Azienda Ospedaliera
SAN PAOLO
POLO UNIVERSITARIO

Gestione della terapia antiretrovirale in gravidanza

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Donne e HIV, una questione di genere- Ravenna , 2 luglio 2013

HIV e fertilità

- Over the past several years, the worldwide HIV epidemic has reached gender parity, and furthermore, over **80%** of HIV-positive women are of **reproductive age**

  Loufty et al, PlosOne Dec 2009

- This combination of factors suggests that many HIV-positive women may **desire to become pregnant** and that pregnancy planning will become an increasingly important component of HIV medicine

- It is important **to understand the fertility desires** and intentions of the current generation of HIV-positive women in order **to develop programs to support them** and their current and future counterparts in planning safer pregnancies that protect the health of the women, their partners and their children

Desiderio di maternità

- Le scelte riproduttive dei soggetti con infezione da HIV sono guidate da una moltitudine di fattori personali, interpersonali, socio-economici, sanitari e di genere *(Cooper 2007, Mattabi 2009)*

- I concetti di *desiderare* e *decidere* di avere figli sono in realtà ben diversi tra loro *(Kannippan 2008; Oosterhoff 2008; Chen 2001)*

Alterazioni del ciclo mestruale

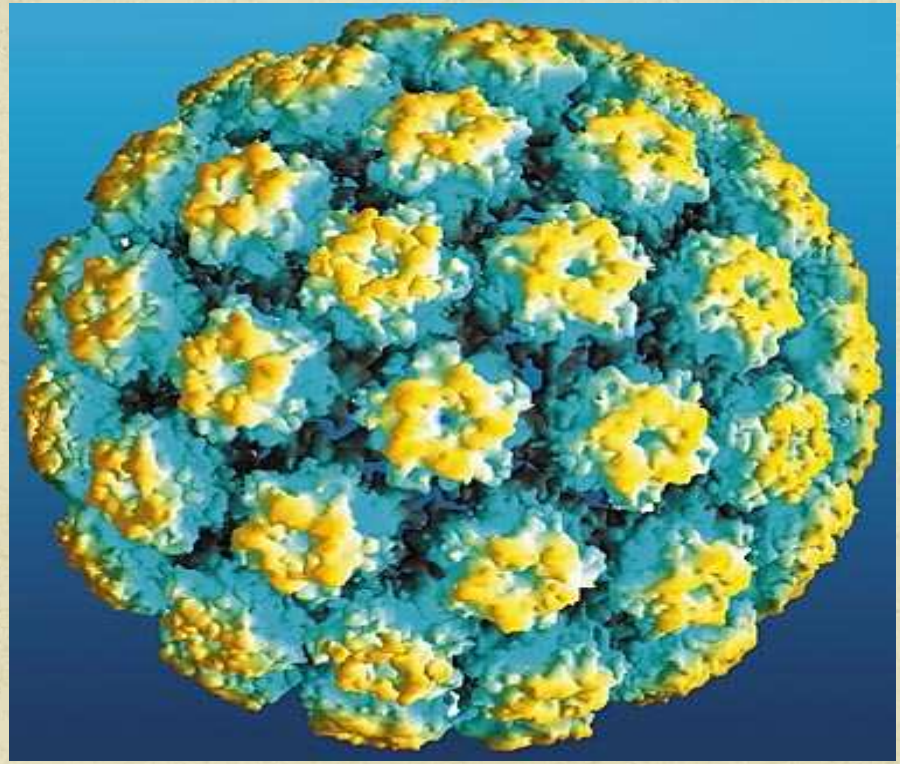
Non è chiaro se le donne HIV positive siano più predisposte ad avere alterazioni del flusso mestruale rispetto alle donne HIV negative

- **In 248 donne HIV+ vs 82 donne HIV-:**
  - le pazienti HIV + presentavano un intervallo tra i cicli > di 6 settimane e < di 3 mesi e maggiore predisposizione a dismenorrea, sindrome premestruale e cicli anovulatori rispetto alle donne HIV –
  - solo il 5% delle donne presentava cicli con intervalli > 6 mesi e questo dato è risultato essere sovrapponibile alla popolazione HIV negativa (Chirgwing KD 1996)

- **Risulta essere ancora controversa l'associazione tra bassi livelli di CD4+ e alterazioni del ciclo mestruale**

(Clark RA 2001)

Malattie a trasmissione sessuale e disturbi ginecologici nella donna in età fertile



Attività degli ormoni sessuali

- Gli ormoni sessuali esercitano un importante ruolo a livello della mucosa genitale

- E' dimostrato un incremento di spessore della mucosa vaginale legato all'azione degli estrogeni, ed un epitelio più spesso potrebbe essere in grado di rendere più difficile l'ingresso dei patogeni responsabili delle MTS e l'azione sulle cellule target (CD4+ , cell. Di Langerhans, macrofagi)

Attività degli ormoni sessuali

- L'azione degli estrogeni porta anche ad una diminuzione del pH cervico-vaginale, rendendo l' ambiente meno favorevole ai patogeni

- Le donne in post-menopausa sono 4-8 volte più suscettibili all'infezione a causa della bassa concentrazione di estrogeni e del conseguente assottigliamento e secchezza della mucosa vaginale

(Zdenek et Al. 2010)

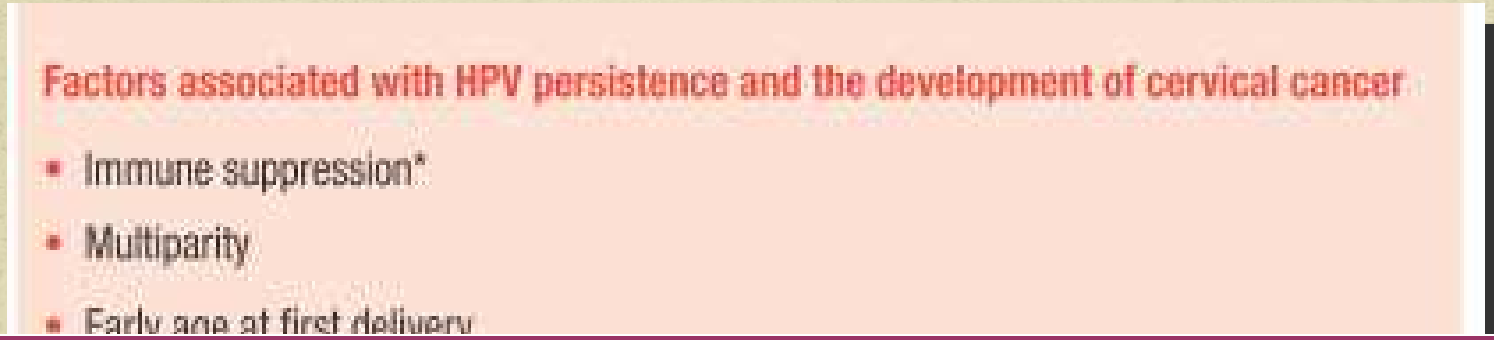
Malattie a trasmissione sessuale nella donna HIV-positiva

- In Italia la MTS più diffusa è la vaginite batterica non gonococcica non clamidiale (27,4%), seguita dalla condilomatosi genitale

- Tra le donne, il 75% delle MTS sono di origine batterica, mentre è limitato il numero di casi di gonorrea e di sifilide

- Alcune particolari condizioni ginecologiche sono più comune, più gravi e/o più difficili da trattare nelle donne HIV-positive rispetto alle sieronegative
- Le donne HIV-positive sono 10 volte più a rischio di avere un Pap-test anormale rispetto alle sieronegative
- Un Pap-test anormale è di solito associato a una bassa conta di CD4 e all'infezione da HPV

HPV- Infezione persistente



Fattori associati con la persistenza di HPV e lo sviluppo del cancro della cervice uterina

-Immunosoppressione
-Multiparità
-Età precoce del primo parto
-Uso a lungo termine di contraccettivi ormonali
-Fumo di sigaretta
-Infezione con altre malattie a trasmissione sessuale
(ad es. Clamidia trachmatis e Herpes virus tipo 2)
-Infezione da HIV : le persone con HIV hanno un piu' alto rischio di infezione da HPV , di persistenza del virus e di essere infettate da un piu' ampio range di ceppi di HPV.

- Nelle donne HIV positive la prevalenza di HPV-DNA a livello della cervice uterina è maggiore rispetto alle sieronegative, pur aggiustando il dato per l'età e abitudini sessuali

- Inoltre alcuni studi indicano che la persistenza dell'infezione da HPV aumenta tra le donne HIV+ rispetto ai controlli sani

Sun et al N Eng J Med, 1999

- Non sembrano esserci differenze significative nella frequenza dei diversi genotipi di HPV (HR e LR) tra donne HIV neg ed HIV pos

- Diversi studi hanno dimostrato un aumentata prevalenza di coinfezione da parte di multipli genotipi di HPV nelle pazienti HIV positive. Il dato non correla con il numero di CD4, suggerendo che sia da riferirsi più probabilmente ad un aumentato numero di partners sessuali piuttosto che al grado di immunodepressione delle pazienti

  Riva et al Clin Microbiol Infect 2007

- Di contro altri autori hanno evidenziato una correlazione significativa tra elevato numero di CD4+ T-cells e clearance di HPV

  Minhee Kang et al poster at CROI 2010

- 154 HIV+ women undergoing pap-test and colposcopy, stratified in two groups (follow-up 6-12 months):
  - significant reduction of HPV positive biopsies in patients on stable HAART as compared to patients undergoing recent tehrapy switch (Uberti-Foppa, 2003)
- 168 HIV+ women (96 on HAART) undergoing pap-test, colposcopy and biopsy (follow-up 12 months):
  - 2 fold higher probability of regression of CIN in patients on HAART vs naive (Heard,2002)

HAART seems to improve the prognosis of cervical cancer but does not eliminate the risk of progression

Desiderio di maternità

- Come la popolazione generale, le donne HIV-positive desiderano avere figli indipendentemente del loro stato di sieropositività *(Chama 2007; Chen 2001; Nobrega 2007;Panozzo 2003;Wesley 2003*) e continuano a farlo anche dopo la diagnosi. *(Craft 2007; Bedimo-Rang 2005; Sowell 2002)*

- Le donne HIV-positive più consapevoli del proprio stato sono quelle meno propense a desiderare di avere e ad avere un bambino dopo la diagnosi *(Pelzer 2008; Nakayia 2006; Baek and Rutenberg 2005; Richter 2002; Feldman and Maposphere 2003)*

Fattori che influenzano positivamente il desiderio di maternità

1. **Età** *(Nobrega 2007; Nakayiawa 2006; Myer 2007; Olgivie 2007)*
2. **Numero di figli in vita, avere già un figlio**

   (Nobrega 2007; Nakayiawa 2006; Myer 2007;

   Sherr and Barry 2004, Chen 2001)
3. **Prospettiva di maternità** *(Smith and Mbakwem 2007;*

   Cooper 2007; Sherr and Barry 2004; Kannippan 2008)
4. **PMTC e programmi terapeutici** *(Peltzer 2008; Cooper 2007;*

   Oosterhoff 2008; Kannippan 2008; Myer 2007; Nakayiawa 2006)
5. **Stato di salute soggettivo** *(Chen 2001)*

Fattori che influenzano positivamente il desiderio di maternità

6. **Influenze coniugali, familiari, sociali e culturali** *(Oosterrhoff 2007; Ko and Muecke 2005; Craft 2007)*
7. **Stigma** *(Cooper 2007; Craft 2007;)*
8. **Etnia** *(Chen 2001)*

Fattori che disincentivano la maternità

1. **Preoccupazione per lo stato di salute del bambino**

   (Cooper 2007; Craft 2007; Kannipan 2008; Oosterhoff 2008; Baek and Rutenberg 2005)

2. **Esperienza di mortalità infantile HIV/AIDS correlata**

   (Cooper 2007; Craft 2007;)

3. **Atteggiamento dei "caregivers"** *(Nobrega 2007; Cooper 2007; Oosterhoff 2008; Craft 2007)*

4. **Disapprovazione da parte della comunità, stigma**

   (Nobrega 2007; Cooper 2007; Oosterhoff 2008; Craft 2007)

Dati dal “National Programme on Surveillance on ART in Pregnancy”*

- Tra il 2002 e il 2008 63 casi di gravidanza terminata con IVG sono stati confrontati con 334 casi di gravidanza a termine

- I casi di IVG risultavano correlati con la mancata pianificazione della gravidanza, gravidanze precedenti, bassa conta di CD4, partner sieropositivo

**Floridia M et al, AIDS Care, Vol 22, No 1, January 2010, 50-53*

Unplanned pregnancy

Gravidanze non pianificate

- Up to 83% of pregnancies in HIV+ women reported as 'unplanned'
- Risk factors for unplanned pregnancy similar to those for HIV:
  - substance abuse (the woman or her partner)
  - mental illness
  - domestic violence
  - frequent unstable sexual relationships and unsafe sexual practices in adolescents

Fino all'83% delle gravidanze in donne HIV positive risulta essere ' non pianificata'
Fattori di rischio per gravidanze non pianificate
simili o in comune a quelli per l'infezione da HIV:
-uso di sostanze (da parte della donna o del suo partner)
-disagio psichico
-violenza domestica
-frequente instabilità nelle relazioni sessuali e sesso non sicuro in adolescenza

Koenig, LJ et al. Am *J Obstet Gynecol*, 2007

Routine reproductive counselling for women with HIV is important

- In a survey of 700 women with HIV, 22% became pregnant after HIV diagnosis, but
  - 57% of these never discussed pregnancy or treatment options before pregnancy
  - 42% had limited/no knowledge of ART options during early pregnancy
- Among women considering pregnancy, or pregnant at the time of HIV diagnosis
  - 41% did not discuss impact of pregnancy on ART
  - 29% did not discuss adverse effects of ART

Bridge DA, et al. IAS Mexico City 2008

Che cosa è un counselling sul desiderio di maternità?

