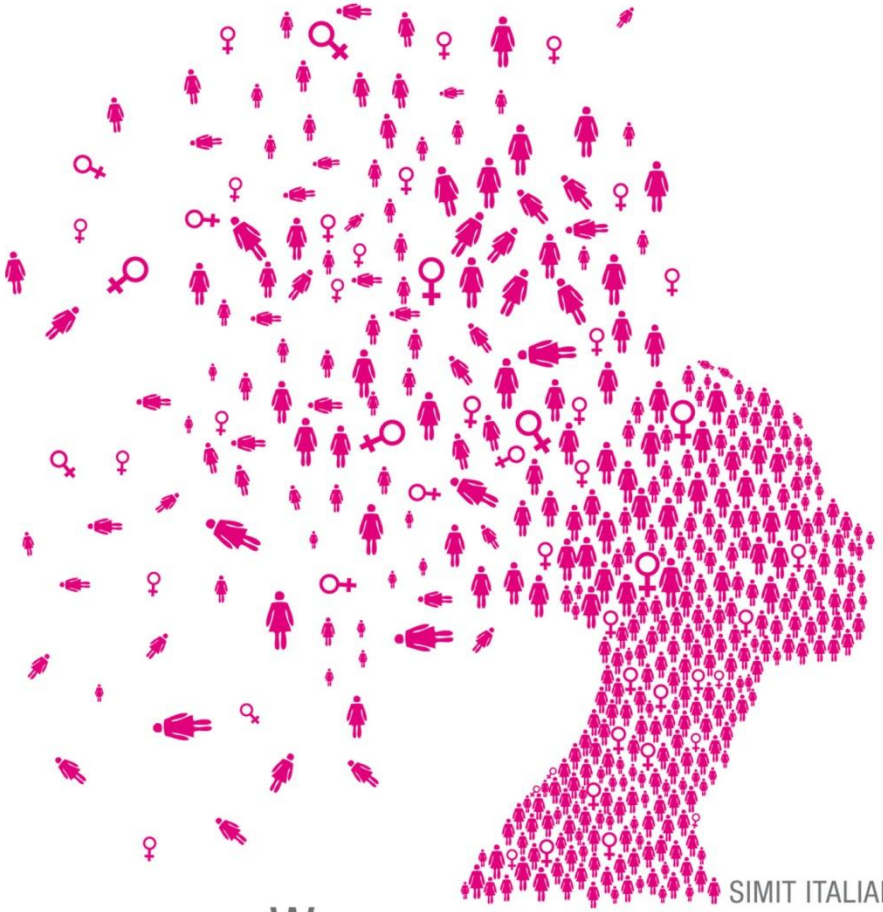


SIMIT ITALIAN PROJECT

Women
Infectivology
Network

WIN

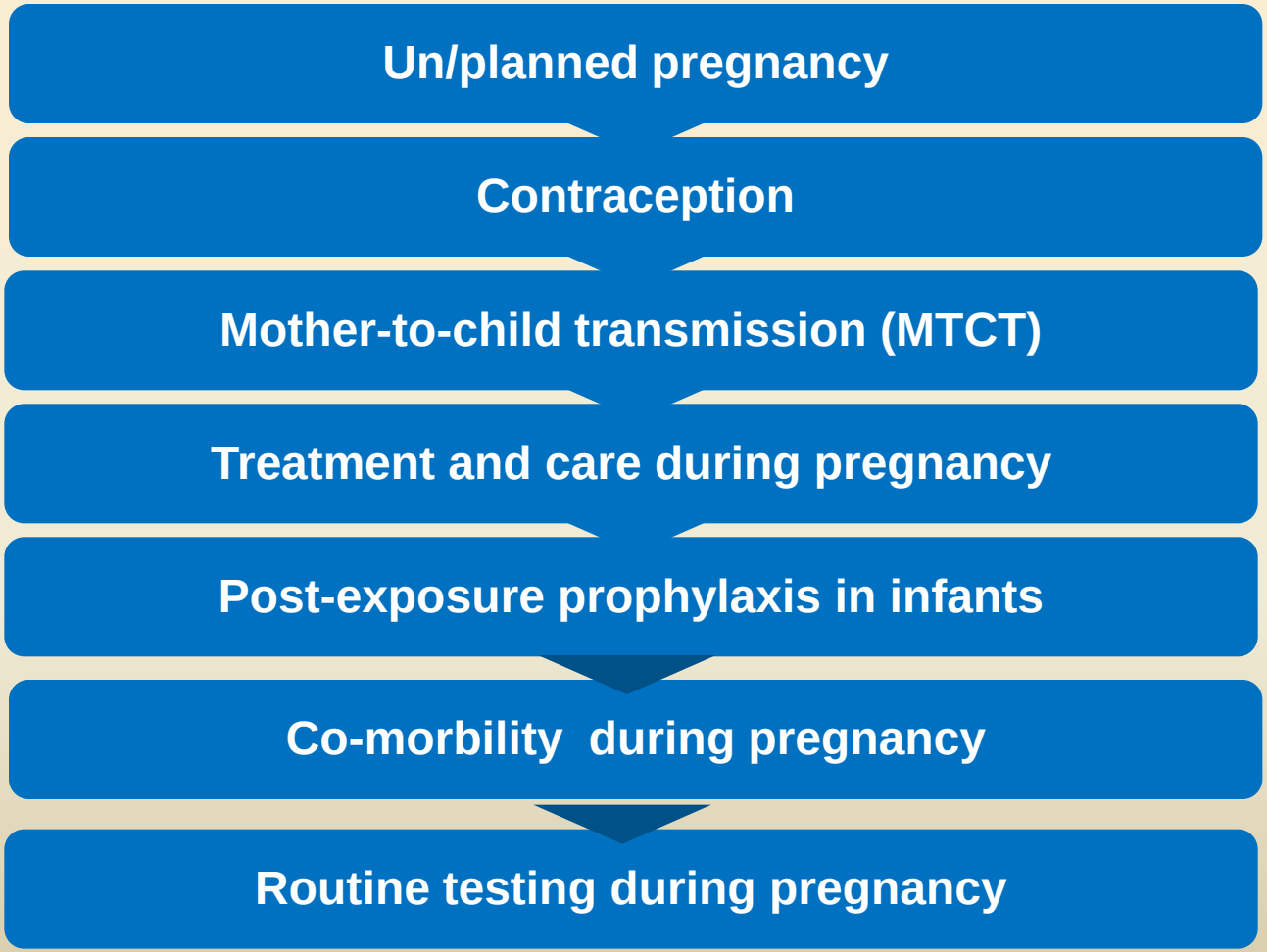
WIN, WOMEN INFECTIVOLOGY NETWORK

11 Donne, per le Donne, contro le malattie infettive in Italia

HIV infection: conception, pregnancy and contraception

