barrier breakage

(Anígilájé et al. BMC Infectious Diseases, 2015,15:132) Berzan B et al BMC Res Notes, 2014 4;7:876)

Guidelines on breastfeeding

| Guidelines | Recommendations related to breastfeeding |
|------------------------|--|
| DHHS (USA) - 2015 | breastfeeding is not recommended for HIV-infected women, including those receiving cART; (maternal cART reduces the risk dramatically but do not eliminate breastmilk transmission) |
| BHIVA UK – update 2014 | complete avoidance of breastfeeding for infants born to HIV-infected mothers, regardless of maternal disease status, VL or treatment but acknowledge rare instances when a mother will breastfeed. |
| WHO | exclusive breastfeeding in low and middle resource settings as it may provide a greater chance of survival even when ARV are unavailable |

Breastfeeding - recommendations

Resource limited setting

Option B+

- ART to **all pregnant and breastfeeding women** regardless of CD4 count or WHO clinical stage - ART continued for life
- Exclusive breastfeeding for first 6 months with complementary food added thereafter; breastfeeding to continue for the first 12 months of life). Breastfeeding should stop once a nutritionally adequate and safe diet without breast-milk can be provided

High income countries

- ART to all **pregnant women** regardless of CD4 count or clinical stage – ART continued for life
- Exclusive infant formula feeding

Could things have been done better?

TO PREVENT HIV TRANSMISSION TO THE CHILD

- COUNSELLING (REPEATED) REGARDING THE RISK OF TRANSMISSION DURING BREASTFEEDING AND THE NEED OF USING CONDOMES!!
- ENGAGEMENT OF THE FATHER – THAT HE HAS TO RESPECT RECOMMENDATIONS - THAT HE IS RESPONSIBLE
- FOLLOW-UP: SOCIAL WORKERS, NURSES (but couple travelled abroad)
- PSYCHOLOGICAL SUPPORT FOR THE MOTHER

HEALTHCARE PROVISION

- PERFORM HIV- RNA for the mother at delivery
- HIV- DNA for the child after birth
- VIRAL SEQUENCING (TO CONFIRM THAT THE FATHER IS THE SOURCE OF INFECTION)
- FATHER ABANDONED cART WITH EFV - RISK OF VIRUS WITH DRM (CLOSE MONITORING IS IMPORTANT!)

Are modes of HIV acquisition in Romanian pregnant women correlated with HIV mother-to child transmission rates and pregnancy outcomes?

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Trends in modes of HIV transmission in Romania (January 2007 - June 2015)

| | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 06.2015 |
|--------------|-----------|------------|-----------|-----------------|------------------|-----------------|-----------------|------------------|-----------------|
| Heterosexual | 354 (79%) | 405 (76%) | 393 (76%) | 409 (75%) | 448 (60%) | 447 (51%) | 511 (55.5%) | 506 (60%) | 189 (57%) |
| MSM | 14 (3%) | 40 (7.5%) | 44 (9%) | 61 (11%) | 100 (13%) | 91 (11%) | 97 (11%) | 126 (15%) | 47 (14%) |
| IVDU | 4 (1%) | 3 (0.6%) | 8 (1.6%) | 15 (2.7 %) | 143 (19%) | 266 (30.6%) | 261 (28%) | 168 (20%) | 77 (23%) |
| MSM/IDU | | | | 1 (%) | 7 (1%) | 7 (1%) | 9 (1%) | 9 (1%) | 4 (1%) |
| MTCT | 9 (2%) | 13 (2.5%) | 23 (4.4%) | 27 (5%) | 22 (3%) | 21 (2.4%) | 27 (3%) | 17 (2%) | 9 (3%) |
| Unknown | 67 (15%) | 71 (13.4%) | 45 (9%) | 32 (6%) | 28 (4%) | 39 (5%) | 14 (1.5%) | 20 (2%) | 7 (2%) |
| TOTAL | 449 | 532 | 514 | 545 | 748 | 871 | 919 | 846 | 333 |

Source: Compartment for Monitoring and Evaluation of HIV/AIDS Infection in Romania INBI “Matei Balș”, 2015

Background: HIV positive Romanian women of childbearing age can be divided into three categories: with HIV acquired sexually (SI), by parenteral route in the first years of life (PI) or by injecting drug use (IDU).

