O generație fără HIV – un obiectiv realistic?

31 octombrie 2018

Management-ul nou născutului expus perinatal HIV

Management of HIV perinatally exposed children in Romania

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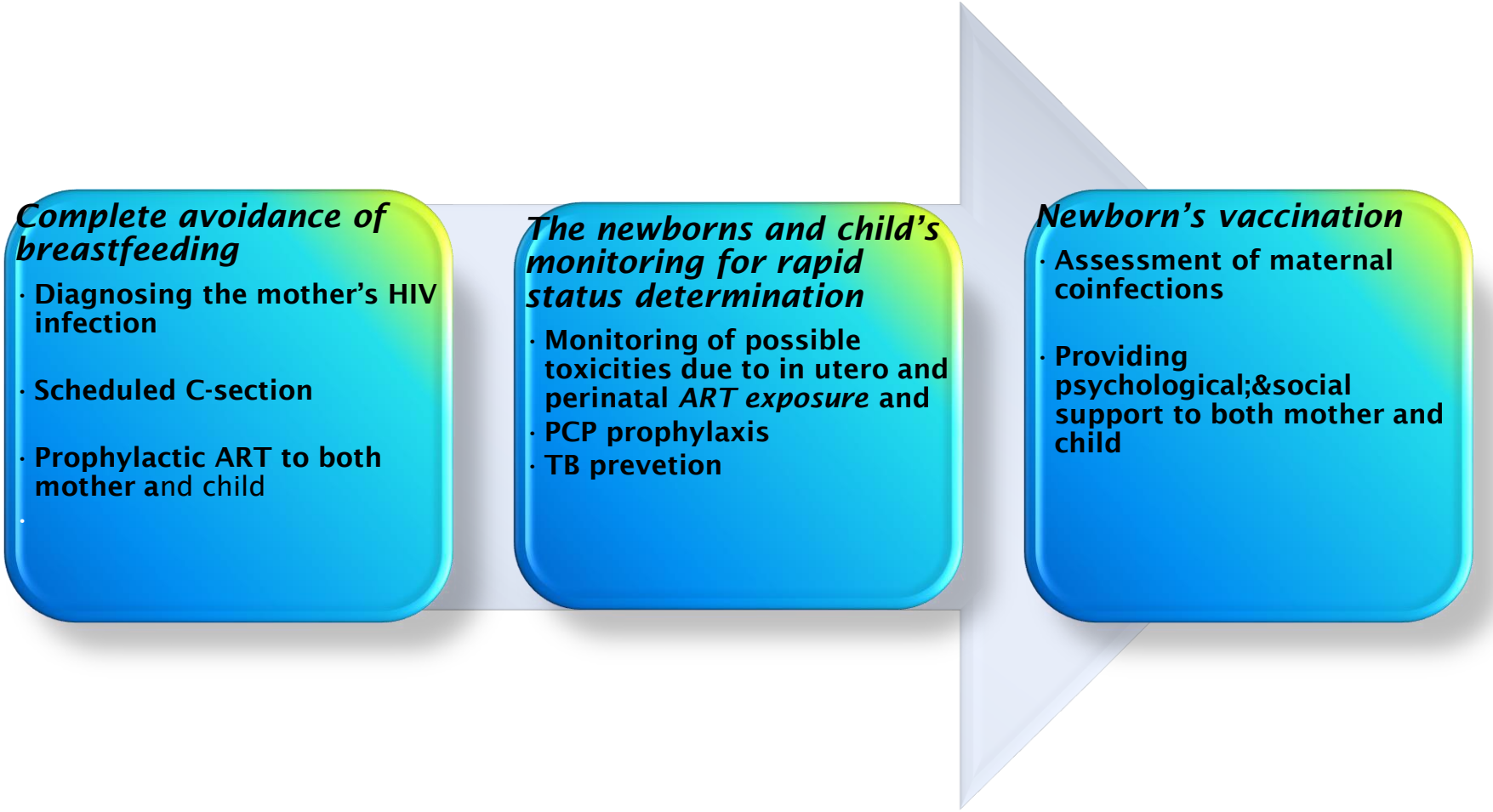
General outline of MTCT in Romania

Mother to child transmission of HIV can be reduced by applying preventive strategies in both mothers and newborns.

In Romania, since the early 2000s the rate of vertical transmission has decreased significantly, the latest percentages, at 31 December 2017 being 2,2%. This value is due to the implementation of a national mother to child transmission programme.

Preventive strategies and management to reduce HIV mother to child transmission in Romania



Preventive strategies correlated with the time of *in utero* HIV transmission

Table 1. Estimated Timing and Risk of Mother-to-Child Human Immunodeficiency Virus Type 1 (HIV) Transmission*

	No Breastfeeding, %		Breastfeeding Through 6 Months, %†		Breastfeeding Through 18 to 24 Months, %‡	
Timing	Relative Proportion	Absolute Rate	Relative Proportion	Absolute Rate	Relative Proportion	Absolute Rate
Intrauterine	25 to 35	5 to 10	20 to 25	5 to 10	20 to 25	5 to 10
Intrapartum	65 to 75	10 to 20	40 to 55	10 to 20	35 to 50	10 to 20
Postpartum breastfeeding						
Early (first 2 months)			20 to 25	5 to 10	20 to 25	5 to 10
Late (after 2 months)			5 to 10	1 to 5	20 to 25	5 to 10
Overall		15 to 30		25 to 35		30 to 45

*Rounded consensus estimates by the authors, based on a critical review of the relevant literature,[12-22] of the absolute transmission rates and proportion of transmission occurring at different time points in the absence of antiretroviral treatment.

†Postpartum transmission estimate at 6 months includes early breastfeeding transmission (first 2 months), which is difficult to distinguish from intrapartum transmission in published studies but likely accounts for more than half of breastfeeding transmission in the first 6 months.[22]

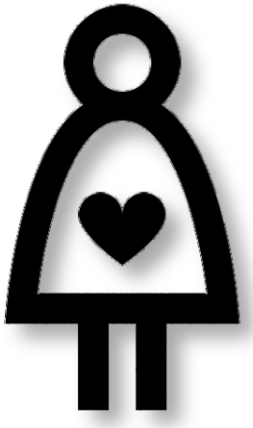
‡Data are cumulative totals; breastfeeding transmission estimates at 24 months include transmission occuring before 6 months.