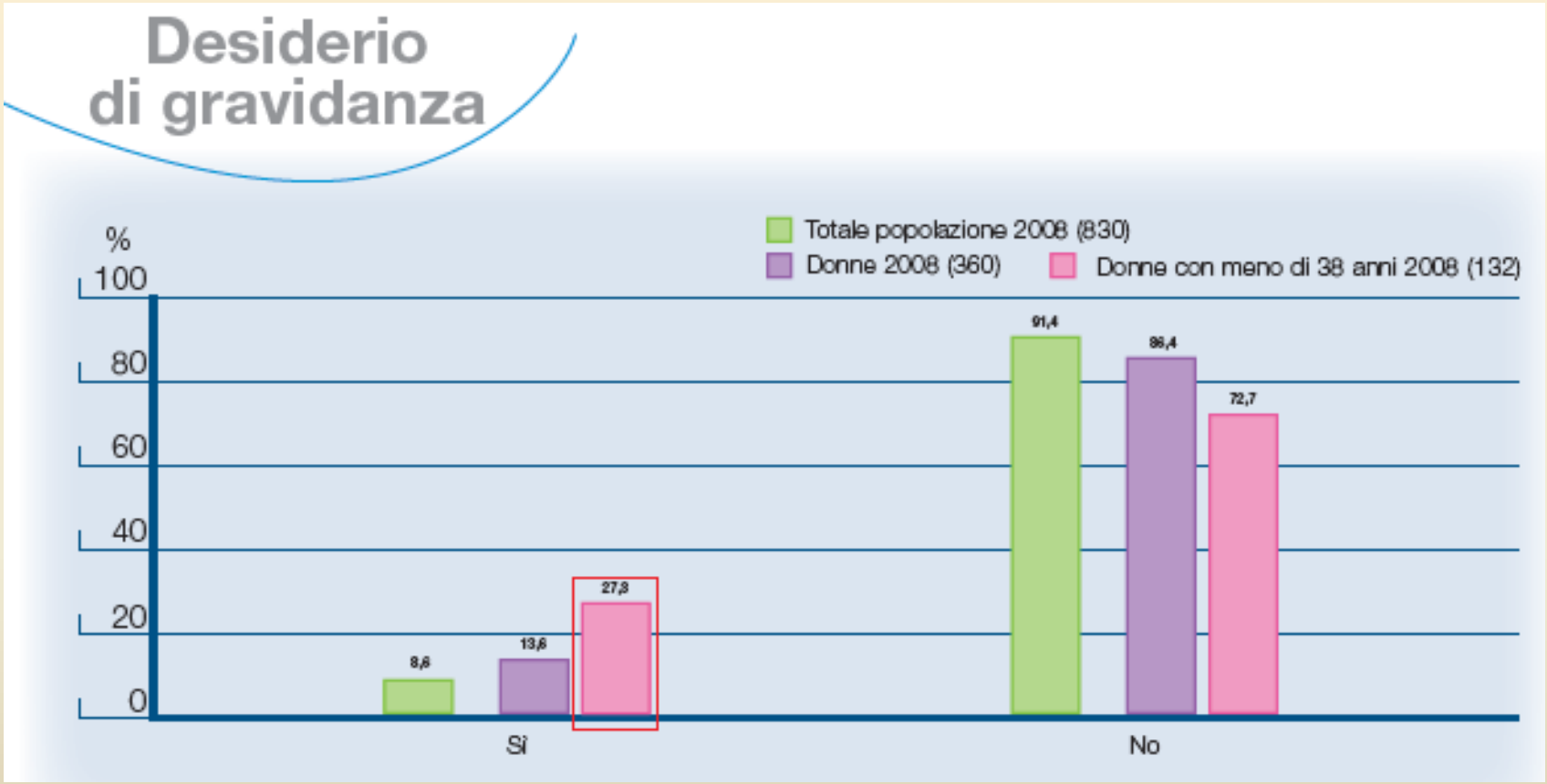
Women Infectivology Network WIN

Contents


Un/planned pregnancy
Contraception
Mother-to-child transmission (MTCT)
Treatment and care during pregnancy
Post-exposure prophylaxis in infants
Co-morbility during pregnancy
Routine testing during pregnancy