The aim of our study was to compare the demographic characteristics, clinical and immunological status, pregnancy outcomes, and mother-to child transmission (MTCT) rates between PI, SI and IDU mothers.

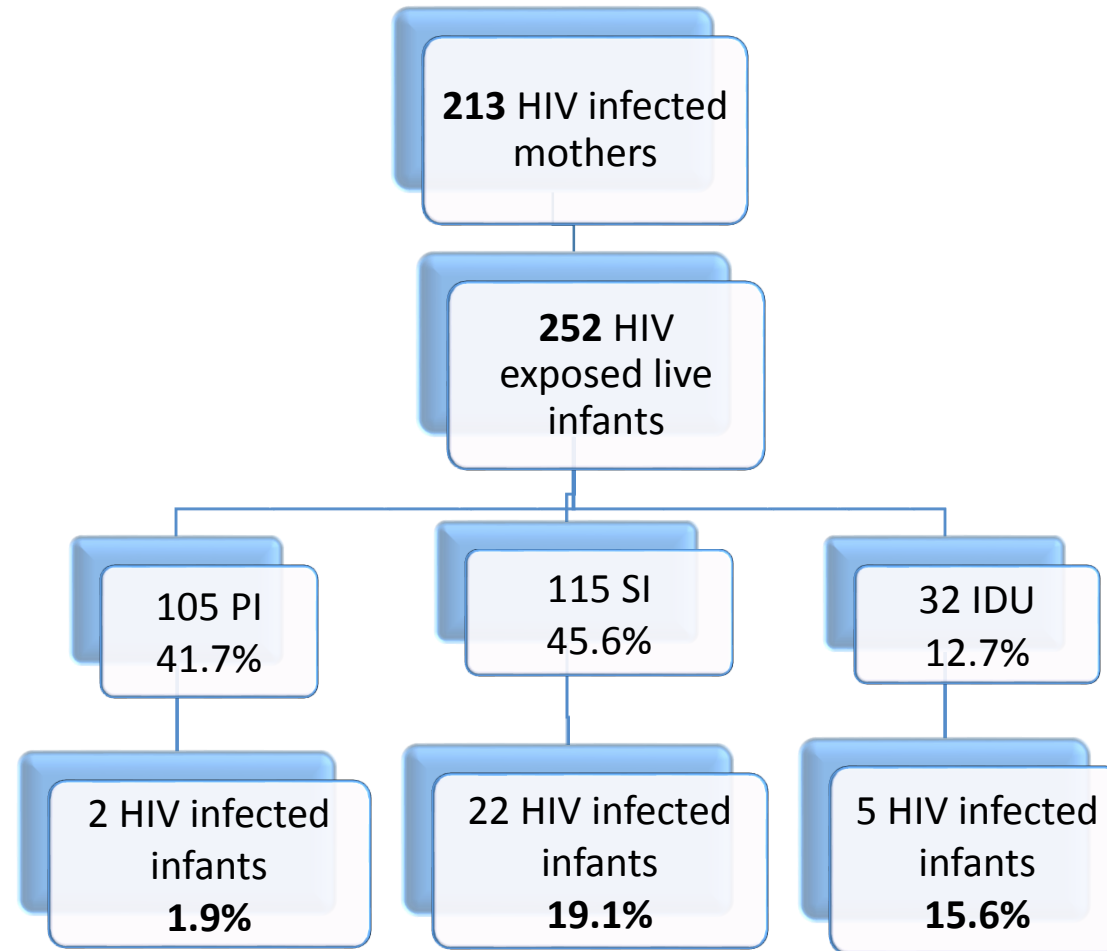
Methods: Prospective cohort study on PI, SI and IDU mothers admitted at “Victor Babes “ Clinical Hospital for Infectious Diseases (VBH) between January 2000 and December 2014.

Statistical analysis was performed using STATA 11 (College Station, Texas, USA). Comparison among the 3 groups of pregnant women were made using ANOVA or Kruskal-Wallis test for continuous and Fischer's exact or chi square test for nominal variables.