Registries that collect data on pregnant women

	APR	NSHPC	EACS	EPF
Purpose	**Identifying any teratogenic effects (mTD) in pregnant women exposed to ARVs**	**Surveillance on MTCT prevalence rates, mTD and other results% research on children's HIV natural history**	**Cohort study in HIV+ pregnant women monitored in 26 centers in 9 EU countries to detect mTD and other outcomes**	**Detecting mTD cases in women exposed to any ART**
Reporting	**Voluntary**	**Mandatory**	**Mandatory for centers**	**Voluntary**
Design	**Prospective**	**Prospective**	**Prospective**	**Prospective**
N	**13,538 (07/2010) LPV/r - 1166**	**12,920 (3/2010) LPV/r ~3000**	**2,645 exposures to ART (2007)**	**13,957 (1990-2009) 2,631 (2005-2009)**
% Raported	**15%**	**95%**	**Unreported**	**70%**
Raports	**Drug class and drugs**	**Drug class**	**Drug class**	**Drug class**
Follow-up of infants	**7 days**	**Continuous HIV+ve (CHIPS) HIV-ve 18 months (CHART)**	**18 months**	**18 months**

APR- Antiviral Pregnancy Registry; NSHPC- National Study of HIV in Pregnancy and Childhood (UK); EACS – European Collaborative Cohort; EPF- French Perinatal Cohort

Key issues related to an HIV+ woman's care



Needs

- Multidisciplinary team
- Counseling for dealing with the HIV effects

Pregnancy

- If pregnant- surveillance for adherence to specific cares
- If not pregnant- willingness to use contraceptives- possible drug interactions
- Coinfections: HBV, HCV,TB

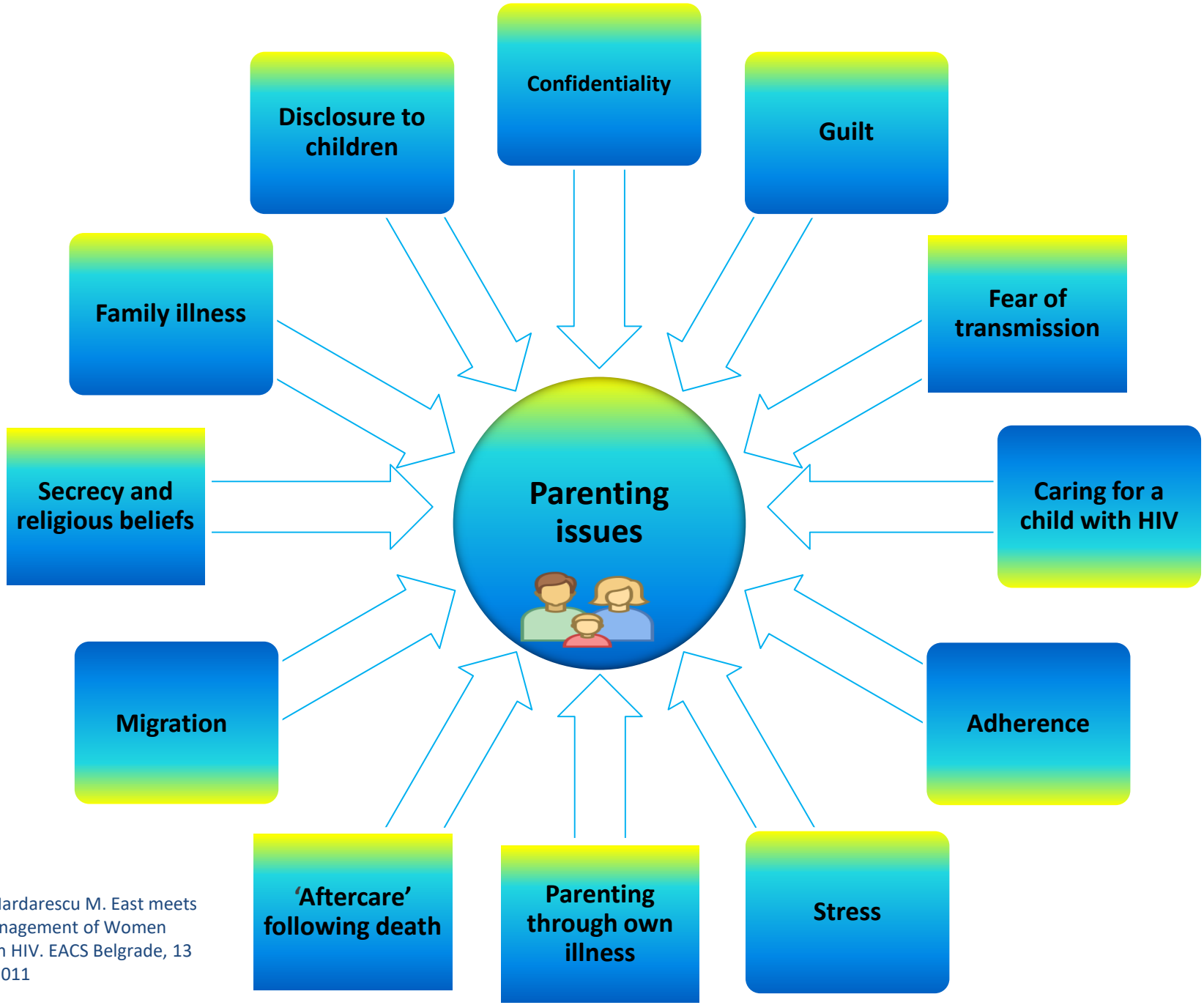
ART effects on pregnancy

- Recent diagnosis? Y/N
- ART for a longer period of time- drug toxicity
- Long term effects of ARTs on the foetus and child