Discutere su:

- **Contraccezione**
- **Riproduzione**
- **Concepire in sicurezza**
- **Impatto di HIV sulla gravidanza**
- **Impatto della gravidanza su HIV**
- **Problematiche del post-partum**

(aderenza alla terapia)

- **Essere in grado di gestire una maternità**
- **Trasmissione verticale**
- **Come sapere se il bambino è sano**
- **Uso di HAART in gravidanza**

- **Tutto questo dovrebbe coinvolgere la coppia**

Interazione tra contraccettivi orali e farmaci antiretrovirali

Efavirenz	• Aumenta i livelli dell'etinil estradiolo (del 37%) • Utilizzare metodi alternativi o addizionali
Nevirapina	• Riduce i livelli dell'etinil estradiolo (del 20%) • Utilizzare metodi alternativi o addizionali
Lopinavir	• Riduce i livelli dell'etinil estradiolo (del 42%) • Utilizzare metodi alternativi o addizionali
Amprenavir	• Utilizzare metodi alternativi o addizionali
Saquinavir	• Dati non disponibili
Nelfinavir	• Riduce i livelli di noretindrone (del 18%) e dell'etinil estradiolo (del 47%) • Utilizzare metodi alternativi o addizionali
Ritonavir	• Riduce i livelli dell'etinil estradiolo (del 40%) • Utilizzare metodi alternativi o addizionali
Indinavir	• Aumenta i livelli di noretindrone (del 26%) e dell'etinil estradiolo (del 24%) • Utilizzare metodi alternativi o addizionali

Reproductive Options for HIV-Concordant and Serodiscordant Couples
(Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

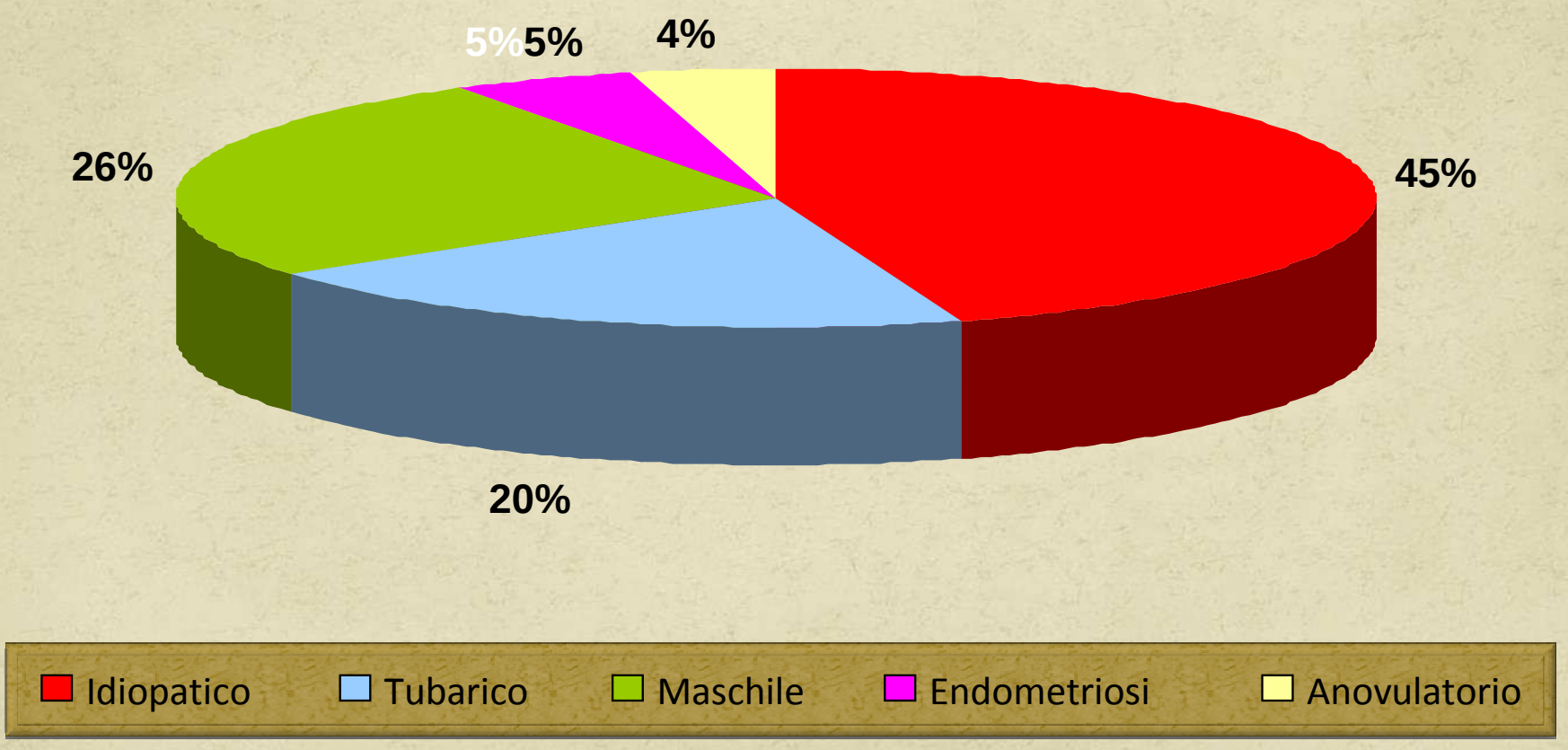
- For serodiscordant couples who want to conceive, expert consultation is recommended so that approaches can be tailored to specific needs, which may vary from couple to couple **(AIII)**. It is important to recognize that treatment of the infected partner may not be fully protective against sexual transmission of HIV.
- Partners should be screened and treated for genital tract infections before attempting to conceive **(AII)**.
- For HIV-infected females with HIV-uninfected male partners, the safest conception option is artificial insemination, including the option of self-insemination with a partner's sperm during the peri-ovulatory period **(AIII)**.
- For HIV-infected men with HIV-uninfected female partners, the use of sperm preparation techniques coupled with either intrauterine insemination or *in vitro* fertilization should be considered if using donor sperm from an HIV-uninfected male is unacceptable **(AII)**.
- For serodiscordant couples who want to conceive, initiation of antiretroviral therapy (ART) for the HIV-infected partner is recommended (**AI** for CD4 T-lymphocyte (CD4-cell) count ≤550 cells/mm^3, **BIII** for CD4-cell count >550 cells/mm^3). If therapy is initiated, maximal viral suppression is recommended before conception is attempted **(AIII)**.
- Periconception administration of antiretroviral pre-exposure prophylaxis (PrEP) for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission **(CIII)**. The utility of PrEP of the uninfected partner when the infected partner is receiving ART has not been studied.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Fattori di infertilità in coppie HIV discordanti

-fonte: Ospedale San Paolo-



VALUTAZIONE GINECOLOGICA

Necessaria valutazione del grado di fertilità di una coppia sieropositiva o sierodiscordante se desiderio di maternità

Quando avviene la trasmissione materno-fetale?

La trasmissione verticale avviene più frequentemente:

- nell'ultimo trimestre di gravidanza per passaggio transplacentare
- durante il travaglio o al momento del parto
- durante l'allattamento

Il 30-50% delle trasmissioni verticali avvengono in utero mentre il 50-70% avvengono immediatamente prima o al momento del parto (*Kuhn et al, 1997*)

Quando avviene la trasmissione materno-fetale?

- Corioamniositi, prolungata rottura delle membrane, ritardato sviluppo intrauterino sembrano svolgere un ruolo nella trasmissione in utero

- La trasmissione durante il parto può essere determinata da microtrasfusioni transplacentari, attraverso il contatto diretto delle mucose fetali con fluidi e sangue infetto o per lesioni cutanee fetali (*Lyall et al,1999*)

Come prevenire la trasmissione materno fetale

Il tasso di trasmissione verticale varia tra il 21 e il 43% in assenza di accesso alle TARV e in presenza di parto vaginale e allattamento materno

Nei paesi in via di sviluppo dove non è possibile accedere alla HAART ma si può utilizzare un regime semplice di terapia ARV il tasso di trasmissione è inferiore al 5%