Un/planned pregnancy and contraception

Desiderio di gravidanza



Indagine POSIT

Planning for pregnancy: Considerations

- What happens if my baby is HIV+? When will I know?
- How do I get pregnant without infecting my partner?
- Will my healthcare workers treat me differently?
- What is the risk that I will infect my partner?
- What is the risk of my baby being infected?
- Will I survive to see my children grow up?
- Will the treatment harm me or my baby?
- Should I bottle- or breastfeed my baby?
- Will pregnancy make my HIV worse?
- Do I have to have a caesarean?

Unplanned pregnancy

- 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

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

Planning for unplanned pregnancies

Anticipate the possibility of pregnancy in all HIV+ women of childbearing potential

Consult guidelines and consider effective ART regimens that need minimal modification if pregnancy occurs

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

What is reproductive counselling?

Advice, education, and discussion on:

- **Effective contraception**
- **Maternal reproductive health issues**
- **Safe conception**
- **Impact of HIV on pregnancy**
- **Impact of pregnancy on HIV**
- **Psychosocial issues, postpartum impact on adherence and outpatient visits**
- **Long-term health of mother and ability to care for children**
- **Mother-to-child transmission**
- **Importance of early and intense antenatal care**
- **Use of ARTs and other drugs in pregnancy**

- Should involve a two way interaction to explore coping, decision-making, emotional reactions and to plan/prepare
- Should involve partners and be culturally relevant

Pre-conception counselling: a risk reduction strategy

- Optimise HIV management
- Choice of ART
- Screen for and treat sexually transmitted infections
- Reproductive options – risks, costs and success rates
- Sex only when woman is in fertile period of her cycle
- Stop unprotected sex as soon as pregnant
- Avoid genital tract irritants
- Refer for assessment if unsuccessful after 6-12 months (earlier if >35 years)
- Possibility of treatment failure and ability to care for child

Reproductive options

HIV+ man & HIV- woman

- IUI, IVF or ICSI following sperm washing
- ??Natural conception (if effective viral suppression)
- Insemination of donor sperm at ovulation

HIV+ woman & HIV- man

- Insemination of partner's sperm at ovulation (if not on ART / detectable viral load)
- ??Natural conception (if effective viral suppression)
- Assisted reproduction in case of fertility disorders
- ??Pre-exposure prophylaxis (PrEP)

HIV+ man & woman

- Insemination of donor sperm or sperm washing to prevent superinfection, reinfection or resistance
- Natural conception
- Assisted reproduction in case of fertility disorders

HIV and fertility

- Evidence that women with HIV have higher incidence of fertility disorders
- Fertility assistance has important ethical and practical implications for patients and professionals
- Fertility treatment options
  - ~ IUI (+/- sperm washing)
  - ~ Donor insemination
  - ~ IVF
  - ~ ICSI
- Limited data on IVF/ICSI success
  - ~ Pregnancy rate substantially lower in HIV+ women

IUI, intra-uterine insemination; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection

The ideal contraceptive

- Reliable
- Safe
- Convenient
- Reversible
- Prevent transmission of HIV
- Not interfere with HAART
- Affordable