Needs, fears and challenges of HIV+ women

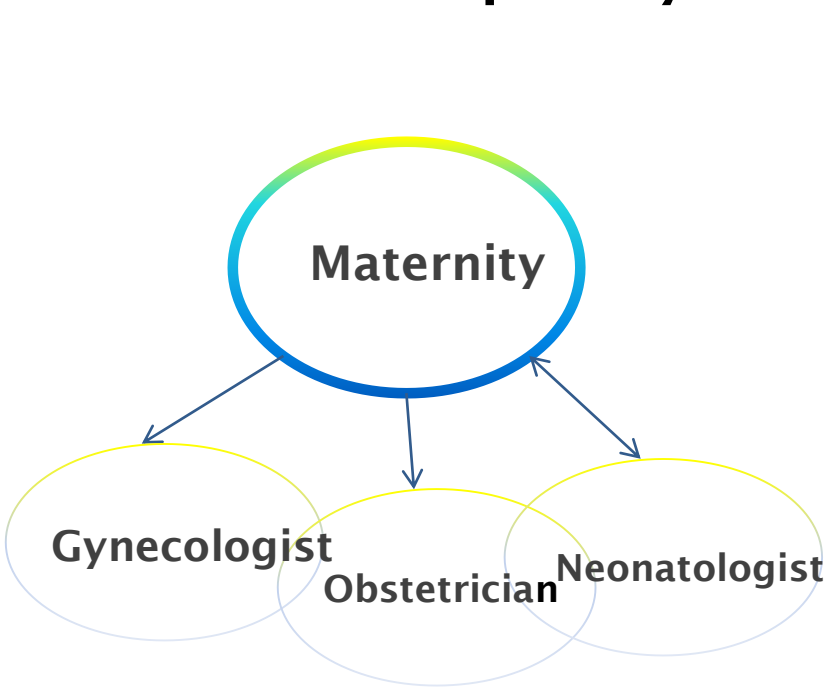
- They may vary based on each woman's profile
- HIV women who carry a higher risk for HIV infection:
  - Often, from countries with high HIV prevalence[1-3]
- Women with late presentation in a sanitary system [1,2]
  - Most probably, diagnosed during antenatal cares[3]
- Women may face significant obstacles in accessing specific HIV cares
  - Fear of high costs for medical services[4]
  - Fear of the HIV test's positive result and stigma associated with it [5]
  - Cultural preconceptions on health, the state of well being and medicine[6]

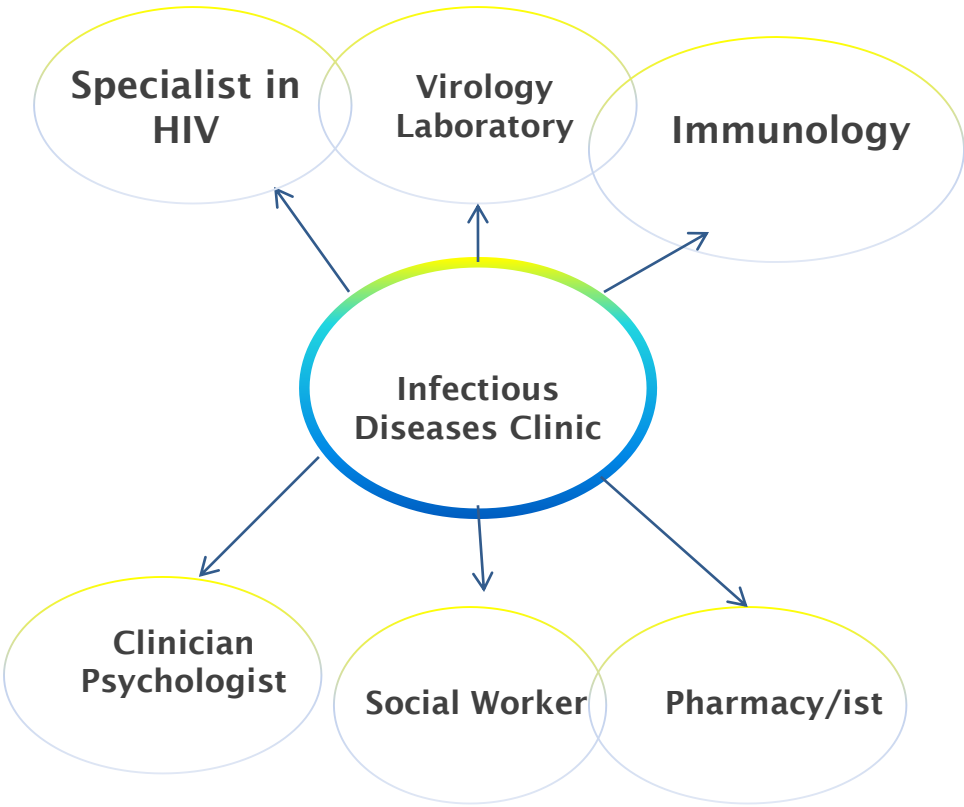
1. Lanoy et al. Antiviral Ther 2007;12:89–96. 2. van Lunzen et al. IAS 2009: abstract MOPEB061. 3. Del Amo et al. Eur J Public Health 2011;21:620–6. 4. Thomas et al. AIDS Care. 2010;22:526–31. 5. Manirankunda et al. AIDS Educ Prev 2009;21:582–93. 6. Thomas et al. Soc Sci Med 2010;70:736–43.



Source: Mardarescu M. East meets West. Management of Women Living with HIV. EACS Belgrade, 13 October 2011