HAART

Parto cesareo elettivo prima dell'inizio del travaglio

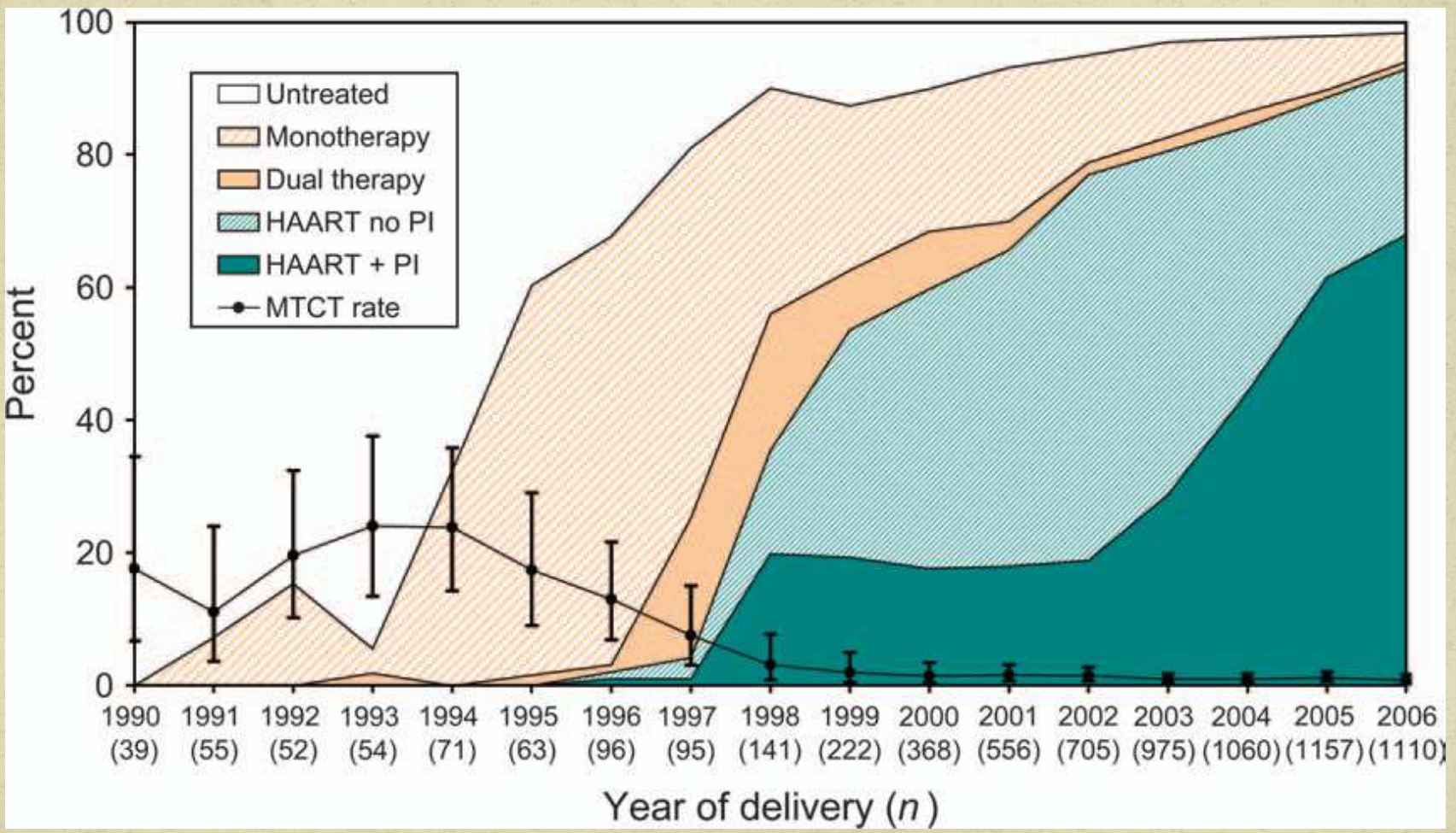
Allattamento artificiale

Il tasso di trasmissione si riduce al di sotto dell'1%

Riduzione della trasmissione verticale di HIV in epoca HAART

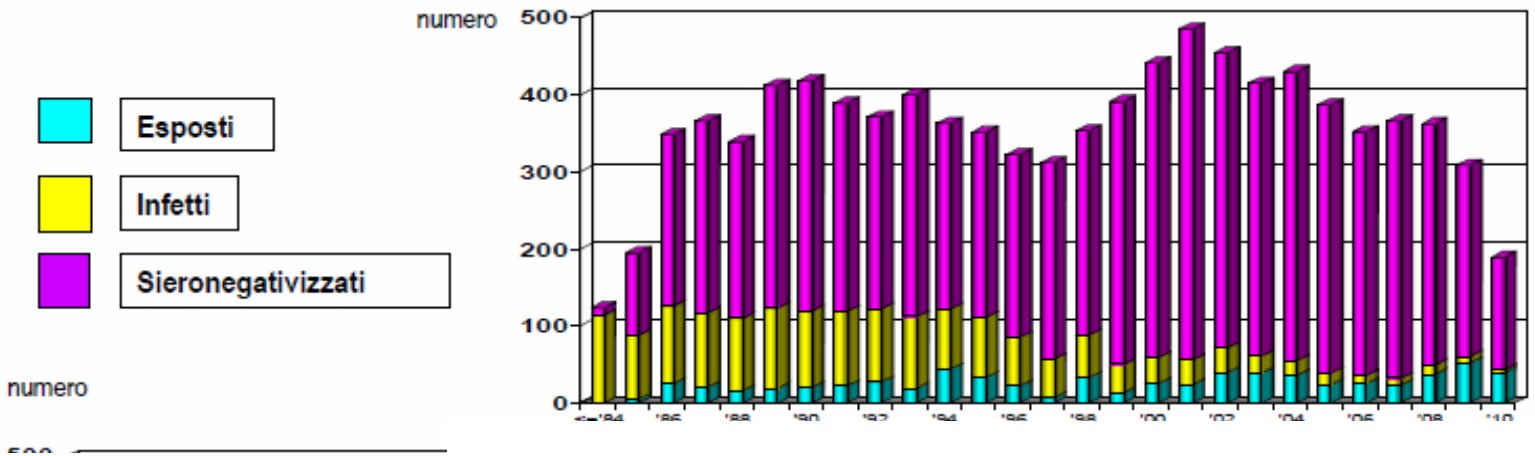
- ✓ Il rischio di trasmissione materno-fetale di HIV si è ridotto con successo solo nei paesi industrializzati (rischio globale 1.2% su 5151 gravide in UK dal 2000-2006, e 0.7% se in terapia con 3 farmaci e programmato parto cesareo)
- ✓ Negli ultimi anni nell'est Europa si è assistito a un incremento del 40% delle nascite di bambini da donne HIV positive
- ✓ Nei Paesi in via di sviluppo il tasso di trasmissione rimane elevato: ogni giorno nascono 1800 bambini sieropositivi

Use of antiretroviral therapy and mother-to-child transmission rates (with 95% CI) by year of delivery, 1990–2006 in the ECS.

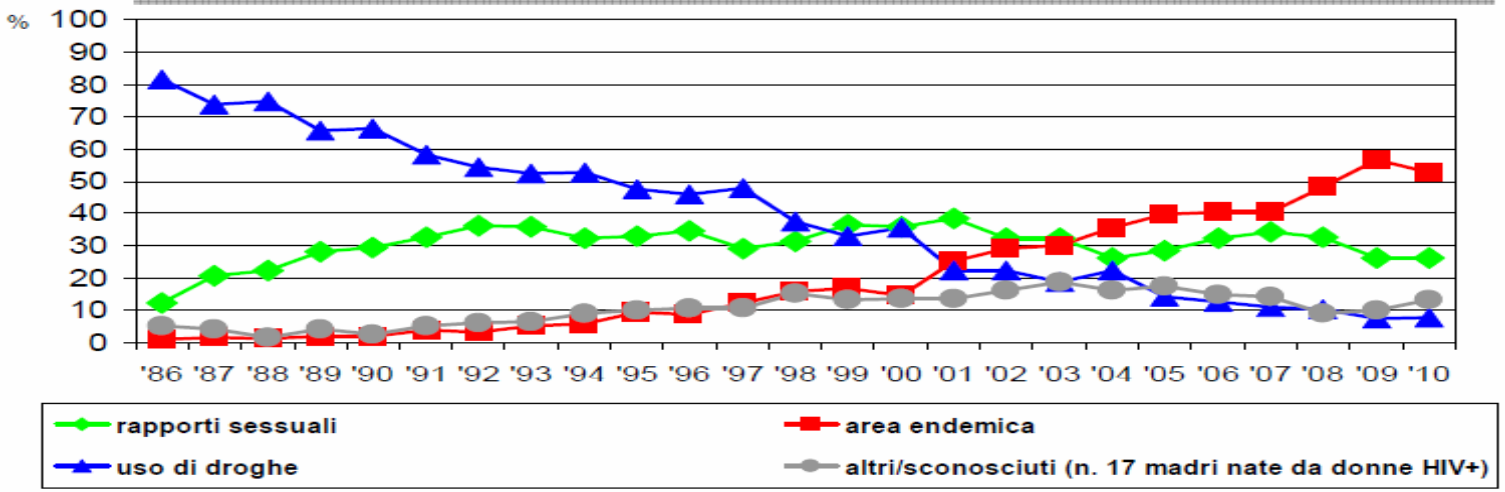


MTCT (mother-to-child transmission)

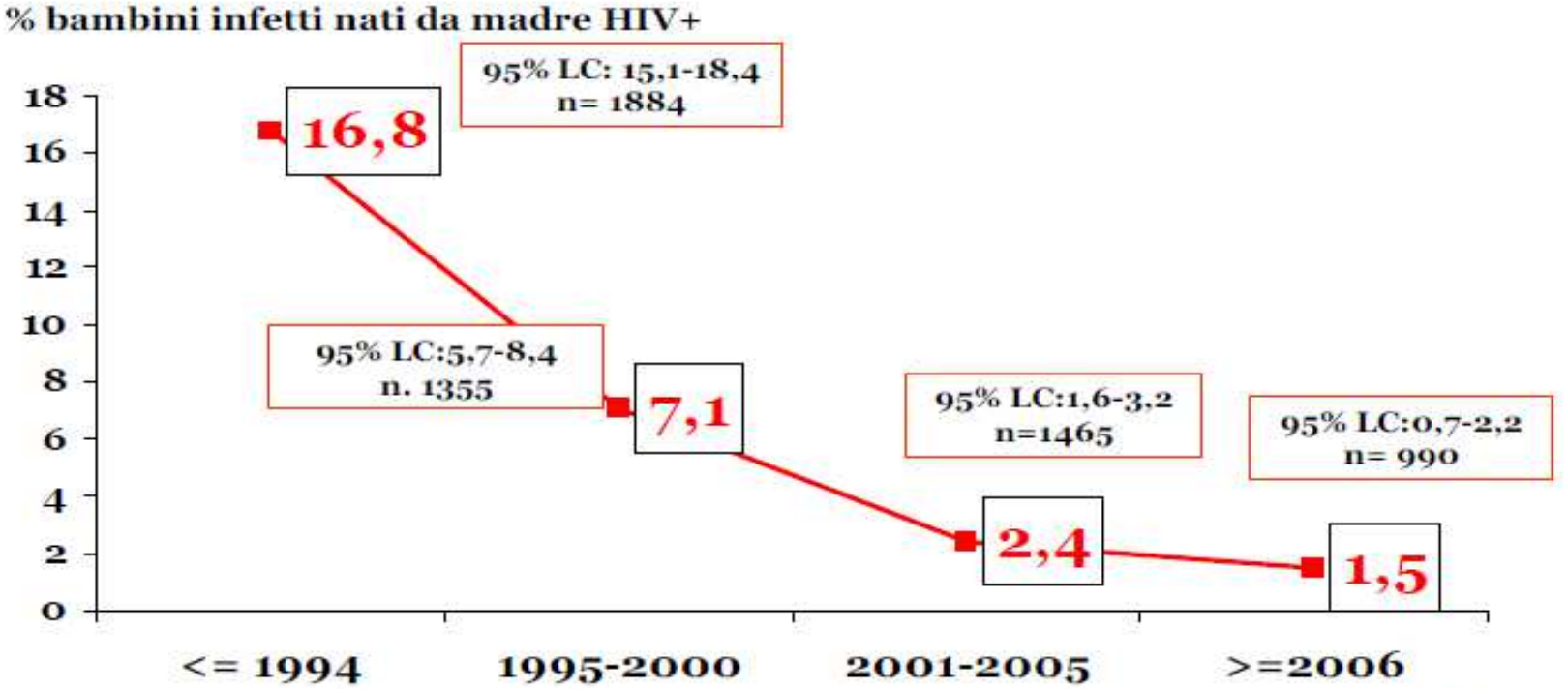
BAMBINI NATI DA MADRE HIV-1+



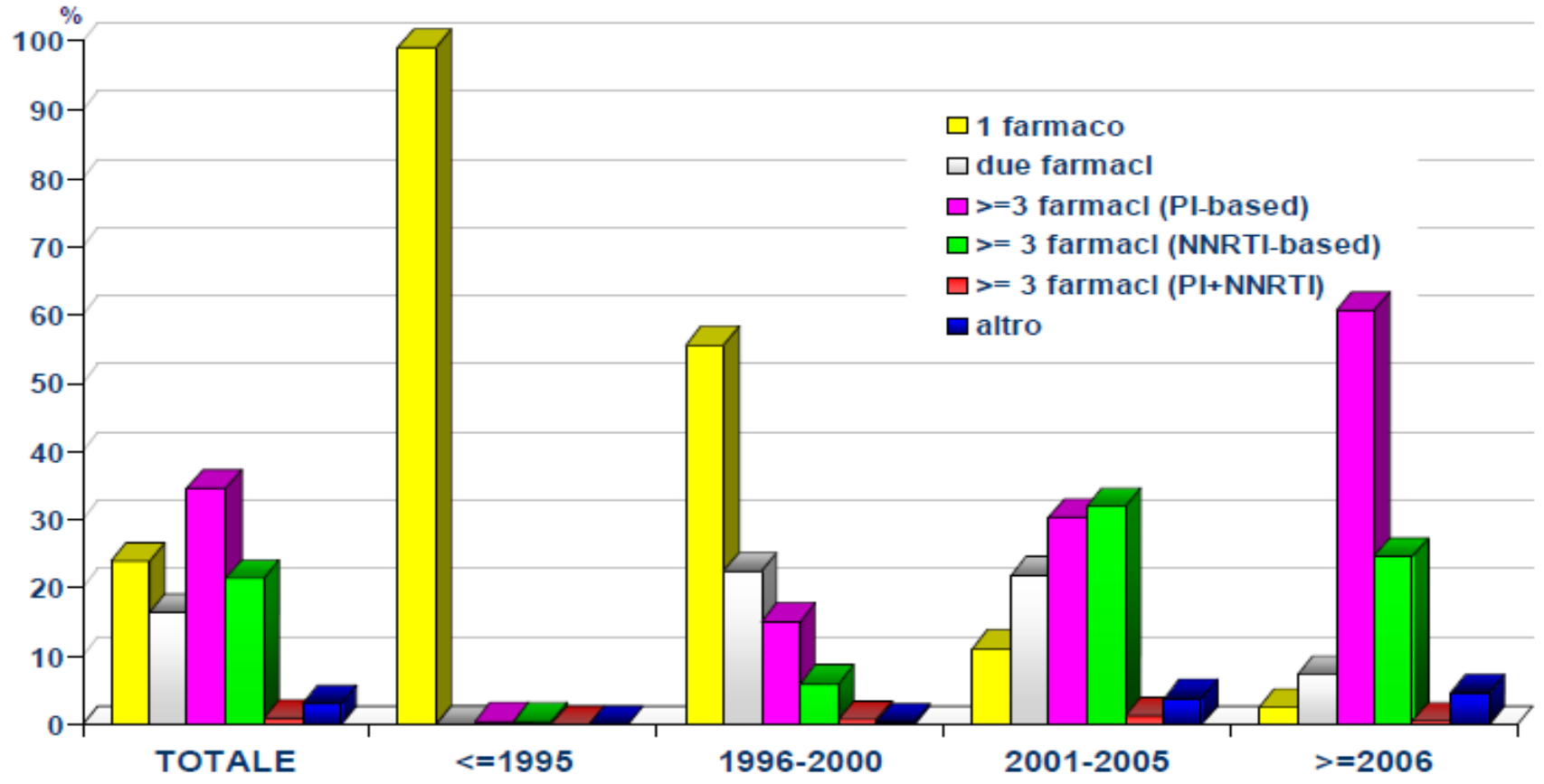
FATTORI DI RISCHIO MATERNO PER L'INFEZIONE DA HIV