. . . . currently means it must involve condoms

Contraception options in HIV

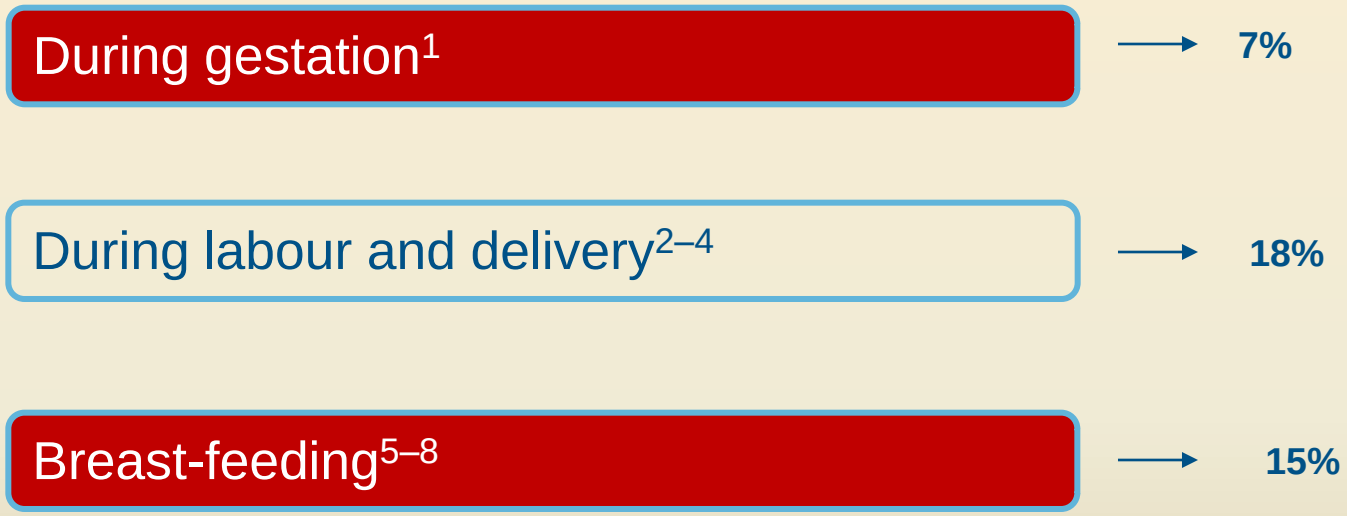
Method	Advantages	Disadvantages
Condoms (male and female)	• STI/HIV protection	• Cooperation needed • Correct technique • Inconvenient / may interfere with sexual intercourse
OCPs	• Effective • Less blood loss	• Drug-drug interactions • Possibly ↑ viral shedding • No STI/HIV protection
Patch, ring, combo injectable	• Effective • Less blood loss	• Drug-drug interactions? • Lack of data • ↑ shedding? • No STI/HIV protection
DMPA	• Low maintenance • Effective	• ↑ shedding? • ↑ viral set-point • No STI/HIV protection
IUD	• Low maintenance • Effective	• Blood loss with Copper T • Shedding with LNG-IUS? • ↑ pelvic infection • No STI/HIV protection
Cervical barrier	• Some STI protection	• ↑ Urinary tract infections • Requires correct technique • No STI/HIV protection
Sterilization	• Low maintenance • Effective	• Irreversible • Cost • Invasive • No STI/HIV protection

Mostad *Lancet* 1997; Wang *AIDS* 2004

Mother-to-child transmission (MTCT)

Mother-to-child transmission (MTCT)

- HIV can be transmitted from mother-to-child (vertical transmission) at various stages of pregnancy and motherhood:



[1]Connor EM et al, NEJM 1994; [2]Kind C et al, NEJM 1999; [3]The International Perinatal Group, NEGM 1999, [4]European Mode of Delivery Collaboration, Lancet 1999; [5]Dunn DT et al, Lancet 1992; [6]Nduati R et al, JAMA 2000; [7]Coustsoudis A,et al, J Infect Dis 2004; [8]Coustoudis et al; Lancet 1999

Minimising the risk of MTCT

Without optimal therapy and prevention the risk of transmitting HIV from a mother to a baby ranges from about 12–45%, depending on the setting and individual circumstances

The risk of MTCT drops to less than 2% with optimal intervention

Factors influencing perinatal mother-to-child transmission

Maternal factors

- Lack of awareness of HIV status
- HIV-1 RNA levels
- Low CD4 lymphocyte count
- Other infections e.g. hepatitis C, CMV, bacterial vaginosis
- Maternal injection drug use
- Lack of ART prophylaxis

Obstetric factors

- Length of ruptured foetal membranes (ROM)
- Chorio-amnionitis
- Vaginal delivery
- Invasive procedures

Infant factors

- Prematurity
- Sex of infant?

Fattori virologici

Numerosi studi hanno osservato una forte correlazione tra aumento del rischio di trasmissione verticale e HIV-RNA > 1000 cp/ml

HIV-1 RNA	Transmission %	N =552
<1000	0	0/ 57
1000 -10,000	16.6	32/193
10,001- 50,000	21.3	39/183
50,001-100,000	30.9	17/ 54
>100,000	40.6	26/ 64

Studio WITS,*Garcia et al*, 1999

Fattori virologici

Non esiste tuttavia una soglia di “sicurezza”: la trasmissione materno-fetale può avvenire anche con livelli di HIV-RNA indeterminabili