Multidisciplinary team for HIV+ mothers&children

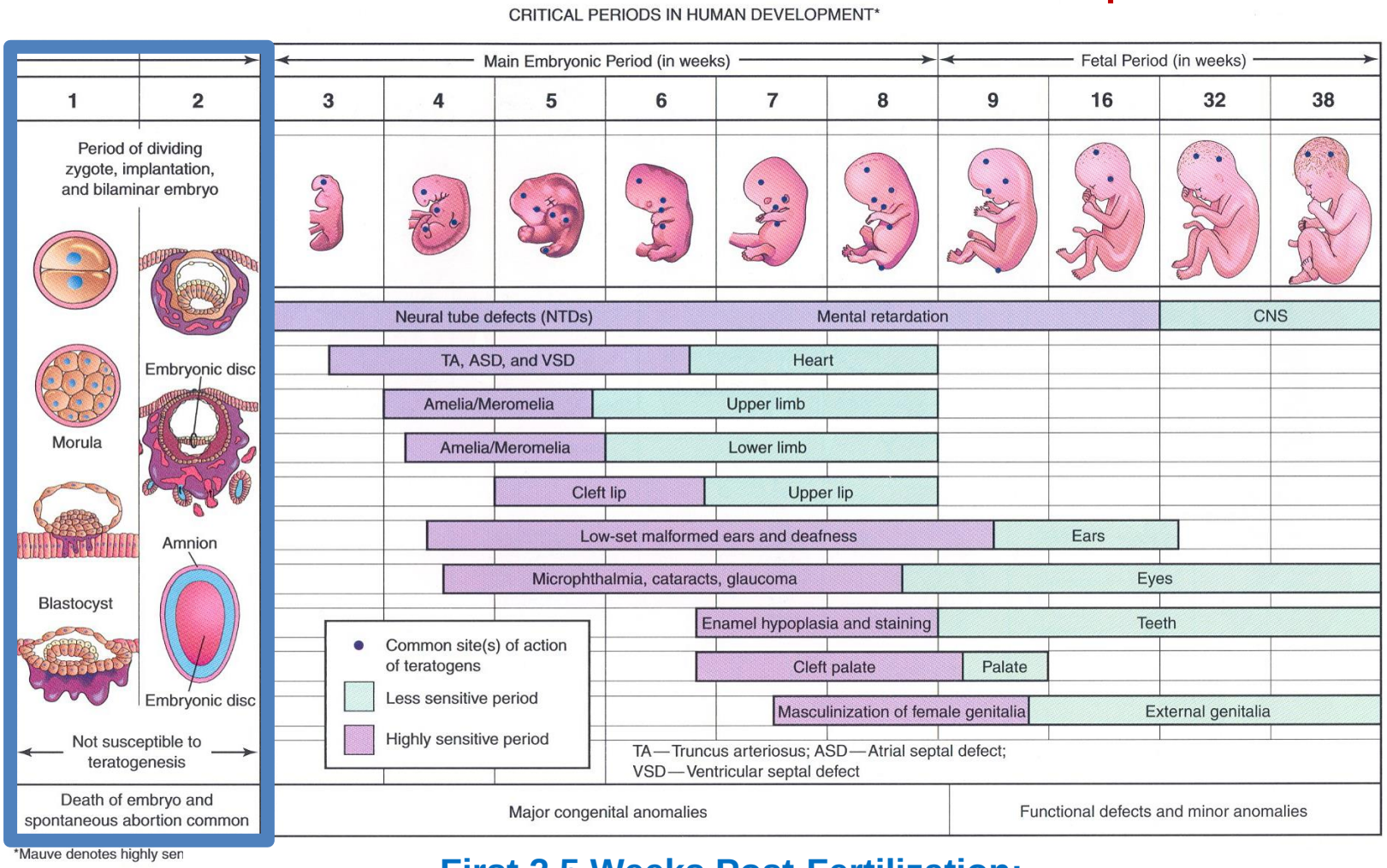




Linkage with

Peadiatric Hospital
NGOs
Social Services

Timing of *In Utero* Exposure Affects Fetal Risk
Critical Periods in Human Development



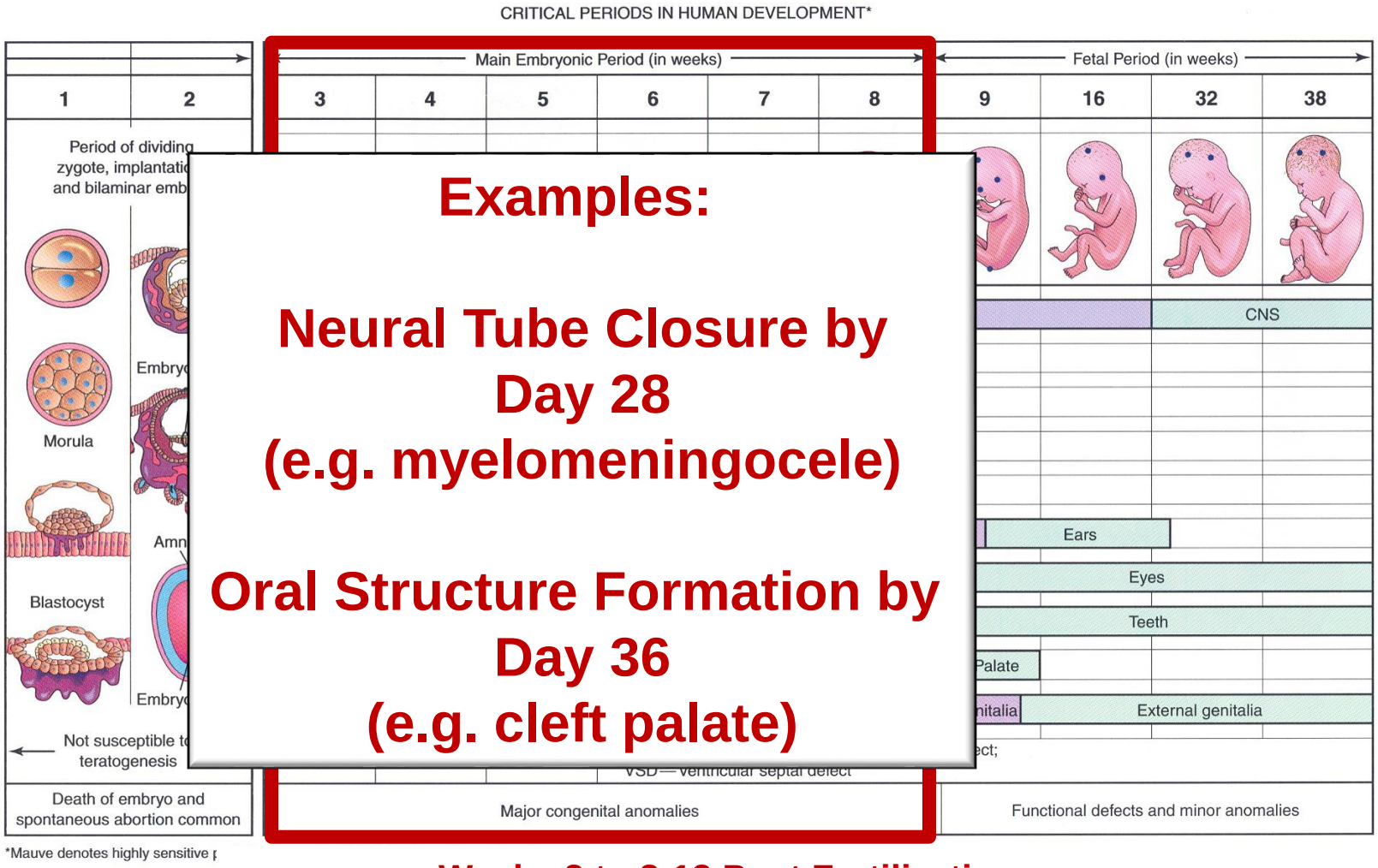
First 2.5 Weeks Post-Fertilization:

Pre-Organogenic Period

generally not sensitive to teratogens

Source: M. Victoria. *What is new in treatment&care (2017/2018).* **ECDC/WHO Joint Meeting HIV in Europe and central Asia in the era of the SDGs: Operationalizing goals and achieving targets** 23-25 April 2018, Berlin, Germany

Timing of *In Utero* Exposure Affects Fetal Risk
Critical Periods in Human Development



Examples:

Neural Tube Closure by Day 28 (e.g. myelomeningocele)

Oral Structure Formation by Day 36 (e.g. cleft palate)

Weeks 3 to 8-12 Post Fertilization

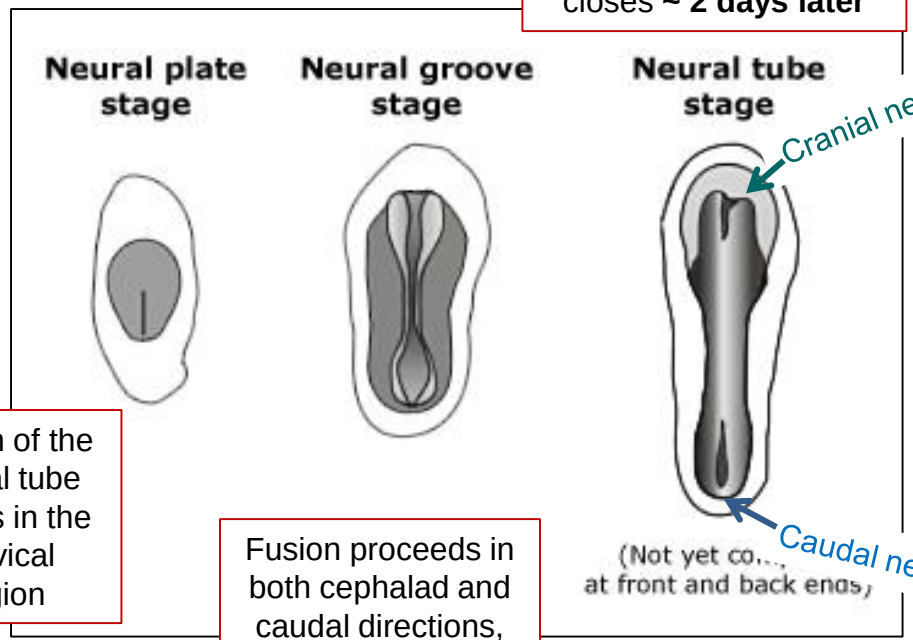
Embryogenesis: Active Organogenesis

most sensitive period to teratogens

Source: M. Victoria. *What is new in treatment&care (2017/2018).* **ECDC/WHO Joint Meeting HIV in Europe and central Asia in the era of the SDGs: Operationalizing goals and achieving targets** 23-25 April 2018, Berlin, Germany

Neural Tube Closure Normally Occurs by 28 Days Post-Conception

Cranial neuropore closes on **25th day after conception**; caudal neuropore normally closes **~ 2 days later**

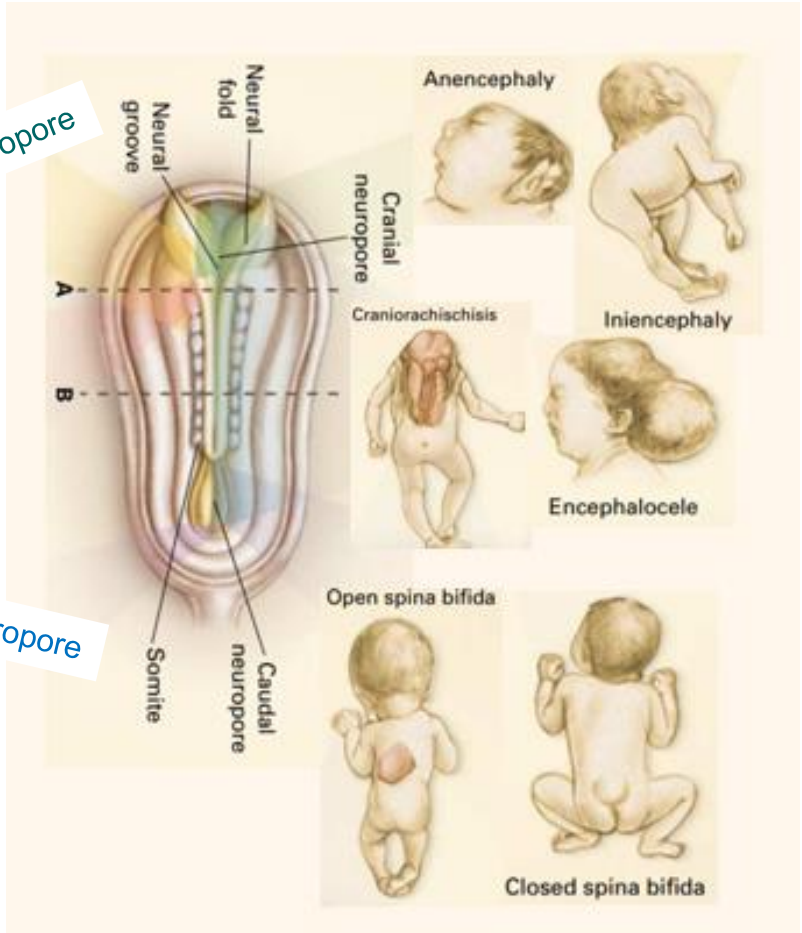


Fusion of the neural tube begins in the cervical region

Fusion proceeds in both cephalad and caudal directions, forming anterior and posterior neuropores