Study period 2000 – 2014 in a single center in Bucharest

2498 HIV infected patients
1138 (45.5%) HIV infected women

564 (22.6%) parenterally HIV infected young adults alive
265 (46.9%) - women

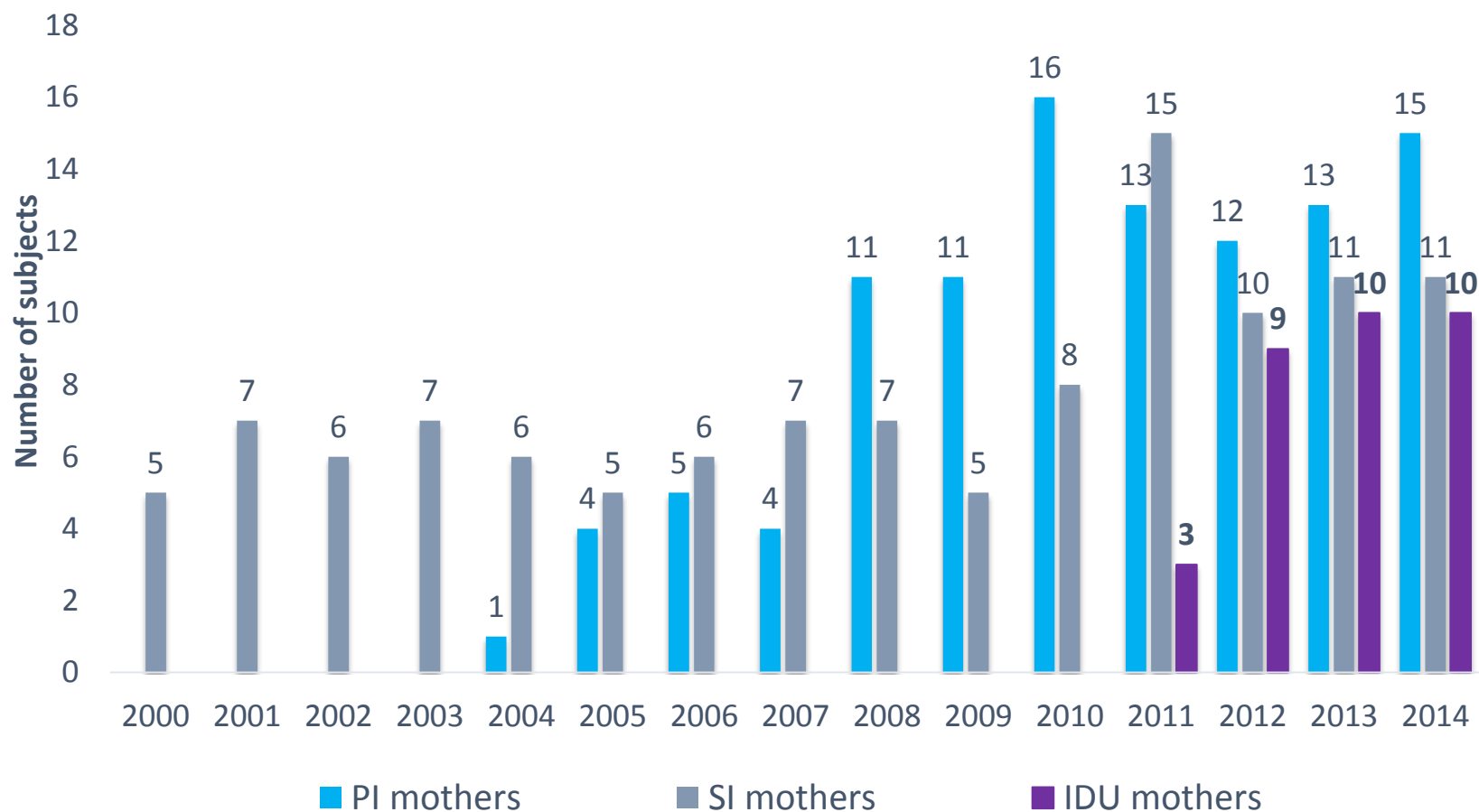


$P = 0.0001$

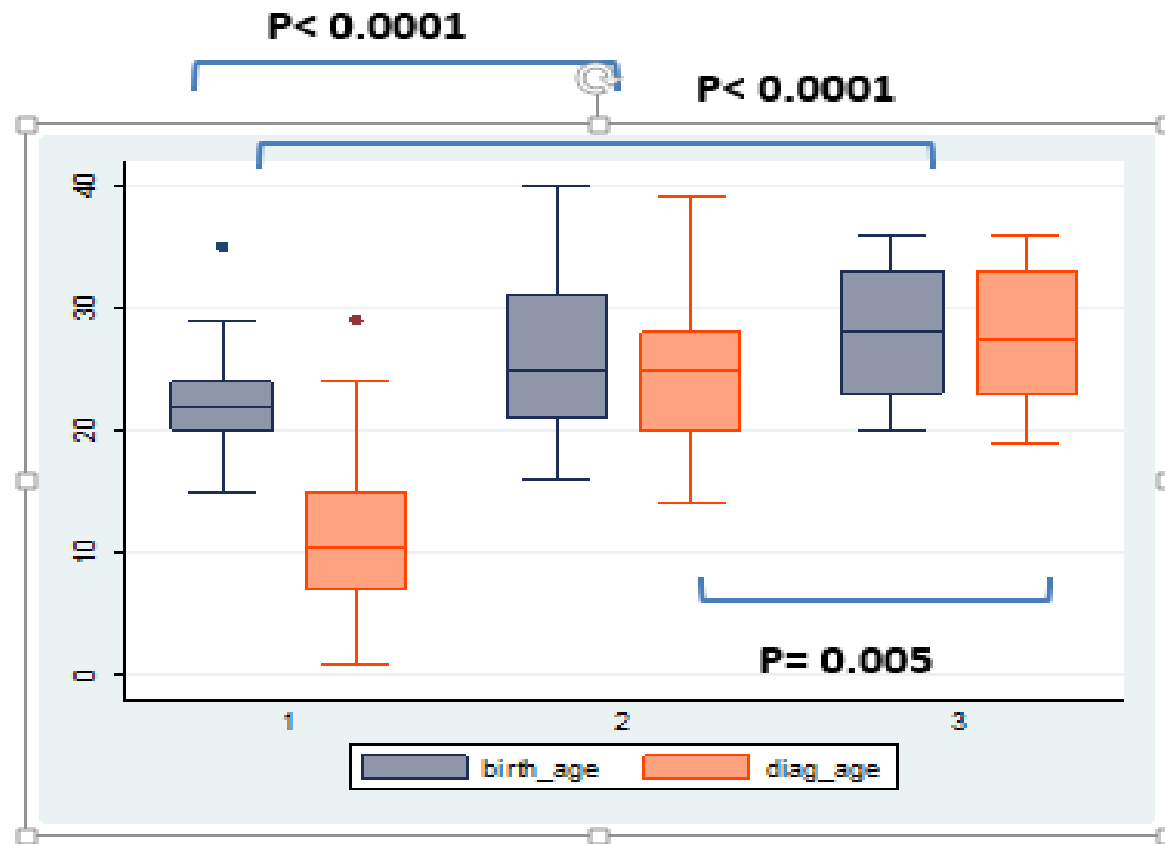
overall MTCT rate: **11.5%** (29/252)

11 children born to SI mothers were diagnosed after their first year of life.