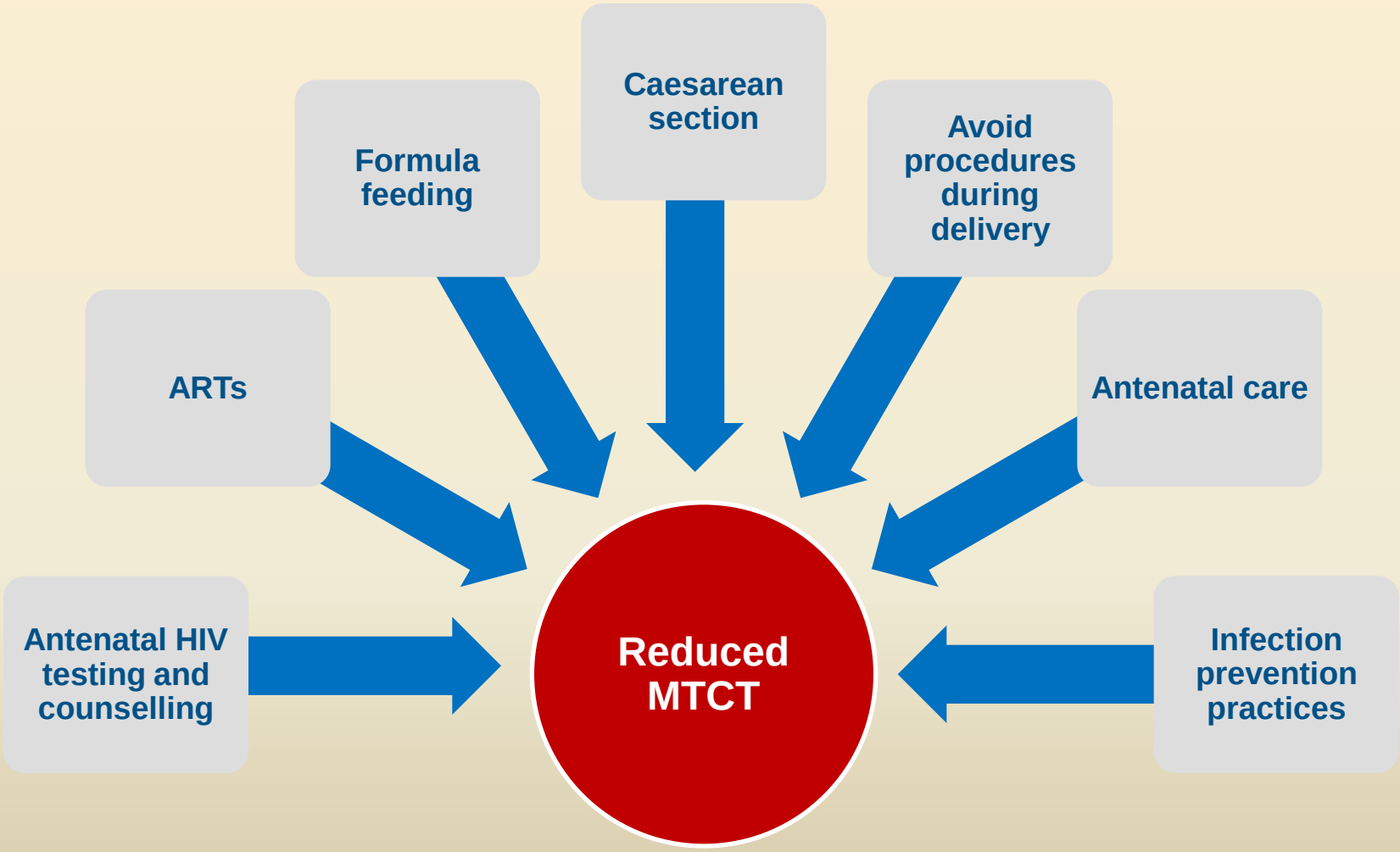
- In una revisione di sette studi prospettici sono stati osservati 44 casi di trasmissione verticale in 1202 pazienti con HIV-RNA < 1000 cp/ml al momento del parto. All’analisi multivariata è stato osservato che la trasmissione si riduce in presenza di TARV (OR 0.10; p<0.001) *(Joannidis et al, 2001)*

Fattori immunologici

Bassi valori di linfociti CD4+ sembrano essere associati a un più alto rischio di trasmissione

- Valori di CD4+ < 700 cell/mmc sono associati a un aumentato rischio di trasmissione verticale *(European Collaborative Study 1999)*
- Il 43% di trasmissione verticale è stato osservato nelle donne con CD4+ < 200 cell/mmc *vs* il 15% nelle pazienti con CD4+ > 600 cell/mmc (*Mayaux et al*, 1997)

Interventions to reduce MTCT



Caesarian section vs vaginal delivery

- Among 560 women with undetectable HIV RNA levels, elective C-section was associated with a 90% reduction in MTCT risk compared with vaginal delivery or emergency C-section

- C-section may be no better than vaginal birth in full-term pregnancies in women with viral load <400

ECS. Clin Infect Dis 2005; Warszawski J, et al. AIDS, 2008

Post-partum morbidity

- The risk of PPM with ECS is higher than that associated with vaginal delivery, yet lower than with NECS.

- Among HIV-1-infected women, more advanced maternal HIV-1 disease stage and concomitant medical conditions (e.g., diabetes) are independent risk factors for PPM.

Cochrane Database SysT Rev 2005

Breast feeding

- 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)