UpToDate Online 17.2: McLone DG, Bowman RM

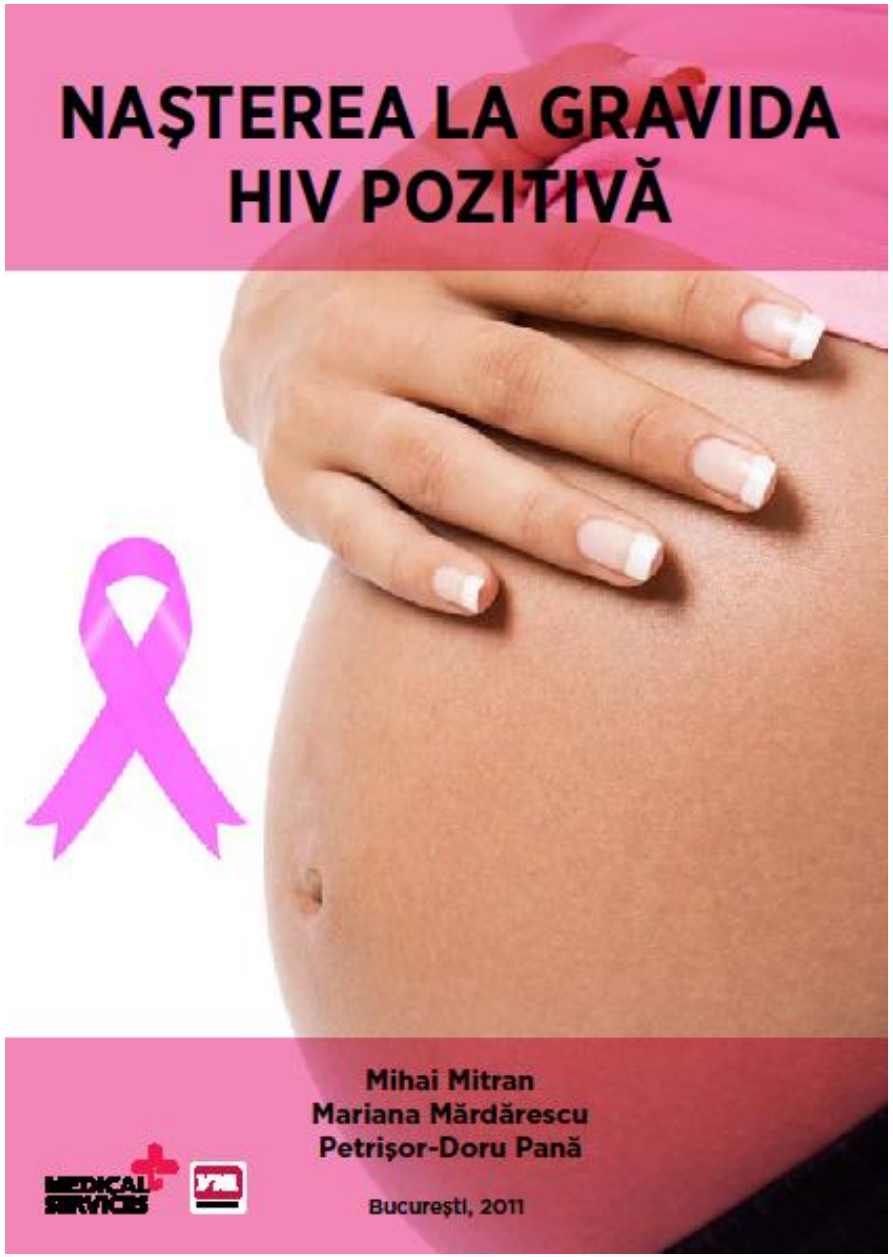
Neural tube defects



NEJM Botto 1999

Source: M. Victoria. *What is new in treatment&care (2017/2018).* **ECDC/WHO Joint Meeting HIV in Europe and central Asia in the era of the SDGs: Operationalizing goals and achieving targets** 23-25 April 2018, Berlin, Germany

Guidelines on the management of HIV pregnant women in Romania



Anexa 1. Conduita antepartum

Trimestrul I
1. Testarea HIV a tuturor gravidelor 2. Nivel CD4, CD8 3. Încărcătură virală 4. Ecografie 5. Analize: grup, Rh, HLG, coagulogramă, biochimie, sumar de urină, urocultură 6. VDRL, TPHA 7. AgHBs, AcHBc 8. Testare toxoplasmă, rubeolă, CMV, HSV, eventual HPV 9. Testare Chlamydia, Mycoplasmă, Ureaplasmă, Gonococ 10. Testare Babeş-Papanicolau 11. Examen de secreţie vaginală
Trimestrul II
1. Triplu test 2. Ecografie 3. Analize: HLG, sumar de urină 4. VDRL, TPHA 5. AgHBs, AcHBc, dacă nu s-au efectuat în trimestrul I 6. Examen de secreţie vaginală 7. Testare pentru streptococ de grup B
Trimestrul III
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Naşterea la gravida HIV pozitivă

Anexa 2. Conduita intrapartum

1.	Testare HIV cu test rapid – dacă nu e testată în cursul sarcinii
2.	Continuarea TARV materne
3.	Naşterea: cezariană sau vaginală
4.	Supraveghere activă în periodul 3

Anexa 3. Conduita post-partum

1.	Continuarea TARV materne
2.	Iniţierea TARV la copil
3.	Antibioterapie maternă profilactică
4.	Profilaxia trombozelor
5.	Ablactare
6.	Toaleta chirurgicală a plăgii operatorii/episiotomie
7.	Suport psihologic, asistenţă socială
8.	Consiliere contraceptivă, planificarea sarcinii
9.	Control după externare la 6 săptămâni şi 3 luni

Anexa 4. Medicaţia ARV la nou-născut

ARV	ZIDOVUDINĂ	LAMIVUDINĂ
La termen	2 mg/kg la 6 ore, oral, 6 săptămâni	2 mg/kg la 12 ore, oral, 6 săptămâni
Prematur	1,5-2 mg/kg la 12 ore, oral	-

The diagnostic of HIV infection in children is also based on clinical, epidemiological and laboratory data

- **Confirmation of HIV infection in children <18 moths:**
  - Virological tests for most newborns and infants, considering that serological tests that show HIV antibodies cannot determine the HIV status of the child due to maternal antibodies

- **In children >18 months whose mothers are HIV+ or in children of any age with different routes of transmission, HIV diagnostic is confirmed:**
  - With 2 positive serological tests, namely two positive Elisa tests from two different blood samples and **one positive Western Blot positive test** (mandatory)

- Elisa is an effective screening test due to high sensitivity and reduced costs. It also highlights anti-HIV antibodies.