TRASMISSION RATE PER PERIODO DI NASCITA
(bambini con oltre 2 mesi di età)



TERAPIE ARV NELLE MADRI IN GRAVIDANZA NEL CORSO DEGLI ANNI (n=5381)



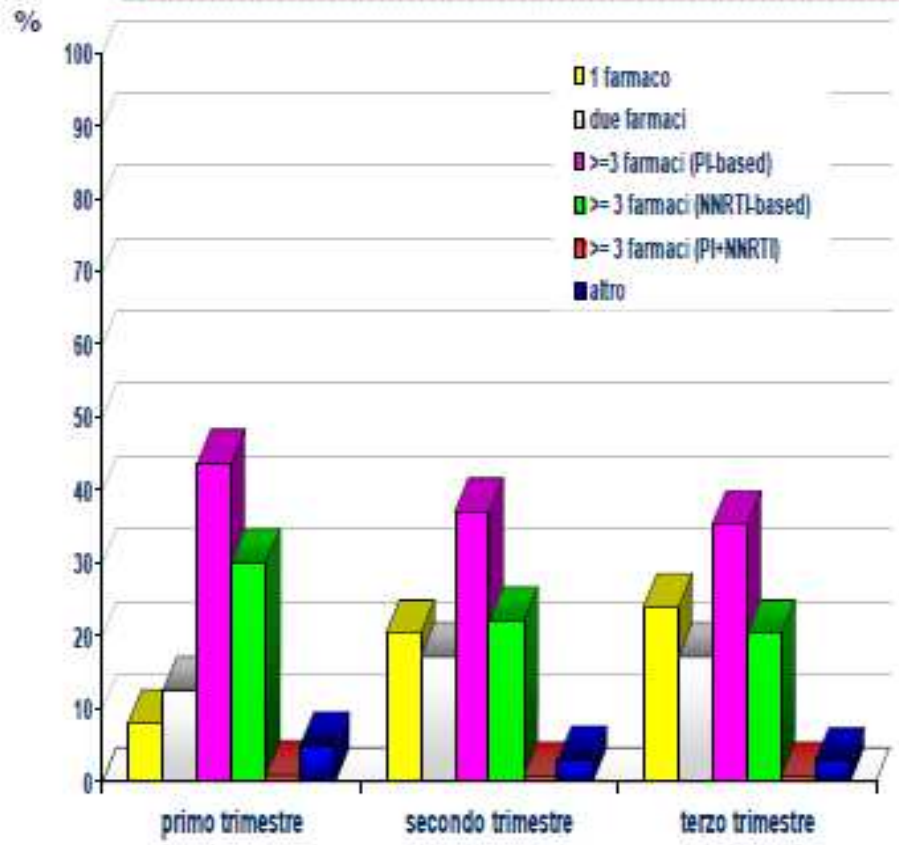
18° Workshop

Registro Italiano per
l'infezione da HIV in Pediatria

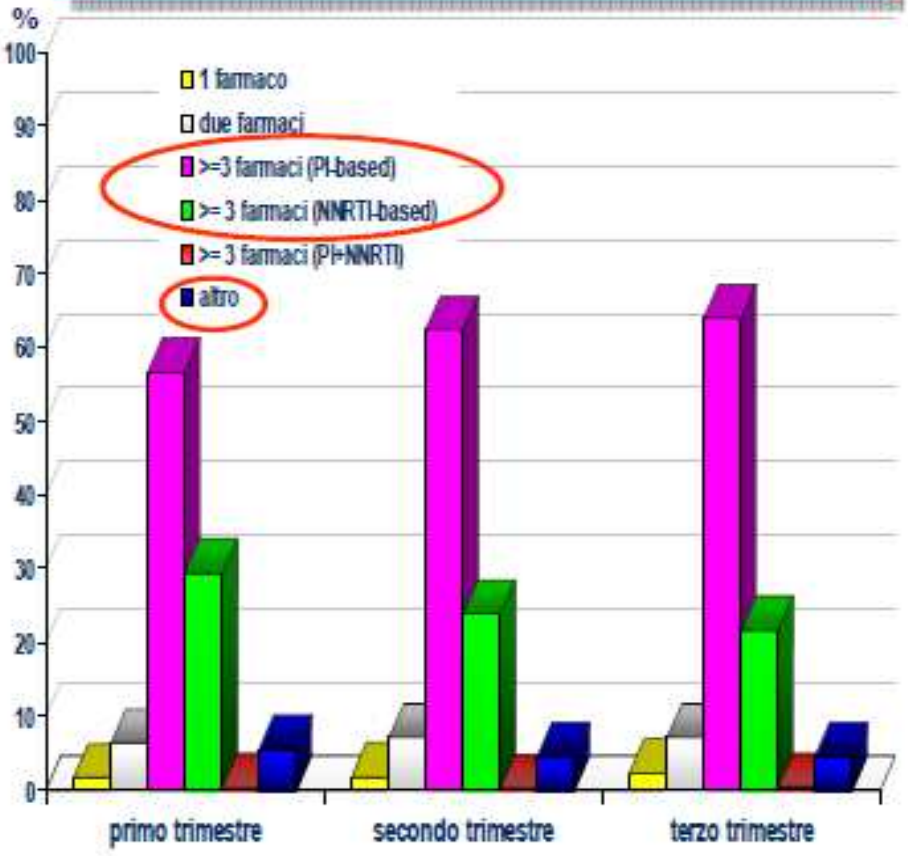
Dipartimento di Scienze Pediatriche
e dell'Adolescenza

Università degli Studi di Torino

TERAPIE ARV NELLE MADRI IN GRAVIDANZA NEL CORSO DEGLI ANNI (n=5381)



TERAPIE ARV NELLE MADRI IN GRAVIDANZA >2005 (n=1715)



Trasmissione perinatale: linee guida italiane 2012

Approccio alla terapia antiretrovirale in gravidanza

- ***L'approccio terapeutico raccomandato è quello basato sullo svolgimento combinato di terapia materna antepartum ed intrapartum e sulla profilassi antiretrovirale al neonato*** **[AI].**

- ***Tale schema terapeutico andrà applicato a tutte le donne con HIV in gravidanza, indipendentemente dai valori di CD4+ e di HIV-RNA*** **[AI].**

- ***Qualora per accesso tardivo all'assistenza non sia possibile applicare la terapia antepartum o quella intrapartum, è fondamentale applicare le restanti componenti dello schema terapeutico*** **[AII].**

Trasmissione perinatale: linee guida italiane 2012

Scenari terapeutici principali

- ***Le gravide che presentano indicazione personale al trattamento antiretrovirale dovranno ricevere un regime di combinazione di potenza analoga rispetto a quanto raccomandato al di fuori della gravidanza*** **[AI]*.***

- ***Se la donna non è ancora in trattamento ed esiste indicazione ad un trattamento immediato, questo dovrà essere iniziato appena possibile*** **[AII]*.***

- ***Per le donne che non rientrano nelle condizioni per cui una terapia antiretrovirale è indicata per la loro salute, la raccomandazione generale è di svolgere in ogni caso un regime di combinazione potente, in quanto regimi di combinazione sono risultati più efficaci nel prevenire la trasmissione verticale*** **[AII]**

Trasmissione perinatale: linee guida italiane 2012

Epoca di inizio del trattamento

- ***Non è possibile, sulla base delle evidenze disponibili, indicare un'epoca ottimale di inizio del trattamento antiretrovirale in gravidanza per le donne che non hanno indicazione personale al trattamento ma in ambito di regimi HAART una più lunga durata di terapia è risultata indipendentemente associata a ridotto rischio di trasmissione.***

- ***L'epoca di inizio trattamento deve garantire una durata di terapia sufficiente a realizzare una completa soppressione virale nelle fasi finali della gravidanza***

- ***Iniziare il trattamento all'inizio del secondo trimestre è una opzione raccomandabile in generale per ottenere i maggiori presupposti di efficacia* [BIII]*, ma l'epoca programmata per l'inizio non dovrà comunque andare oltre le 26 settimane nelle donne con carica virale inferiore a 10000 copie/ml ed oltre le 20 settimane nelle donne con carica virale superiore a 10000 copie/ml* [AII].**

- ***L'inizio del trattamento nel primo trimestre potrebbe avere efficacia aggiuntiva sulla piccola quota di casi di trasmissione che si verifica precocemente in utero. Nelle donne che si presentano oltre le 26 settimane, il trattamento andrà iniziato immediatamente* [AII].**

Trasmissione perinatale: linee guida italiane 2012

Potenza del regime

- ***In tutte le donne, comprese quelle con assenza di indicazione personale al trattamento, la potenza del regime dovrà essere adeguata a realizzare una completa soppressione virale, ed in generale dovranno essere utilizzati regimi di combinazione della stessa potenza di quelli raccomandati per il trattamento dei soggetti adulti*** **[AI]*.***

- ***Nel caso (infrequente) di donne che presentano carica virale inferiore a 1000 copie/mL in assenza di trattamento, è tuttora controverso se siano raccomandabili regimi di potenza minore a quelli raccomandati per il trattamento generale dei soggetti adulti.***

Mechanisms of Action of Antiretroviral Prophylaxis in Reducing Perinatal Transmission of HIV (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendation
• Antiretroviral (ARV) drugs reduce perinatal transmission by several mechanisms, including lowering maternal antepartum viral load and providing infant pre- and post-exposure prophylaxis. Therefore, combined antepartum, intrapartum, and infant ARV prophylaxis is recommended to prevent perinatal transmission of HIV **(AI)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Perinatal Transmission of HIV and Maternal HIV RNA Copy Number (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendation
• All HIV-infected pregnant women should be counseled about and administered antiretroviral drugs during pregnancy for prevention of perinatal transmission, regardless of their HIV RNA levels **(AI)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Antepartum Care (Last updated July 31, 2012; last reviewed July 31, 2012)

General Principles Regarding Use of Antiretroviral Drugs during Pregnancy

Panel's Recommendations

- Initial evaluation of infected pregnant women should include assessment of HIV disease status and recommendations regarding initiation of antiretroviral (ARV) drugs or the need for any modification if currently receiving antiretroviral therapy (ART) (AIII). The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV care.
- Regardless of plasma HIV RNA copy number or CD4 T-lymphocyte count, all pregnant HIV-infected women should receive a combination ARV drug regimen antepartum to prevent perinatal transmission (AI). A combination regimen is recommended both for women who require therapy for their own health (AI) and for prevention of perinatal transmission in those who do not yet require therapy (AII).
- The known benefits and potential risks of ARV use during pregnancy should be discussed with all women (AIII).
- ARV drug-resistance studies should be performed before starting or modifying ARV drug regimens in women whose HIV RNA levels are above the threshold for resistance testing (that is, >500 to 1,000 copies/mL) (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) (AIII). When HIV is diagnosed later in pregnancy, ART or combination ARV prophylaxis should be initiated promptly without waiting for results of resistance testing (BIII).
- In counseling patients, the importance of adherence to their ARV regimens should be emphasized (AII).
- Considerations regarding continuing the ARV regimen for maternal treatment after delivery are the same as in non-pregnant individuals. The pros and cons of continuing versus discontinuing ARV drugs postpartum should be discussed with women so they can make educated decisions about postpartum ARV use before delivery (AIII). Those decisions should be made in consultation with the provider who will assume responsibility for the women's HIV care after delivery.
- Coordination of services among prenatal care providers, primary care and HIV specialty care providers, mental health and drug abuse treatment services, and public assistance programs is essential to ensure that infected women adhere to their ARV drug regimens (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive) (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- All HIV-infected pregnant women should receive a potent combination antiretroviral (ARV) regimen to reduce the risk of perinatal transmission of HIV (AI). The choice of regimen should take into account current adult treatment guidelines, what is known about the use of specific drugs in pregnancy, and the risk of teratogenicity (Table 5).
- The decision as to whether to start the regimen in the first trimester or delay until 12 weeks' gestation will depend on CD4 T-lymphocyte (CD4-cell) count, HIV RNA levels, and maternal conditions such as nausea and vomiting (AIII). Earlier initiation of a combination ARV regimen may be more effective in reducing transmission, but benefits must be weighed against potential fetal effects of first-trimester drug exposure.
- Combination ARV regimens should include a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone that includes one or more NRTIs with high levels of transplacental passage (zidovudine, lamivudine, emtricitabine, tenofovir, or abacavir) (AIII).
- ARV drug-resistance studies should be performed before starting the ARV regimen if HIV RNA is above the threshold for resistance testing (that is, >500–1,000 copies/mL) (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) (AI). If HIV is diagnosed later in pregnancy the ARV regimen should be initiated promptly without waiting for the results of resistance testing (BIII).
- Nevirapine can be used as a component of the ARV regimen in pregnant women with CD4 cell counts ≤250 cells/mm^3. In pregnant women with CD4 cell counts >250 cells/mm^3, however, nevirapine should be used only if the benefit clearly outweighs the risk because the drug is associated with an increased risk of hepatic toxicity (AII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Therapy (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- In general, HIV-infected women receiving antiretroviral therapy (ART) who present for care during the first trimester should continue treatment during pregnancy, assuming the regimen is tolerated and effective in suppressing viral replication (AIII).
- The Panel recommends that efavirenz be continued in pregnant women receiving efavirenz-based ART who present for antenatal care in the first trimester provided the regimen is resulting in virologic suppression (see text) (CIII).
- Pregnant women receiving and tolerating nevirapine-containing regimens who are virologically suppressed should continue the regimen, regardless of CD4 count (AIII).
- HIV antiretroviral drug-resistance testing is recommended for pregnant women who have detectable viremia (that is, >500–1,000 copies/mL) on therapy (see Failure of Viral Suppression) (AI).