Cochrane Database SysT Rev 2009

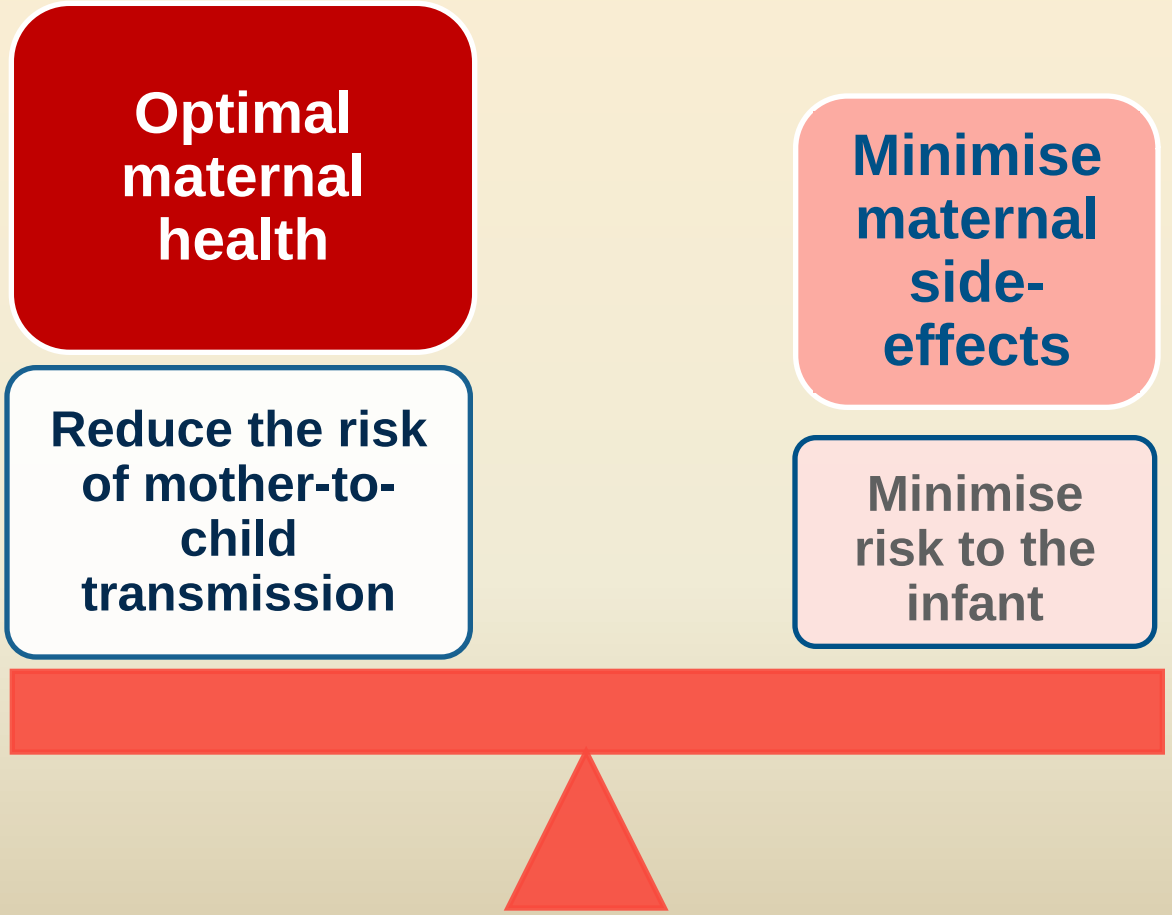
Treatment and care during pregnancy

Antenatal care in HIV

Antenatal care provides an opportunity to:

- ~ Advise about other STIs and general sexual and reproductive health
- ~ Offer continued advice about safe sex
- ~ Offer essential health advice about nutrition and the dangers of substance use (alcohol, smoking, illicit drugs)

Goals of treatment in pregnancy



Cambiamenti fisiologici durante la gravidanza che influenzano la cura della paziente HIV+

MODIFICAZIONI	IMPLICAZIONI
↑ Volume intravascolare (50%)	Alterazione del volume di distribuzione dei farmaci idrofilici e lipofilici
Emodiluizione	Accentuazione dell'anemia legata all'HIV o agli NRTI
↓ Albumina plasmatica e proteine totali	Interferenza di legame con aumento della frazione libera del farmaco
↑ Volume di filtrazione glomerulare (50%)	Aumento della clearance dei farmaci eliminati a livello renale
Alterazione del metabolismo dei farmaci	I livelli di indinavir e nelfinavir possono diminuire durante il 3° trimestre
Rallentamento della motilità intestinale per aumento del progesterone con allungamento tempo svuotamento gastrico	Nausea e vomito nei primi mesi possono interferire con l'aderenza alla terapia Aumento PH gastrico con alterazione assorbimento acidi e basi deboli
↑ Flusso uteroplacentare nel terzo trimestre	Un'adeguata idratazione diventa sempre più importante

General guidelines: HIV treatment in pregnancy

Pregnancy Scenario	Recommendation
1. Women becoming pregnant while already on ART	1. Maintain ART but switch drugs that are potentially teratogenic
2. Women becoming pregnant while treatment naïve and who fulfill the criteria (CD4) for initiation of ART	2. Start ART - at start of 2nd trimester is optimal
3. Women becoming pregnant while treatment naïve and who do not fulfill the criteria (CD4) for initiation of ART	3. Start ART at start of W28 of pregnancy (at the latest 12 weeks before delivery); start earlier if high plasma viral load or risk of prematurity
4. Women whose follow up starts after W28 of pregnancy	4. Start ART immediately

European AIDS Clinical Society (EACS) Guidelines for the Clinical Management and Treatment of HIV Infected Adults in Europe. 2008

HIV drug resistance testing is recommended

- All women who are pregnant and treatment-naïve before starting treatment or prophylaxis with ART
- All women receiving antenatal antiretroviral therapy with persistently detectable HIV RNA levels or with suboptimal viral suppression after initiation of antiretroviral therapy
- For optimal prevention of perinatal transmission, empiric initiation of antiretroviral therapy before results of resistance testing are known may be warranted, with adjustment as needed after the results are available

Available at: http://aidsinfo.nih.gov/guidelines. Revision: July 8, 2008

What do the treatment guidelines recommend?