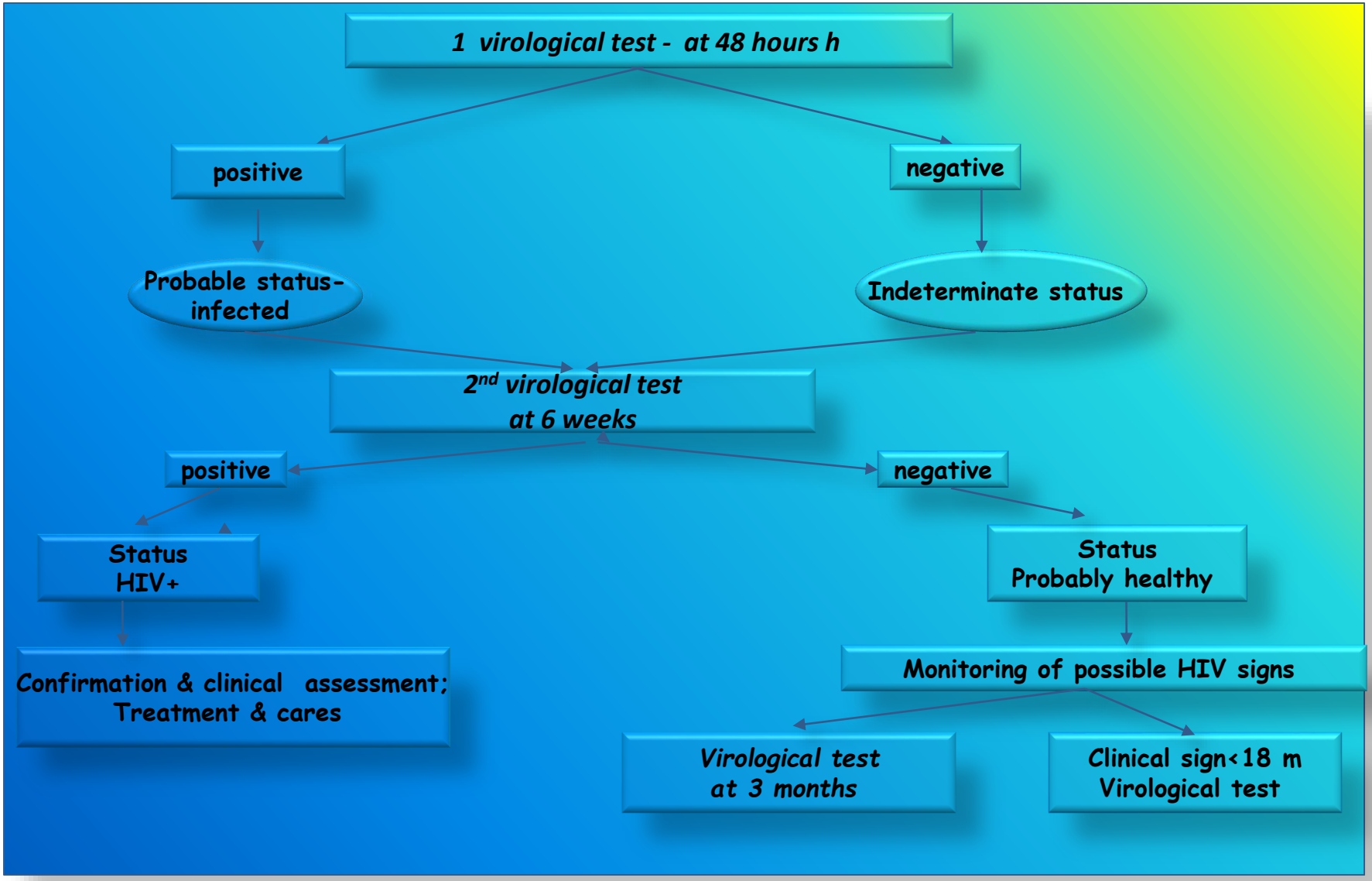
- Western Blot separates specific proteins, based on molecular weight, forming stripes in an electrophoresis gel. The test's results can be:
  - Negative
  - Pozitive: at least two stripes: P24, GP41, GP120/160
  - Indeterminate: only one stripe

- HIV DNA-PCR identifies: HIV pro-viral DNA from the peripheral blood, namely in mononuclear cells

- HIV DNA-PCR detects the virus in the serum, quantifying viraemia.

- P24 antigen, the standard test or via immune associated complexes has reduced sensitivity in children <3 months. When present, it allows early diagnosis of HIV.

Virological diagnosis of new borns who received with formula



Time of DNA/RNA-PCR testing

At birth

The first 48h: to identify , as early as possible, children infected "in utero".

14-21 days: to identify children infected *intrapartum*

1-2 months

4-6 months: to identify all *perinatally* exposed newborns

Monitoring principles of the HIV perinatally exposed newborn in Romania

Newborns to HIV positive mothers are considered at risk of infection, hence:

Multidisciplinary& complex monitoring	*Clinical&biological assessment*	*Clinical&biological assessment*
• ART prophylaxis in mother and child • Schedueled C-section • Formula	• HIV-RNA: first 48 hours (not from the umbilical cord) • 2, 6,12 weeks • 6 months • Every six months until 18 or 24 months	• CD4 count at baseline • Elisa, Western Blot at birth • Elisa, Western Blot at 6 months and every 6 months until 18 or 24 motnhs

Monitoring agenda of the HIV perinatally exposed newborn

- Complete blood count (CBC) prior to administering Zidovudine

- Assessment of maternal co-infections:
  - TBC, syphilis, hepatitis B, C, CMV, herpes-simplex (relative rates of transmission from mother to child)
  - Slight possibility of reactivation in immunocompromised pregnant women – transmission risk for the newborn