Special Situations — HIV/Hepatitis B Virus Coinfection (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- Screening for hepatitis B virus (HBV) infection with hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs) is recommended for all pregnant women who have not been screened during the current pregnancy (AII).
- The HBV vaccine series should be administered to pregnant women who screen negative for hepatitis B (that is, HBsAg negative, anti-HBc negative, and anti-HBs negative) (AII).
- Pregnant women with chronic HBV infection should be screened for antibodies to hepatitis A virus (HAV), and those who screen negative should receive the HAV vaccine series (AII).
- Interferon alfa and pegylated interferon alfa are not recommended during pregnancy (AIII).
- The management of HIV/HBV coinfection in pregnancy is complex and consultation with an expert in HIV and HBV is strongly recommended (AIII).
- All pregnant women with HIV/HBV coinfection should receive antiretroviral therapy (ART), including a dual nucleoside reverse transcriptase inhibitor (NRTI)/nucleotide analogue reverse transcriptase inhibitor (NtRTI) backbone with two drugs active against both HIV and HBV (AII). Tenofovir plus lamivudine or emtricitabine is the preferred dual NRTI/NtRTI backbone of antepartum ART in HIV/HBV-coinfected pregnant women (AI).
- If antiretroviral (ARV) drugs are discontinued postpartum in women with HIV/HBV coinfection, frequent monitoring of liver function tests for potential exacerbation of HBV infection is recommended, with prompt reinitiation of treatment for both HIV and HBV if a flare is suspected (BIII).
- Pregnant women with HIV/HBV coinfection receiving ARV drugs should be counseled about the signs and symptoms of liver toxicity, and liver transaminases should be assessed 1 month following initiation of ARV drugs and at least every 3 months thereafter (BIII).
- Within 12 hours of birth, infants born to women with HBV infection should receive hepatitis B immune globulin and the first dose of the HBV vaccine series. The second and third doses of vaccine should be administered at ages 1 and 6 months, respectively (AI).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Special Situations — HIV/Hepatitis C Virus Coinfection (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- Screening for hepatitis C virus (HCV) infection is recommended for all HIV-infected pregnant women who have not been screened during the current pregnancy (AIII).
- Interferon alfa and pegylated interferon alfa are not recommended and ribavirin is contraindicated during pregnancy (AIII).
- Recommendations for antiretroviral (ARV) drug use during pregnancy are the same for women who have chronic HCV as for those without HCV coinfection (BIII).
- Pregnant women with HIV/HCV coinfection receiving ARV drugs should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 1 month following initiation of ARV drugs and then every 3 months thereafter (BIII).
- Decisions concerning mode of delivery in HIV/HCV-coinfected pregnant women should be based on standard obstetric and HIV-related indications alone (see Intrapartum Care) (BIII).
- Infants born to women with HIV/HCV coinfection should be evaluated for HCV infection with anti-HCV antibody testing after age 18 months (AII). Infants who test positive for anti-HCV antibodies should undergo confirmatory HCV RNA testing. If earlier diagnosis is indicated or desired, HCV RNA virologic testing can be performed between ages 3 and 6 months (AIII).
- Women who are found to have chronic HCV infection should also be screened for hepatitis A virus (HAV) and hepatitis B virus (HBV) because they are at increased risk of complications from those two infections. Women with chronic HCV who are negative for hepatitis A immunoglobulin G should receive the HAV vaccine series (AIII). If they are not infected with HBV (that is, hepatitis B surface antigen negative, hepatitis B core antibody negative, and hepatitis B surface antibody negative), they should receive the HBV vaccine series (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Postpartum Care

Postpartum Follow-Up of HIV-Infected Women (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations
+ Contraceptive counseling should be included in the prenatal period as well as immediately postpartum as a critical aspect of postpartum care (AIII).
+ Decisions about continuing antiretroviral (ARV) drugs after delivery should take into account current recommendations for initiation of antiretroviral therapy (ART), current and nadir CD4 T-lymphocyte counts and trajectory, HIV RNA levels, adherence issues, whether a woman has an HIV-uninfected sexual partner, and patient preference (AIII).
+ For women continuing ARV drugs postpartum, arrangements for new or continued supportive services should be made before hospital discharge because the immediate postpartum period poses unique challenges to adherence (AII).
+ Women with a positive rapid HIV antibody test during labor require immediate linkage to HIV care and comprehensive follow-up, including confirmation of HIV infection. If infection is confirmed, a full health assessment is warranted, including evaluation for associated medical conditions, counseling related to newly diagnosed HIV infection, and assessment of need for ART and opportunistic infection prophylaxis (AII).
+ Breastfeeding is not recommended for HIV-infected women in the United States, including those receiving ART (AII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Infant Antiretroviral Prophylaxis (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- The 6-week neonatal component of the zidovudine chemoprophylaxis regimen is recommended for all HIV-exposed neonates to reduce perinatal transmission of HIV (AI).
- Zidovudine, at gestational age-appropriate doses, should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery (AII).
- Infants born to HIV-infected women who have not received antepartum antiretroviral (ARV) drugs should receive prophylaxis with zidovudine given for 6 weeks combined with three doses of nevirapine in the first week of life (at birth, 48 hours later, and 96 hours after the second dose), begun as soon after birth as possible (AI).
- In other scenarios, the decision to combine other drugs with the 6-week zidovudine regimen should be made in consultation with a pediatric HIV specialist, preferably before delivery, and should be accompanied by counseling of the mother on the potential risks and benefits of this approach (BIII).
- In the United States, the use of ARV drugs other than zidovudine and nevirapine cannot be recommended in premature infants because of lack of dosing and safety data (BIII).
- The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV, including infant care.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Initial Postnatal Management of the HIV-Exposed Neonate (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- A complete blood count and differential should be performed on newborns as a baseline evaluation (BIII).
- Decisions about the timing of subsequent monitoring of hematologic parameters in infants depend on baseline hematologic values, gestational age at birth, clinical condition of the infants, the zidovudine dose being administered, receipt of other ARV drugs and concomitant medications, and maternal antepartum ARV therapy (CIII).
- If hematologic abnormalities are identified in infants receiving prophylaxis, decisions on whether to continue infant antiretroviral (ARV) prophylaxis need to be individualized. Consultation with an expert in pediatric HIV infection is advised if early discontinuation of prophylaxis is considered (CIII).
- Some experts recommend more intensive monitoring of hematologic and serum chemistry and liver function assays at birth and when diagnostic HIV polymerase chain reaction tests are obtained in infants exposed to combination ARV drug regimens *in utero* or during the neonatal period (CIII).
- A recheck of hemoglobin and neutrophil counts is recommended 4 weeks after initiation of prophylaxis for infants who receive combination zidovudine/lamivudine-containing ARV prophylaxis regimens (AI).
- Routine measurement of serum lactate is not recommended. However, measurement can be considered if an infant develops severe clinical symptoms of unknown etiology (particularly neurologic symptoms) (CIII).
- Virologic tests are required to diagnose HIV infection in infants <18 months of age and should be performed within the first 14 to 21 days of life, at 1 to 2 months, and at 4 to 6 months of age (AII).
- To prevent *Pneumocystis jirovecii* pneumonia (PCP), all infants born to women with HIV infection should begin PCP prophylaxis at ages 4 to 6 weeks, after completing their ARV prophylaxis regimen, unless there is adequate test information to presumptively exclude HIV infection (see USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and Infected Children) (AII).
- Health care providers should routinely inquire about premastication of foods fed to infants, instruct HIV-infected caregivers to avoid this practice, and advise on safer feeding options (AII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- Children with *in utero*/neonatal exposure to antiretroviral (ARV) drugs who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction (CIII).
- Follow-up of children with exposure to ARVs should continue into adulthood because of the theoretical concerns regarding the potential for carcinogenicity of nucleoside analogue ARV drugs (CIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Teratogenicity (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations
• All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see details at http://www.APRegistry.com) (AIII).
• Non-pregnant women of childbearing potential should undergo pregnancy testing before initiation of efavirenz and receive counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on efavirenz-containing regimens (AIII).   ○ Alternate ARV regimens that do not include efavirenz should be strongly considered in women who are (1) planning to become pregnant or (2) sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the woman's health (BIII).
• Because the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy and pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, and unnecessary changes in ARV drugs during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, efavirenz can be continued in pregnant women receiving an efavirenz-based regimen who present for antenatal care in the first trimester, provided the regimen produces virologic suppression (see HIV-Infected Pregnant Women Who are Currently Receiving Antiretroviral Treatment) (CIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Combination Antiretroviral Drug Regimens and Pregnancy Outcome (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendation
• Clinicians should be aware of a possible small increased risk of preterm birth in pregnant women receiving protease inhibitor (PI)-based combination antiretroviral regimens; however, given the clear benefits of such regimens for both a woman's health and prevention of mother-to-child transmission, PIs should not be withheld for fear of altering pregnancy outcome (AII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

FDA classification

- **Category A**: Controlled studies show no risk. Adequate, well-controlled studies in pregnant women failed to demonstrate risk to the fetus
- **Category B**: No evidence of risk in humans. Either animal findings show risk, but human findings do not, or, if no adequate human studies have been done, animal findings are negative.
- **Category C**: Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk, or lacking as well. However, potential benefits may justify the potential risk.
- **Category D**: Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweight the potential risk
- **Category X**: Controindicated in pregnancy. Study in animals or humans, or investigational or postmarketing reports, have shown fetal risk which clearly outweights any possible benefit to the patients

Classificazione FDA

	Farmaci	FDA	Teratogenicità/Carcinogenicità
NRTI	**Zidovudina**	C	Neoplasie vaginali nei roditori, aumento di malformazioni fetali associate a tossicità materna
	Didanosina	B	Non teratogena (animali)
	Zalcitabina	C	Idrocefalo nei roditori
	Stavudina	C	Ritardo di ossificazione e aumento mortalità neonatale nei roditori; tumori colecisti e fegato ad alte dosi nei roditori
	Lamivudina	C	Mortalità embrionale precoce (roditori)
	Abacavir	C	Anasarca, basso peso e malformazioni scheletriche nei roditori; tumori del fegato e della tiroide nei roditori
	Emtricitabina	B	Non teratogena (animali), non studi passaggio transplacentare
NtRTI	**Tenofovir**	B	Non teratogeno (primati); adenomi epatici nei ratti; osteomalacia e ritardo di crescita se somministrato ad alte dosi durante l'accrescimento (animali)
NNRTI	**Nevirapina**	B	Non teratogena (animali); adenomi epatici nei roditori
	Delavirdina	C	Difetto del setto interventricolare, ritardo di crescita intrauterina e ↑ mortalità infantile nei roditori; embriotossicità e abortività nei conigli
	Efavirenz	**D**	Anencefalia, anoftalmia, microftalmia, palatoschisi nei primati; nei neonati idrocefalo, mielomeningocele, anomalie del tubo neurale, idronefrosi, onfalocele. Adenomi e carcinomi epatici nei roditori
	Etravirina	**B**	Non teratogena (animali), non studi passaggio transplacentare