Distribution per year of pregnant women by mode of HIV acquisition: parenterally (PI mothers), by sexual mode (SI mothers) and by injecting drug use (IDU mothers)



Age at HIV diagnosis and age at delivery: comparison between PI, SI and IDU mothers



1 - PI mothers
2 - SI mothers
3 - IDU mothers

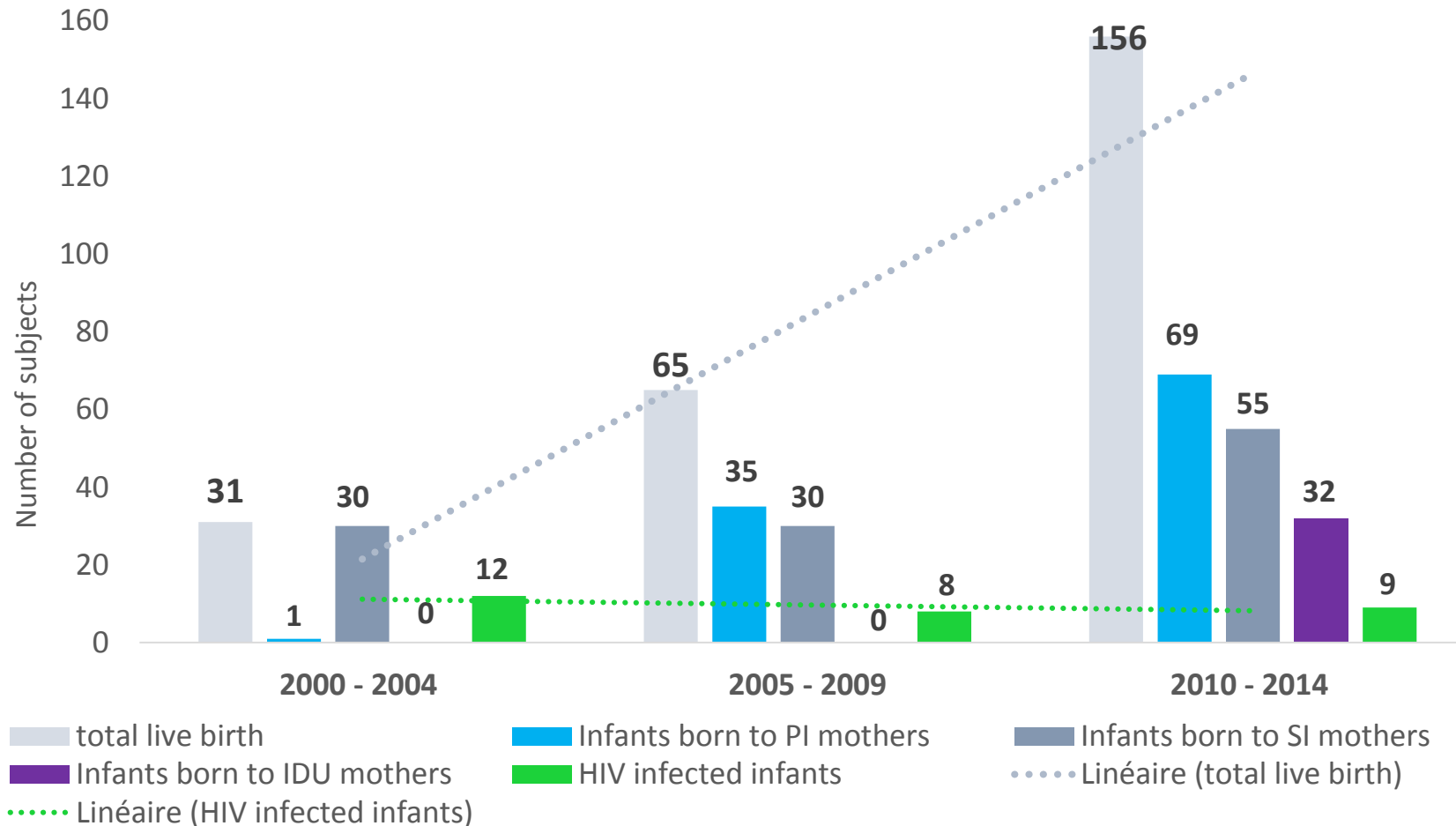
Demographic and clinical characteristics: comparison between PI, SI, IDU mothers