- Summary of European (EACS), UK (BHIVA) and French guidelines for initiating therapy in women who wish to become pregnant:

  - Boosted protease inhibitors **are preferred**
  - Nevirapine **as an alternative**
  - Efavirenz **teratogenic potential**

US guideline recommendation categories: Perinatal antiretroviral use

	PIs	NNRTIs	NRTIs	Entry Inhibitors	Integrase Inhibitors
Recommended	Lopinavir/r	Nevirapine	Zidovudine* Lamivudine*		
Alternative	Indinavir Ritonavir Saquinavir HGC Nelfinavir		Abacavir# Didanosine Emtricitabine† Stavudine		
Insufficient data	Amprenavir Atazanavir Fosamprenavir Darunavir Tipranavir		Tenofovir DF†	Enfuvirtide Maraviroc	Raltegravir
Not recommended		Efavirenz† Delavirdine	Zalcitabine		

*Zidovudine and lamivudine are included as a fixed-dose combination in Combivir; zidovudine, lamivudine, and abacavir are included as a fixed-dose combination in Trizivir.

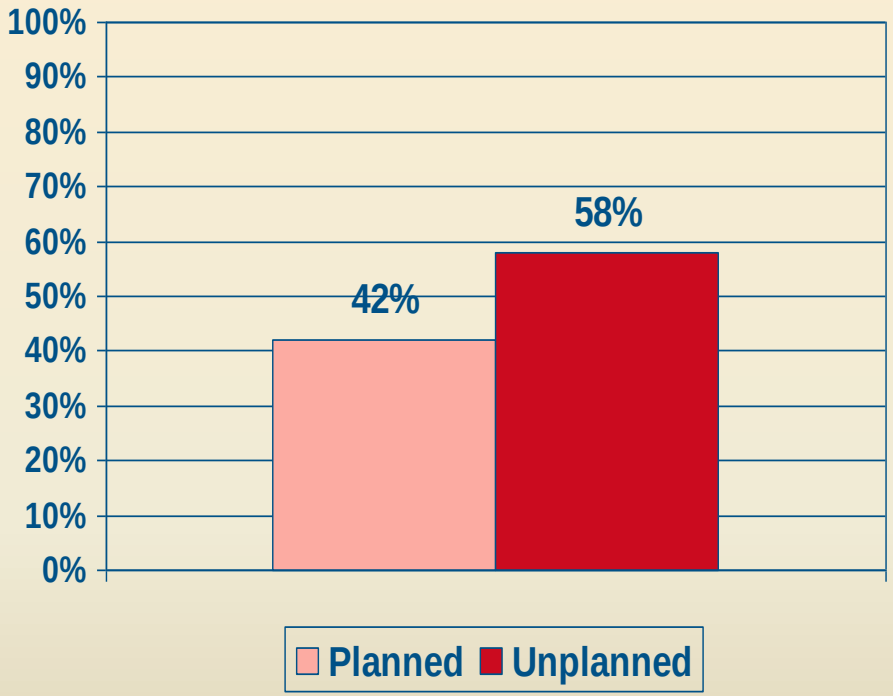
† Emtricitabine and tenofovir are included as a fixed-dose combination in Truvada; emtricitabine, tenofovir, and efavirenz are included as a fixed-dose combination in Atripla.

Triple NRTI regimens including abacavir have been less potent virologically compared to PI-based HAART regimens. Triple NRTI regimens should be used only when an NNRTI- or PI-based HAART regimen cannot be used (e.g., due to significant drug interactions). A study evaluating use of zidovudine/lamivudine/abacavir among pregnant women with HIV RNA <55,000 copies/mL as a class-sparing regimen is in development.

Available at: http://aidsinfo.nih.gov/guidelines. Revision: July 8, 2008

ART regimen at conception frequently suitable only for non-pregnant women

- Among 334 women receiving ART, less than half (42.4%) report current pregnancy as planned
  - A large number of different regimens were being prescribed including:
    - ddI+d4T-based regimens (9.6%)
    - EFV-based regimens (13.5%)
- Once pregnant, patients receiving EFV or ddI often had to change ART (OR 13.2 *P*<0.001 & 1.8 *P*=0.033, respectively)



Physicians should consider child-bearing potential when initiating ART

Floridia M *et al. Antiviral Therapy* 2006

Rate of birth defects in live born infants

Prospective cases with known trimester exposure to LPV/r and complete follow up data

	Overall (%)	[95% CI]
Number of Live Births*	955	
Number of Outcomes with at least One defect**	23 (2.4%)	[1.5% - 3.6%]
Exact 95% CI for prevalence of Birth Defects for Exposures in:		
1st Trimester	5/267 (1.9%)	[0.6%-4.3%]
2nd/3rd Trimester	18/688 (2.6%)	[1.6%-4.1%]
Any trimester	23/955 (2.4%)	[1.5% - 3.6%]
Exact 95% CI for Risk of Birth Defects for 1st Trimester Exposure Relative to 2nd/3rd Trimester Exposures	0.72	(0.27, 1.91)

*Excludes 1 singleton live birth with no defects due to unspecified trimester of exposure. Includes 920 singleton and 35 multiple live birth outcomes.
** Defects meeting the CDC criteria only. Excludes reported defects in pregnancy losses <20 weeks. An outcome is defined as a live or stillborn infant, or a spontaneous or induced pregnancy loss ≥20 weeks gestation.