Classificazione FDA

	Farmaci	FDA	Teratogenicità
IP	Amprenavir	C	Deficit di ossificazione e iperplasia timica nei roditori; malformazioni scheletriche e abortività nei conigli; adenoma epatocellulare nei ratti
	Darunavir	B	Tumori fegato e tiroide nei roditori
	Fosamprenavir	C	Epatomi benigni e carcinoma epatocellulare, aumento abortività, alterazioni scheletriche da ridotta ossificazione, basso peso alla nascita (ratti)
	Indinavir	C	Coste soprannumerarie nei roditori; adenomi tiroidei nei ratti
	Lopinavir/rtv	C	Basso peso e ritardo di ossificazione nei roditori a dosi tossiche; adenomi epatocellulari nei ratti
	Nelfinavir	B	Non teratogeno (animali); adenomi e carcinomi tiroidei nei ratti Criptorchidismo, ridootto peso e ritardo ossificazione nei roditori
	Ritonavir	B	Non teratogeno (animali) Non teratogeno (conigli); riduzione peso alla nascita (ratti);
	Saquinavir	B	adenomi epatici nei ratti
	Atazanavir	B	Deficit di ossificazione e ridotto peso alla nascita (ratti)
	Tipranavir	C	

Classificazione FDA

	Farmaci	FDA	Teratogenicità
Inibitori della fusione	T-20	B	Non teratogeno; non mutageno; noto passaggio nel latte (ratti)
Antagonisti del CCR5	Maraviroc	B	Non teratogeno; non mutageno
Inibitori dell'integrasi	Raltegravir	C	Non teratogeno; in corso studi sulla carcinogenesi

Antiretroviral drug: pharmacokinetic and toxicity

	PKs in pregnacy	Placental transfer to fetus	Data in pregnacy
AZT	Not alterated	High	No evidence of teratogenicity
3TC	"	"	"
ABC	"	"	Hypersensitivity reaction in 5-8%
DDI	"	Moderate	Lactic acidosis with DDI e D4T
FTC	↓ level 3rd trim	High	No evidence of teratogenicity
D4T	Not alterated	"	"
TDF	↓ level 3rd trim	"	↓ Fetal growth and bone demineralization
NVP	Not alterated	"	No evidence of teratogenicity
EFV	↓ level 3rd trim	Moderate	Significant malformations observed
ETV	Insufficent data	Insufficent data	Insufficent data
RPV	Insufficent data	Insufficent data	Insufficent data
LPV/r	↓ level 2nd 3rd trim	Low	No evidence of teratogenicity
ATV/r	↓Level vs non pregnancy	"	"
SQV/r	Not alterated	"	PR or QT interval prolongations
NFV	"	Minimal	No evidence of teratogenicity
DRV/r	Insufficent data	"	Insufficent data
FPV/r	"	Low	"
T20	"	"	"
MVC	"	Unkown	"
RAL	Variability value	High	"

Nevirapine and Hepatic/Rash Toxicity (Last updated September 14, 2011; last reviewed July 31, 2012)

Panel's Recommendations
• Nevirapine-based regimens should be initiated in women with CD4 T-lymphocyte (CD4-cell) counts >250 cells/mm^3 only if the benefits clearly outweigh the risks because of the drug's potential for causing hepatic toxicity/hypersensitivity reaction (AII).
• Women who become pregnant while receiving nevirapine-containing regimens and who are tolerating the regimen well can continue on therapy regardless of CD4-cell count (AII).
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Nucleoside Reverse Transcriptase Inhibitor Drugs and Mitochondrial Toxicity (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations
• The combination of stavudine and didanosine should not be prescribed during pregnancy because of reports of lactic acidosis and maternal/neonatal mortality with prolonged use in pregnancy (AII).
• Mitochondrial dysfunction should be considered in uninfected children with perinatal exposure to antiretroviral (ARV) drugs who present with severe clinical findings of unknown etiology, particularly neurologic findings (AII).
• Long-term clinical follow-up is recommended for any child with *in utero* exposure to ARV drugs (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Protease Inhibitor Therapy and Hyperglycemia (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendation
• HIV-infected women taking antiretroviral drug regimens during pregnancy should undergo standard glucose screening at 24 to 28 weeks' gestation (AIII). Some experts would perform earlier glucose screening in women receiving ongoing protease inhibitor-based regimens initiated before pregnancy, similar to recommendations for women with high risk factors for glucose intolerance (BIII).

Tossicità NRTI in gravidanza

- Inducono danno mitocondriale, neuropatia, miopatia, pancreatite, steatosi epatica, acidosi lattica
- Casi di acidosi lattica fatale (morte della madre e del feto) con l'associazione stavudina e didanosina
- In Francia disfunzioni mitocondriali in bambini esposti a NRTI (Blanche et al,1999)
- In USA nessuna disfunzione mitocondriale osservata in 16000 bambini esposti a NRTI (Perinatal Safety Rewiew Working Group, 2000)

Tossicità NNRTI in gravidanza

- NVP può causare con maggiore frequenza rash ed epatotossicità (usare con cautela nelle gravide che non l'hanno mai utilizzata in precedenza)

- EFV causa nei primati anomalie del tubo neurale

  (il dosaggio dell'alfa-fetoproteina materna tra 15ª e 20ª settimana può essere utile per evidenziare tali anomalie)

Utilizzo di Efavirenz

4.6 Fertilità, gravidanza ed allattamento

Donne in età fertile: vedere sotto e paragrafo 5.3. Efavirenz non deve essere usato durante la gravidanza a meno che la condizione clinica della paziente non richieda questo trattamento.

Donne in età fertile devono eseguire test di gravidanza prima di iniziare il trattamento con efavirenz.

Contraccezione in uomini e donne: devono essere sempre utilizzati contraccettivi meccanici in associazione con altri metodi (per esempio, contraccettivi orali o altri contraccettivi ormonali, vedere paragrafo 4.5). A causa della prolungata emivita di efavirenz, si raccomanda l'uso di adeguate misure contraccettive nelle 12 settimane successive all'interruzione del trattamento.

Gravidanza: a partire da Luglio 2010, il Registro delle Gravidanze in corso di trattamento con Antiretrovirali (Antiretroviral Pregnancy Registry, APR) ha ricevuto report prospettici di 718 gravidanze con esposizione nel primo trimestre a regimi contenenti efavirenz, che sono esitate in 604 nati vivi. In un bambino è stato riportato un difetto del tubo neurale, e la frequenza e l'andamento degli altri difetti alla nascita sono stati simili a quelli osservati in bambini esposti a regimi non contenenti efavirenz, così come in controlli HIV negativi. L'incidenza di difetti del tubo neurale nella popolazione generale è compresa tra 0,5 - 1 caso per 1000 nati vivi. Nel complesso, ci sono stati sei report retrospettivi di casi riferibili a difetti del tubo neurale, incluso il meningomielocele, tutti in madri esposte a regimi contenenti efavirenz durante il primo trimestre. Una relazione causale di tali eventi con l'uso di efavirenz non è stata stabilita, ed il denominatore è sconosciuto. Poiché i difetti del tubo neurale si verificano durante le prime 4 settimane di sviluppo fetale (il momento in cui i tubi neurali si saldano), questo potenziale rischio riguarderebbe donne esposte ad efavirenz durante il primo trimestre di gravidanza.

No difference in prevalence of birth defects for infants exposed prenatally to ATV/r to that of the general population[1]

Earliest Exposure to ARV	Exposure to any ART (June 2003-January 2010	Exposure to ATV (June 2003-January 2010)
First trimester No. of defects/live births Prevalence (95% CI)	 127/4563 2.8% (2.3%–3.3%)	 8/368 2.2% (0.9%-4.2%)
Second/Third trimester No. of defects/live births Prevalence (95% CI)	 158/6184 2.6% (2.2%–3.0%)	 5/199 2.5% (0.8%-5.8%)
Any trimester No. of defects/live births Prevalence (95% CI)	 285/10,747 2.7% (2.3%–3.0%)	 13/567 2.3% (1.2%-3.9%)

Note: The number of defects represents the number of outcomes with at least 1 defect. An outcome is defined as a live or stillborn infant, or a spontaneous or induced abortion. Excludes reported defects in pregnancy losses <20 weeks.

The general population rate for birth defects reported in the CDC MACDP is 2.72% (95% CI, 2.68–2.76) and is not significantly different from infants prenatally exposed to ATV

ATV/r use may be considered during pregnancy only if potential benefit justifies the potential risk[2]

1. Esker et al. HIV10 2010. Glasgow, UK, poster 113. 2. SmPCs. Available at http://www.ema.europa.eu Accessed December 2011.

BMS AI424182: phase I study design
ATV/r in pregnancy

Multicentre (South Africa, Puerto Rico and USA), open-label, prospective, single-arm Phase I

HIV-1 infected pregnant women were enrolled in (Jun 2006 – Sep 2008)

Screening & Enrolment

Original Protocol
ATV/r 300/100 24 h PK
Third trimester (28–36 weeks)

Interim PK analysis occurs when n=12

Decision point: determine if an increased dose of ATV/r 400/100 should occur in the 3rd trimester

Prespecified criteria

If the geometric mean ATV AUC_{tau} for these 12 patients is < 30,000 ng h/mL but ≥ 15 000 ng h/mL

OR

If >2 of 12 patients have ATV C_{min} < 150 ng/mL, but 10 of 12 patients have ATV C_{min} ≥ 50 ng/mL

Dose increase to 400/100 mg in third trimester

Post interim Analysis
If pre-specified criteria met
Dose escalation required

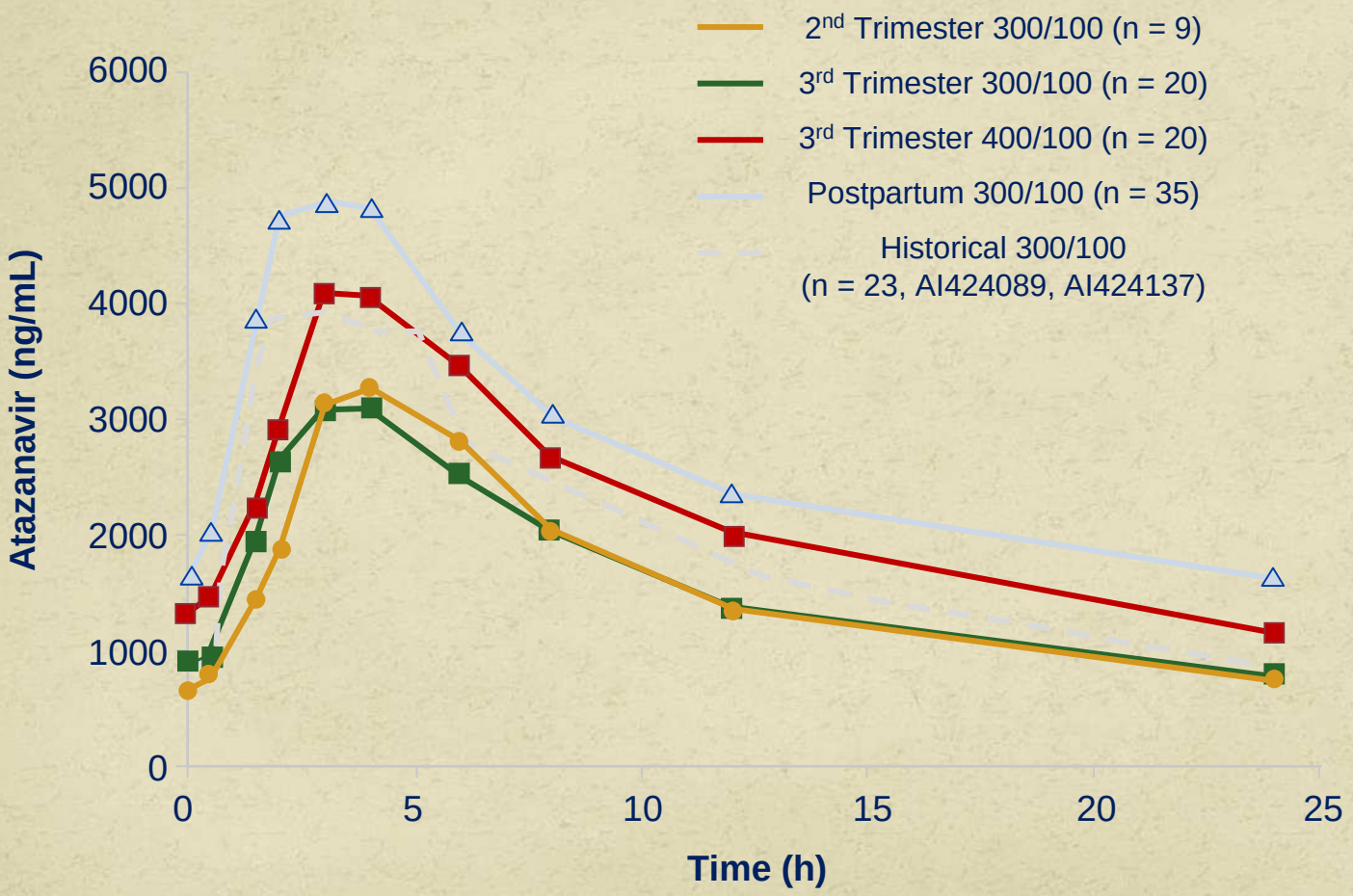
If possible
ATV/r 300/100 24 h PK
Second trimester
(18–24 week)

ATV/r 400/100 24 h PK
Third trimester (30-36 weeks)

tau is the length of the dosing interval

Conradie et al, HIV Med 2011;12:570–9.