| Maternal characteristics | | PI (n = 105) | SI (n = 115) | IDU (n = 32) | P value |
|--|--------------|--------------------|------------------|--------------------|------------------|
| Age [years] at HIV diagnosis | median (IQR) | 11 (7,15) | 25 (20,28) | 26.5 (21.5,33.5) | 0.0001 |
| Age [years] at delivery | median (IQR) | 22 (20,24) | 25 (21,29) | 28.5 (22.5,33.5) | 0.0001 |
| HIV serostatus known before pregnancy | n (%) | 96 (91.4) | 40 (34.7) | 5 (15.6) | <0.0001 |
| Living in serodiscordant couple | n (%) | 63 (60.0) | 39 (33.9) | 3 (9.37) | <0.0001 |
| Single mother | n (%) | 28 (26.6) | 21 (18.2) | 14 (43.7) | 0.01 |
| Co-infected with HCV | n (%) | 4 (3.8) | 1 (0.86) | 30 (93.7) | <0.0001 |
| Co-infected with HBV | n (%) | 17 (16.1) | 7 (6.08) | 1 (3.1) | 0.02 |
| CD4 count at delivery [cells/mm ³] | median (IQR) | 546 (352,695) | 512 (366,703) | 540 (469,682) | 0.70 |
| HIV-RNA log ₁₀ at delivery [copies/mL] | median (IQR) | 1.3 | 2.63 (1.3, 4.03) | 4.21 (2.88, 4.82) | <0.001 |
| HIV-RNA log ₁₀ undetectable at delivery | n (%) | 56 (53.3) | 23 (20.0) | 2 (6.3) | <0.0001 |

Pregnancy characteristics in PI, SI and IDU mothers

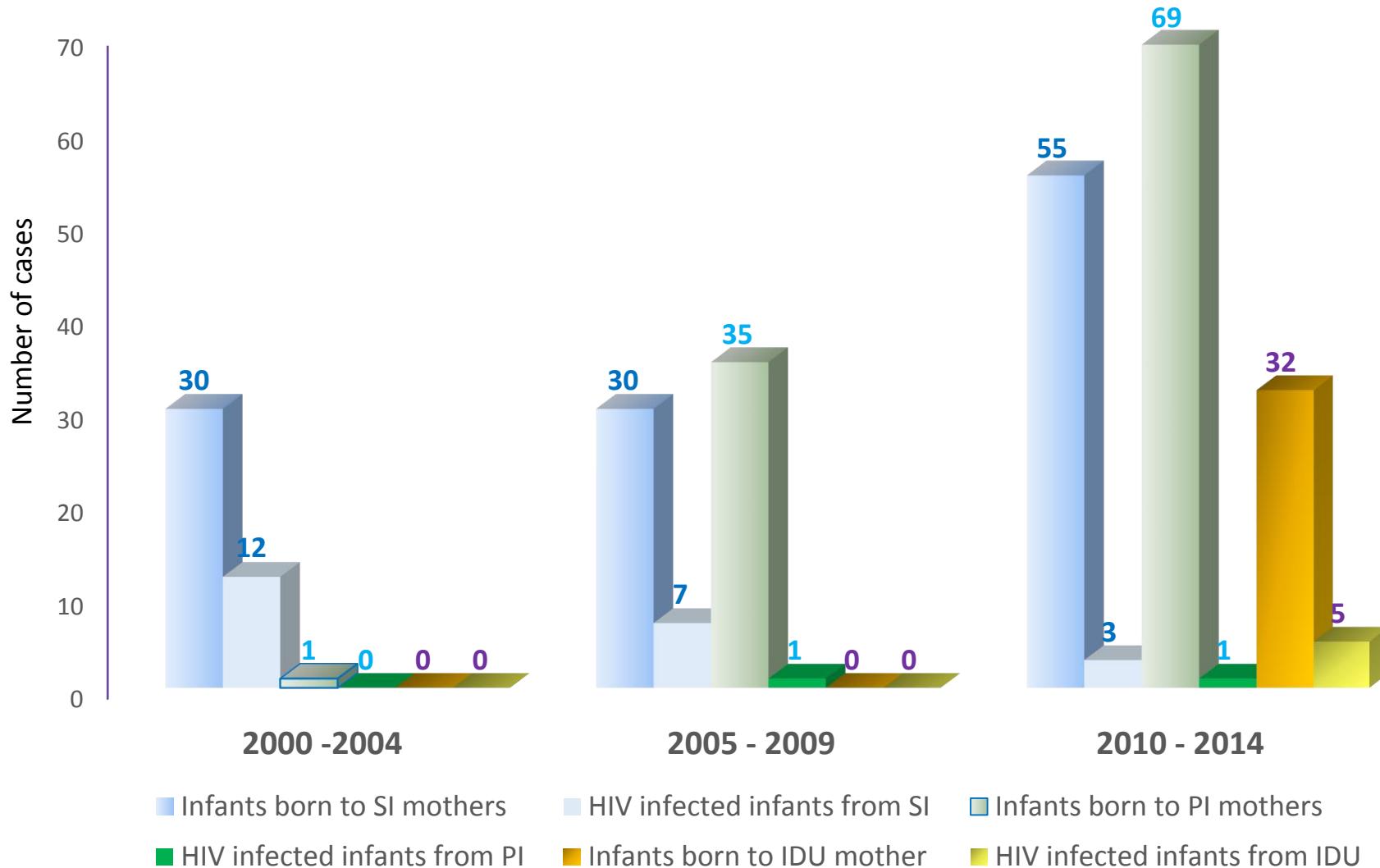
| Characteristics | | PI (n = 105) | SI (n = 115) | IDU (n = 32) | P value |
|----------------------------|-------|------------------|------------------|------------------|-------------|
| cART during pregnancy | n (%) | 98 (93.3) | 61 (53.0) | 8 (25.0) | <0.0001 |
| Salvage cART regimens | n (%) | 14 (13.3) | 1 (0.86) | 0 (0.0) | 0.001 |
| Vaginal delivery | n (%) | 14 (13.3) | 41 (35.6) | 15 (46.8) | <0.0001 |
| Elective caesarean section | n (%) | 71 (67.6) | 50 (43.4) | 6 (18.7) | <0.0001 |
| Breastfeeding mothers | n(%) | 2 (1.9) | 25 (21.7) | 3 (9.3) | <0.0001 |
| Preterm birth (< 37 weeks) | n (%) | 23 (21.9) | 17 (14.7) | 10 (31.2) | 0.09 |
| Multiple pregnancies | n (%) | 20 (19.0) | 8 (6.9) | 3 (9.37) | 0.02 |
| Abandonment | n (%) | 1 (0.95) | 5 (4.34) | 7 (21.8) | <0.0001 |
| Infant birthweight | n (%) | | | | <0.0001 |
| ≥ 3000 g | | 42 (40.8) | 50 (49) | 4 (14.8) | |
| 2500 - 2999 g | | 33 (32.0) | 17 (16.7) | 4 (14.8) | |
| 2000 - 2499 g | | 22 (21.3) | 32 (31.3) | 16 (59.3) | |
| < 2000 g | | 6 (5.8) | 3 (2.9) | 3 (11.1) | |