The overall prevalence of birth defects of 2.4% in LPV/r exposed pregnancies is lower than the CDC's Registry overall prevalence of 2.67%

Atazanavir-based HAART in pregnancy

D. Ripamonti[1], D. Cattaneo[2], M. Airoldi[1], L. Frigerio[1], P. Bertuletti[1], M. Ruggeri[1], G. Remuzzi [2], F. Suter[1], F. Maggiolo[1]

Ospedali Riuniti[1], Mario Negri Institute for Pharmacological Research[2], Bergamo, Italy

Atazanavir overall exposure at steady state during the third trimester of pregnancy is similar to that observed in the non-pregnant state.

Over the whole dosing interval therapeutic drug concentrations are well above the wild-type HIV IC_{90} (approximately 40 folds).

Atazanavir crosses the placenta at a 13% ratio with clear positive linear correlation to maternal plasma levels. Consequently, even considering maternal C_{trough} levels the fetus exposure to atazanavir would fell into a therapeutic range roughly 4 folds higher than wild-type HIV IC_{90}. On the other hand, a limited, but still therapeutic, placental transfer of atazanavir may protect the fetus against the potential toxic effects of the drug.

Since pregnancy does not appear to alter plasma exposure to atazanavir, no dose adjustment is required in pregnant women.

Pharmacokinetic results suggest that a standard boosted atazanavir dose is a reasonable component of HAART during pregnancy.

Ruolo della gravidanza come fattore di progressione dell'infezione da HIV

- Sia in pazienti HIV+ che HIV- si osserva durante la gravidanza una riduzione del numero assoluto ma non della percentuale dei CD4+ per effetto fisiologico dell'emodiluizione *(European Collaborative Study and the Swiss HIV Pregnancy Cohort, 1997)*
- Non si osservano differenze significative nelle variazioni nel tempo del numero di CD4+ tra donne gravide e non *(O' Sullivan et al, 1995)*
- I livelli di HIV-RNA rimangono sostanzialmente stabili durante la gravidanza in assenza di trattamento *(Burns et al, 1998)*

Post-exposure prophylaxis for infants

Post-exposure prophylaxis (PEP) for infants

Monotherapy

For most infants:

- ZDV monotherapy BID for 4 weeks

or

- Alternative suitable ART monotherapy if maternal therapy does not include ZDV

OR

Triple therapy

For infants born to:

- untreated mothers
- mothers with detectable viral RNA despite combination therapy

Co-morbility during pregnancy

Hepatitis B Virus Coinfection

- Screening for hepatitis B surface antigen
- Interferon-based therapies and ribavirin are not recommended during pregnancy
- Treatment should include tenofovir plus 3TC or emtricitabine (FTC)
- Hepatic toxicity should be carefully monitored
- Infants born to women with hepatitis B infection should receive hepatitis B immunoglobulin (HBIG) and initiate the three-dose hepatitis B vaccination series within 12 hours of birth

Hepatitis C Virus Coinfection

- Screening for hepatitis C virus (HCV) infection is recommended
- Interferon- base therapies and ribavirin are not recommended during pregnancy
- Hepatic toxicity should be carefully monitored
- Mode of delivery should be based on HIV infection alone
- Infants should be screened for HCV infection by HCV RNA testing between 2 and 6 months of age and/or HCV antibody testing after 15 months of age

Psychosocial, mental health and emotional well being

- Evaluate psychological status before conception, during pregnancy and parenting
  - ~ Even in patients with no mental illness, new pathology can occur, such as postpartum depression

- Patients presenting with a history of mental disorders or using psychotropic drugs should receive specialised care and surveillance
  - ~ to re-evaluate psychotropic treatment safety and efficacy during pregnancy
  - ~ to follow antiretroviral and psychotropic treatment adherence

Routine testing during pregnancy

Prevalence of HIV among pregnant women in Europe and North America

Country	Prevalence (%)
Estonia[1]	0.48
Ukraine[1]	0.34
Ireland[1]	0.31
Belarus, Latvia, Romania, Russian Federation, Spain, UK[1]	0.1–0.2
Germany, Italy, Sweden, Poland, Norway[1]	<0.1
Canada[2,3]	0.033–0.037
Bulgaria, Czech Republic, Finland, Lithuania, Serbia and Montenegro, Slovakia, Slovenia[1]	<0.03

Higher pockets of HIV prevalence among pregnant women have been reported in several countries e.g. in parts of Ukraine and in and around London in the UK

1. Downs AM, et al. IAS, 2006
2. Jayaraman et al. Can Med Assoc J, 2003
3. Remis SR, et al. Can J Infect Dis, 2003

HIV testing routinely available in pregnancy

Austria	✓	Moldova, Republic of	✓
Bulgaria	✓	Netherlands	✓
Byelorussia	✓	Norway	✓
Canada		Poland	✓
Czech Republic	✓	Portugal	✓
Denmark		Russian Federation	✓
Estonia	✓	Slovakia	✓
France	✓	Slovenia	
Germany	✓	Spain	✓
Greece		Switzerland	✓
Hungary		Ukraine	✓
Italy		UK	✓
Malta	✓		

Adapted from Mounier-Jack et al., HIV Med, 2008

Testing recommendations

- HIV test offered to all women in early pregnancy, or as soon as possible if late presentation for antenatal care
- Repeat testing during pregnancy for women with ongoing HIV risk
- Rapid HIV testing for women presenting for labour
- Test results available to appropriate staff on labour wards