BMS AI424182: ATV/r PK/PD in pregnancy



ATV/r use may be considered during pregnancy only if potential benefit justifies the potential risk[2]

1. Conradie et al, HIV Med 2011;12:570–9.
2. SmPCs. Available at http://www.ema.europa.eu Accessed December 2011.

BMS AI424182[1]: PK results after ATV exposure during antepartum/postpartum periods

	Second trimester 300/100 mg (n = 9)	Third trimester 300/100 mg (n = 20)	Third trimester 400/100 mg (n = 20)	Postpartum 300/100 mg (n = 36)	Historical* 300/100 mg (n = 23)
C_{max} Geometric mean (ng/mL)	3729	3291	4211	5649	4485
Geometric mean ratio (90% CI)	0.83 (0.65, 1.06)	0.73 (0.56, 0.96)	0.94 (0.76, 1.17)	1.26 (1.09, 1.46)	-
AUC_{tau} Geometric mean (ng h/mL)	34 399	34 252	46 602	60 533	43 388
Geometric mean ratio (90% CI)	0.79 (0.61, 1.03)	0.79 (0.63, 0.99)	1.07 (0.84, 1.37)	1.40 (1.19, 1.64)	-
C_{min} Geometric mean (ng/mL)	664	668	917	1421	662
Geometric mean ratio (90% CI)	1.00 (0.65, 1.54)	1.01 (0.73, 1.39)	1.39 (0.96, 2.00)	2.15 (1.65, 2.80)	-

AUCt = Area under concentration-time curve in one dosing interval; CI = confidence interval; C_{max} = maximum observed plasma concentration; C_{min} = trough observed plasma concentration 24 hour post dose

ATV/r use may be considered during pregnancy only if potential benefit justifies the potential risk[2]

1. Conradie et al. HIV Med 2011;12:570–9.
2. SmPCs. Available at http://www.ema.europa.eu Accessed December 2011.

Contents of new ATV label: section 4.2 Posology and method of administration (1)

Pregnancy and Postpartum

During the second and third trimesters of pregnancy:

REYATAZ 300 mg with ritonavir 100 mg may not provide sufficient exposure to atazanavir, especially when the activity of atazanavir or the whole regimen may be compromised due to drug resistance. Since there are limited data available and due to inter-patient variability during pregnancy, Therapeutic Drug Monitoring (TDM) may be considered to ensure adequate exposure.

The risk of a further decrease in atazanavir exposure is expected when atazanavir is given with medicinal products known to reduce its exposure (e.g., tenofovir or H_2-receptor antagonists).

- If tenofovir or an H_2-receptor antagonist is needed, a dose increase to REYATAZ 400 mg with ritonavir 100 mg with TDM may be considered (see sections 4.6 and 5.2).
- It is not recommended to use REYATAZ with ritonavir for pregnant patients who are receiving both tenofovir and an H_2-receptor antagonist.

Atazanavir SmPC. *Available at http://www.ema.europa.eu Accessed December 2011

Tossicità PI in gravidanza

- Possono causare iperglicemia, diabete mellito e chetoacidosi diabetica (condizioni di cui la gravidanza è fattore predisponente, tuttavia non sembrano esserci correlazioni tra l'uso degli IP e l'aumento del rischio di iperglicemia)
- Iperlipidemia

Malignancies

- A number of studies have found that NRTI exposure is associated with both mutagenesis and other forms of DNA damage.[51–54] This has raised concerns about *in utero* ARV exposure elevating the risk of cancers later in life, although available data have been reassuring regarding short-term risk.
- **The PACTG 219/219C study found no increase in early childhood cancer associated with ARV exposure,**[55] when comparing HIV-uninfected children with or without exposure to any ARV. The children's median age at last study visit was 3.1 years (range: 0.5 months to 14.9 years).
- Similarly, the French Perinatal Cohort found overall incidence of cancer in HIV-exposed uninfected children followed to median age 5.4 years did not differ significantly from that expected for the general population.[56] However, 5 cases of central nervous system cancer were observed compared with 1.6-2.1 expected cases; a higher cancer risk was observed with exposure to DDI 3TC containing regimens compared with exposure to AZT alone, although only 4% of women received such regimens.
- It is important to note that childhood studies will not provide definitive answers on the ultimate effect of antiretroviral drugs in this area; follow-up into adulthood will be required.

Growth and Development

- Mixed data on effect of in *utero* exposure to combination drug regimens on growth; effect, if exists, seems transient
- Very limited studies on neurodevelopment suggest that more advanced maternal disease may be an additional important confounder.
- PACTG 219/219C evaluated neurologic development in HIV-exposed uninfected children and found no overall association between ARV exposure *in utero* and abnormal neurologic assessment at 2 years of age.[49] However, HIV-exposed uninfected children with low birth weights had significantly better assessment scores if exposed to ARV *in utero*

La ARV è associata ad un aumentato rischio di parti pre-termine e basso peso alla nascita?

- PACTG 185, 2000: non si osservano differenze di aumentato rischio di parti pre-termine e basso peso alla nascita tra donne HIV positive (AZT monoterapia) vs negative

- European Collaborative Study and the Swiss Cohort Study 2000: bambini esposti ad HAART comprendente PI mostrano un aumento del rischio di prematurità di 2.6 volte in più vs quelli nati da madri non in terapia. Non si osservano differenze di peso alla nascita tra i gruppi considerati

- Cotter AM 2006: in 134 donne in terapia HAART con PI si osserva un aumento del rischio di prematurità di 1.8 volte in più vs le donne in monoterapia o HAART con NNRTI. Non si osservano differenze di peso alla nascita tra i gruppi considerati

Breastfeeding

- Complete avoidance of breastfeeding is efficacious in preventing MTCT of HIV.
- However this intervention has significant associated morbidity (e.g., diarrheal morbidity if formula is prepared without clean water).
- If breastfeeding is initiated, two interventions are efficacious in preventing transmission:
    1) exclusive breastfeeding during the first few months of life
    2) chronic antiretroviral prophylaxis to the infant (nevirapine alone, or nevirapine with zidovudine)

Utilizzo di Efavirenz

Allattamento: non è noto se efavirenz sia escreto nel latte materno. Studi sui ratti hanno stabilito che efavirenz viene escreto nel latte raggiungendo concentrazioni molto maggiori di quelle che esistono nel plasma materno. Il rischio per i neonati non può essere escluso. L'allattamento deve essere interrotto durante il trattamento con SUSTIVA. Si raccomanda alle madri con infezione da HIV di non allattare i bambini al seno in nessun caso, per evitare di trasmettere loro il virus HIV.

Fertilità: l'effetto di efavirenz sulla fertilità di ratti maschi e femmine è stato valutato solo a dosaggi che hanno raggiunto l'esposizione sistemica al medicinale equivalente o inferiore a quella raggiunta nell'uomo, alle dosi di efavirenz raccomandate. In questi studi, efavirenz non ha compromesso ne' l'accoppiamento ne' la fertilità dei ratti maschi o femmine (dosi fino a 100 mg/kg/bid) e non ha interessato ne' lo sperma ne' la prole dei ratti maschi trattati (dosi fino a 200 mg/bid). La funzione riproduttiva della prole nata da ratti femmina che hanno assunto efavirenz non è stata influenzata.

Antiretroviral Pregnancy Registry

- International registry jointly sponsored by manufacturers of all ARVs covers the period 1 January 1989 through 31 January 2011 (previously known as the Zidovudine in Pregnancy Registry)
- Voluntary registration of prenatal exposures by treating providers
- Overseen by Advisory Committee representing CDC, NIH, FDA, and various specialists
- From January 2003 the registry started systematically collecting data on Hepatitis B mono-infected women

www.APRegistry.com (website)
registry@kendle.com (e-mail)

Antiretroviral Pregnancy Registry:

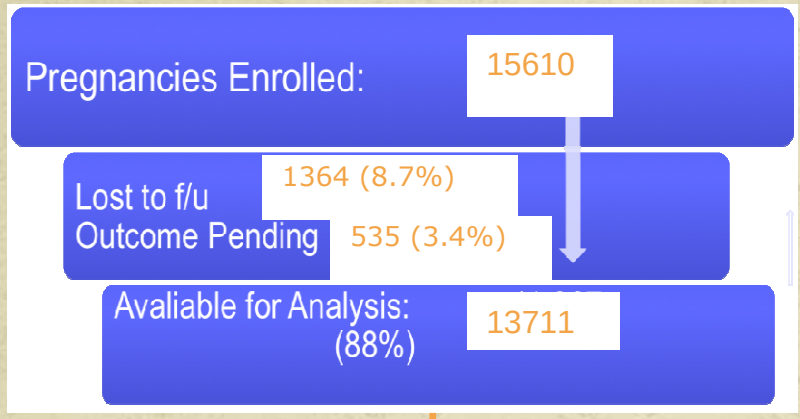
Objectives

- Provide early warning signal of major teratogenicity
- Estimate risk of major birth defects and compare to that of general population
- Collect supplementary data from animal toxicology, clinical, and epidemiological studies

Limitations

- The lack of other developmental or functional defects
- Not systematically collected, although the Advisory Committee carefully reviews each pregnancy outcome received
    - Underreporting or differential reporting
    - Underascertainment or different underascertainment of birth defects