Distribution per years of live infants born to PI, SI and IDU mothers (VBH 2000 - 2014)



The MTCT rate decreased from 38.7% (12/31) between 2000-2004 to 12.3% (8/65) in 2005-2009 and to 5.7 % (9/156) in 2010-2014 ($p=0.0002$)

Distribution of HIV infected infants by modes of HIV acquisition in mothers



Conclusions

- There were important differences in the demographic characteristics and pregnancy outcomes between the groups, the MTCT rate being strikingly higher in SI and IDU vs. PI mothers.
- Most of the PI mothers were aware of their HIV status, received cART and were undetectable at delivery. IDU were usually single mothers, coinfectd with HCV and often discovered with HIV after delivery.

Key messages

Measures to prevent the risk of HIV transmission to infants through breastfeeding:

- **Preventing transmission between discordant couples !!**
- Early identification of incident infection in postpartum women (by periodic re-testing) and immediate testing of their children is crucial.
- Counselling of postpartum women and their partners regarding the risk of HIV transmission during breastfeeding (including the recommendation for condom use).
- Integrated health educational interventions and promotion of HIV care and support services (education for HIV infected couples but also for health care professionals)
- Identifying barriers to HIV adherence.
- Creating women's psychosocial support groups
- Laboratory system strengthening to prevent delayed postpartum diagnosis



Thank you!