Antiretroviral Pregnancy Registry: data on 31 January 2011

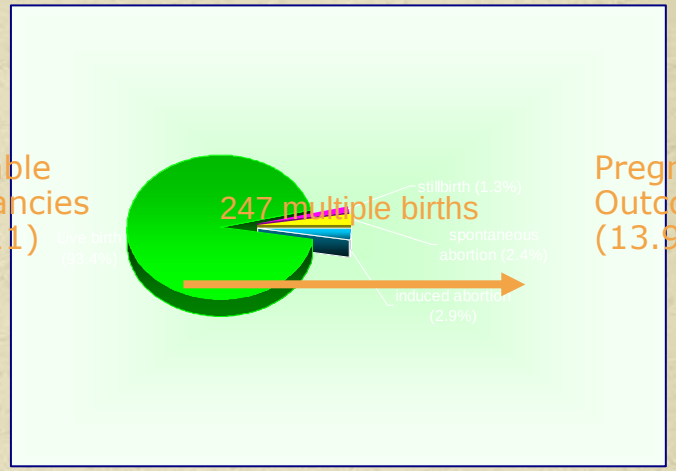


94% (12885) woman HIV+

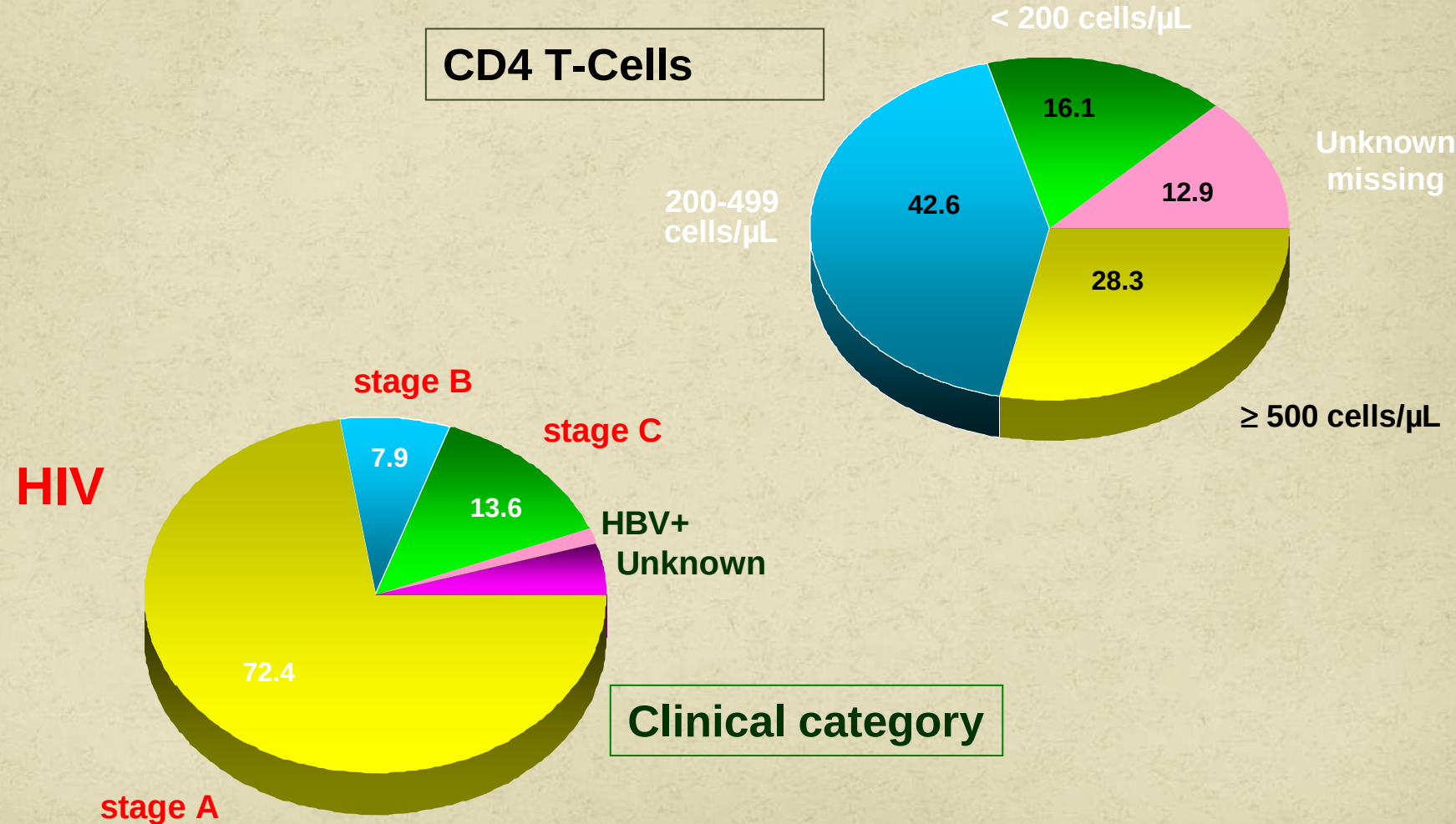
(147 HIV/HBV coinfected)

4.8% (665) missing or unknown

1.2% (161) HBV mono-infection



Maternal demographics:
report from ***prospective study in 13.711 pregnancy***



Antiretroviral Pregnancy Registry 2011

Antiretroviral Pregnancy Registry: definition of Birth defect

- A "birth defect" follows the CDC guidelines and is defined as any **major structural malformation or chromosomal defect diagnosed or with signs/symptoms before 6years of age**
- Any cluster of two or more conditional abnormalities
- **Any structural or chromosomal defect detected in the prenatal evaluation of pregnancy** or in the gross or patgologic examination of an abortus,fetus, or deceased infant.
- **The registry excludes birth defects attributed to prematurity itself** (e.g. patent ductus arterious, patent foramen ovale, and inguinal hernias)

APR: Summary of antiretroviral classes by trimester of earliest exposure* through 31 January 2011

Class of ARV(s):	First Trimester	Second Trimester	Third Trimester	All Trimesters
All exposures	6236	5520	1953	13711
NRTI + PI	2015	2731	811	5557 **(40.5%)**
NRTI only	1350	1622	682	3654 (26.6%)
NRTI+NNRTI	1116	717	306	2140 (15.6%)
NRTI+NtRTI+PI	659	249	66	974 **(7.1%)**
NRTI+NNRTI+PI	234	82	33	349
NRTI+NtRTI+NNRTI	174	33	9	216
All Other	688	86	46	821

* Exposures represents earliest trimester of exposure to an antiretroviral drug. Pregnant women may have been on other medications during pregnancy

Antiretroviral Pregnancy Registry: data summary

Table 7: Confidence Intervals for Birth Defects [1] - All Prospective Registry Cases with Follow-up Data Closed Through 31 January 2011

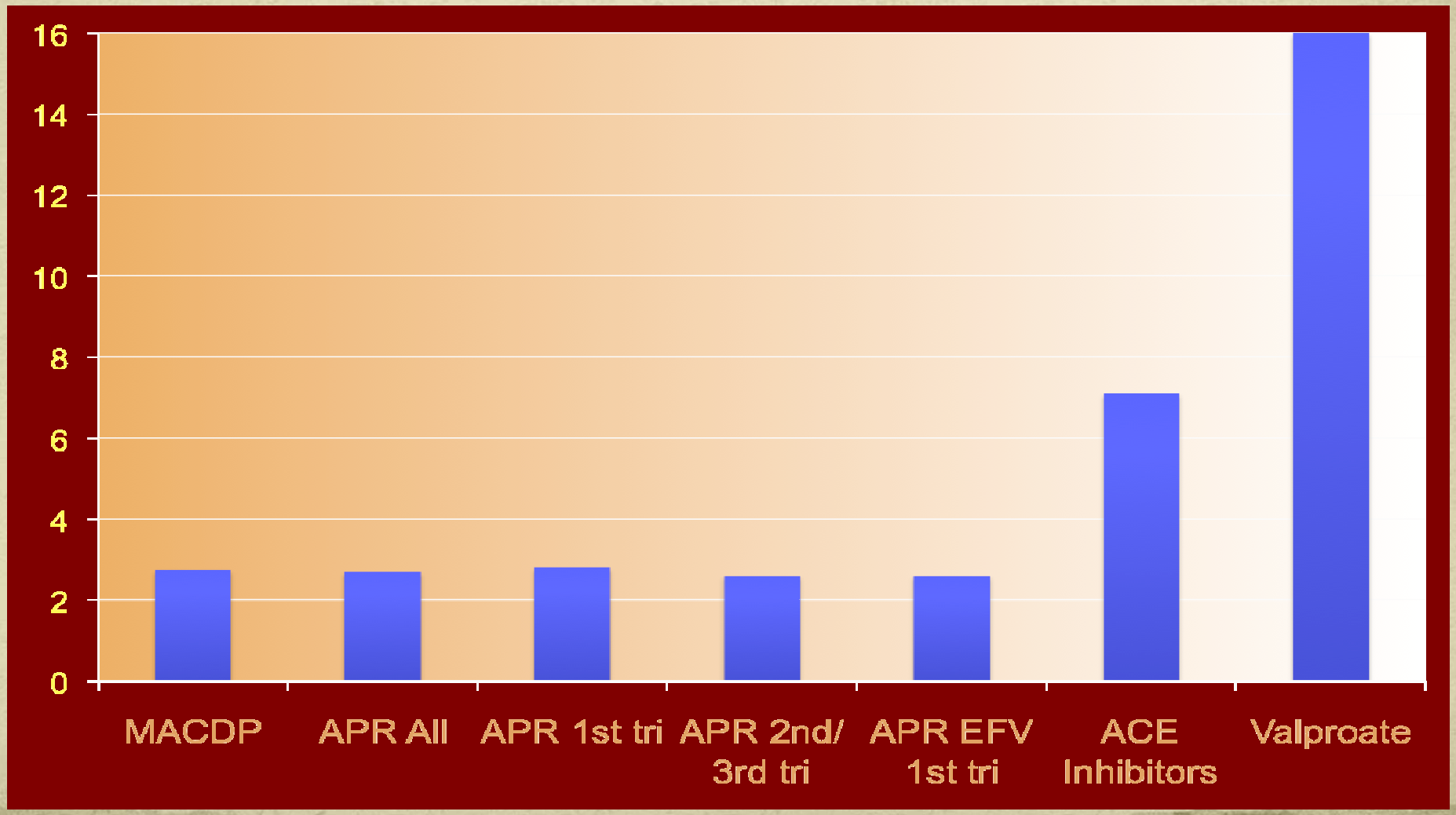
	Overall
Number of Live Births	13040
Number of Outcomes with at Least One Defect [2]	371 (2.8%)
95% Confidence Intervals for Prevalence of Birth Defects for Exposures in:	
First Trimester	164/5555 (3.0%) 2.5% - 3.4%
Second/Third Trimester	205/7483 (2.7%) 2.4% - 3.1%
Any Trimester	371/13040 (2.8%) 2.6% - 3.1%
Risk of Defects for First Trimester Exposures Relative to Second/Third Trimester Exposures	1.08 (0.88, 1.32)

[1] Defects meeting the CDC Criteria only. Excludes reported defects in pregnancy losses < 20 weeks.
[2] An outcome is defined as a live or stillborn infant, or a spontaneous

Clinical studies in pregnacy

1st trimester 13 / 267	4.9%
2nd – 3rd trimester 22 / 1167	1.9%
1st to 2nd- 3rd trimester prevalence ratio	2.58

Overall Birth Defects:
ARVs vs ACE Inhibitors vs Valproate



APR: n° of birth defects by trimester of earliest exposure to each drug

	1st trimester Defects / live biths	prevalence	2nd- 3rd trimester Defects / live biths	prevalence
Proportion of defects related to drug	**164 / 5555**	**3%**	**205 / 7483**	**2.7%**
Any PI	90 / 2932		127 / 4607	
ATV	12 / 502	2.4%	6 / 266	2.3%
LPV	16 / 738	2.2%	41 / 1720	2.4%
DRV	4 / 69		1 / 66	
NFV	46 / 1193	3.9%	84 / 2698	3.1%
RTV	33 / 1401	2.4%	53 / 2104	2.5%
Any NRTI	187 / 6456		220 / 8171	
ABC	22 / 744	3%	30 / 1038	2.9%
DDI	19 / 406	4.7%	20 / 460	4.3%
FTC	17 / 641	2.7%	9 / 393	2.3%
3TC	118 / 3864	3.1%	169 / 6230	2.7%
D4T	19 / 797	2.4%	6 / 194	3.1%
AZT	118 / 3620	3.3%	212 / 7935	2.7%
TDF	26 / 1092	2.4%	13 / 639	2%
Any NNRTI	41 / 1505		49 / 1506	
EFV	17 / 623	2.7%	2 / 70	2.9%
NVP	25 / 987	2.5%	48 / 1479	3.2%
ETR	0 / 20		0 / 17	

Birth defects and ART in the French perinatal Cohort , a Prospective Exhaustive Study among 13124 live births from 1994 to 2010

CROI 2013

- Prospective study multicenter (90) in France
- Franch Perinatal Cohort: 13.124 births
- Children followed during 2 years
- Inclusion criteria: livebirths from pregnant HIV+ from 1994-2010
- Exclusion criteria: woman not treated during pregnancy
- Primary object: birth defect according to EUROCAT and MACDP classifications and association between exposure ART and birth defect with univariate and multivariate logistic regression

Birth defects and ART in the French perinatal Cohort , a Prospective Exhaustive Study among 13124 live births from 1994 to 2010

CROI 2013

RESULTS:

- Birth defect prevalence: 4.4% (95% 4.0-4.7 CI, N: 575) according EUROCAT and 7% (95% 6.5-7.4 CI, N: 914) according MACDP (witch included minor defects when 2 were present in the same child)

- Significant association during 1 trimester between:
  - exposure EFV and neurological defects: adjusted odds ratio (aOR) 3.15 (1.09-9.09)
  - exposure ZDV and congenital heart defects : aOR 2.34 (1.39-3.94)
  - exposure ddI and head and neck birth defect: aOR 2.89 (1.03-8.11)

Birth defects and ART in the French perinatal Cohort , a Prospective Exhaustive Study among 13124 live births from 1994 to 2010

CROI 2013

CONCLUSIONS

- Rate of livebirth defect underestimated by including only live births
- Specific associations between in utero exposure to EFV and neurological defects
- WHO and US department of Health and Human Health guidelines have been changed authorized the use of EFV even in the 1 trimester
- Association between EFV and neurologicl defect has been previously in other study so caution with this exposure

Take home message……..

- La terapia antiretrovirale in gravidanza è indispensabile per ridurre la trasmissione materno fetale dell'HIV (terapia materna antepartum, intrapartum e profilassi al neonato) indipendentemente dal valore dei CD4 e dalla VL materna.
- La scelta della terapia deve basarsi sull'efficacia farmacologica, deve considerare le condizioni cliniche materne (stadio della malattia, farmacocinetica, resistenze ….) e le caratteristiche di sicurezza del farmaco sul bambino
- Monitoraggio clinico e laboratoristico stretto per intervenire precocemente su eventuali eventi avversi
- Studi clinici sulla tossicità dei farmaci nei bambini esposti alla ARV sono limitati nel tempo. Utili studi che valutano gli effetti a lungo termine di tali farmaci
- E' indispensabile potenziare il registro nazionale/internazionale sulle gravide segnalando tutte le gravidanze e le esposizioni alle terapie antiretrovirali
- Adeguato counselling e non usare farmaci potenzialmente teratogeni in donne età fertile che non usano metodi contraccettivi efficaci.

....GRAZIE