- Children with HIV exposure in utero/neonatal who develop organ and systemic failures, particularly, at the level of the nervous or cardiac system will be assessed for potential mitochondrial dysfunctions

Recomandări de dozare a medicamentelor ARV pt nou-născutul expus perinatal infecției HIV

ZDV la ≥ 35 săptămâni vârsta gestațională la naștere:

De la naștere-6 săptămâni:
4 mg/Kg oral, de 2 ori/zi (2<3 Kg- 1ml; 3-4 Kg-1,5 ml; 4-5 Kg- 2 ml) (ZDV 10 mg/ml sirop- de 2 ori/zi

ZDV ≥ 30- < 35 săptămâni vârsta gestațională la naștere:

De la naștere- 2 săptămâni:
2mg/Kg, oral, de 2 ori/zi
De la 2 săptămâni- 4-6 săptămâni:
3 mg/Kg, oral, de 2 ori/zi

ZDV < 30 săptămâni vârsta gestațională la naștere:

De la naștere la 4 săptămâni:
2 mg/Kg, oral, de 2 ori/zi.
De la 4 săptămâni- 6 săptămâni:
3 mg/Kg, oral, de 2 ori/zi

Source: Table 7. Neonatal Dosing for Prevention of Perinatal Transmission of HIV-Panel on ARV Theraphy and Medical Management of HIV-infected Children-Guidelines for the Use of ARV Agents in Pediatric HIV Infections-Apr.2017-E 13

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NVP ≥ 37 săptămâni vârsta gestațională la naștere

De la naștere-6 săptămâni:

6 mg/Kg, oral, de 2 ori/zi (NVP-sirop-10 mg/ml)

NVP 34-<37 săptămâni vârsta gestațională la naștere

De la naștere la 1 săptămână:
4 mg/Kg, oral, de 2 ori/zi
De la 1 săptămână- 6 săptămâni:
6 mg/Kg, oral, de 2 ori/zi

3TC ≥32 săptămâni vârsta gestațională la naștere:

De la naștere la 4 săptămâni:

2 mg/Kg, oral, de 2 ori/zi (3TC-sirop-10 mg/ml).

De la 4 săptămâni-6 săptămâni:

4 mg/Kg, oral, de 2 ori/zi

Source: Table 7. Neonatal Dosing for Prevention of Perinatal Transmission of HIV-Panel on ARV Theraphy and Medical Management of HIV-infected Children-Guidelines for the Use of ARV Agents in Pediatric HIV Infections-Apr.2017-E 13

Prophylaxis of Pneumocystis jirovecii in HIV perinatally exposed newborns

PJP prophylaxis will be applied to all HIV perinatally exposed newborns.

Dosage:

Cotrimoxazole (TMP/SMZ) syrup/6mg/kg/day TMP every day, since 4-6 weeks of life until HIV infection is presumptively/definitvely excluded

Feeding principles for HIV perinatally exposed newborns

According to the international recommandations, breastfeeding represents an essential risk factor for mother to child transmission of HIV.

Hence, breastfeeding will be replaced with formula, irrespective of the mother's viral load or ART therapy

Vaccination of the perinatally HIV exposed newborn

- The vaccination scheme of the perinatally HIV exposed newborn follows the recommendations from the National Vaccination Guideline.
- Most recommended vaccines can be safely administered to HIV exposed/infected children.
- All inactivated vaccines can be administered, safely, to persons with weak immunity.
- Furthermore, due to the increased risk of vaccine preventable diseases, with increased severity in infected children, it is recommended that specific vaccines are applied, such as: pneumococcal conjugated vaccine and flu vaccine.
- **Patients with severely damaged immunity will not receive live-attenuated vaccines (!!!).**

Vaccination of the perinatally HIV exposed newborn

TB immunization principles:

- TB prevalence in the country's population (vs WHO's recommendations)
- TB exposure risk for the child
- Prevalence of HIV infection
- HIV coverage and efficacy of PMTCT measures
- Virological diagnostic during the first months of life

Vaccination of the perinatally HIV exposed newborn

- The benefits of BCG vaccination outlast the risks for children with no signs/symptoms for HIV, born to mothers with known or unknown HIV status. In this context, these children need BCG vaccination.

- HIV exposed children, with decreased HIV transmission risk (mother's V.L. <50 c/ml at ≥ 36 weeks of pregnancy), with low risk of TB exposure, can be safely vaccinated for BCG at birth, prior to the ultimate confirmation/exclusion of HIV.

- **In Romania, BCG vaccination of the HIV perinatally exposed child is applied at 8 weeks, after the second virological assessment.**

Hospital discharge&follow-up

Prior to discharge several aspects should be considered:

- the family's capacity to provide adequate cares to their new-born:
  - formula feeding;
  - norms of hygiene;
  - correct prophylaxis administration;
  - capacity to follow the medical recommendations;
  - medical check-ups;
  - into the records and surveillance of a general practitioner

Basic monitoring principle for the HIV perinatally exposed uninfected newborn:
monitoring by 5-7 years of age, with, at least,
one assessment per year by the infectious diseases specialist.

Thank you!

References

- Compartment for Monitoring and Evaluation of HIV/AIDS Data in Romania – www.cnlas.ro
- M. Mardarescu, C. Petre. *Managementul nou-nascutului si sugarului expus infectiei HIV. Update 2018.* National Institute for Infectious Diseases "Prof. Dr. Matei Bals".
- M. Mardarescu. *Romania's way to 2nd and 3rd 90s.* ECDC/WHO Joint Meeting HIV in Europe and Central Asia in the era of the SDGs: Operationalising goals and achieving Targets. 23-25 April, 2018, Berlin.
- Mardarescu et All. *Risk factors involved in late detection of HIV mother to child transmission - data from the National Registry of HIV pregnant women and perinatally exposed children in Romania.* 2nd Vilnius Summit on Communicable Diseases, October 4-7 2017.
- Mardarescu et All. *Surveillance of HIV-infected women-users of psychoactive substances and the consequences of drug use on their newborns' development in Romania.* 16th European AIDS Conference, October 25-27, 2017 Milan, Italy
- Mardarescu et All. *Risk factors involved in the late detection of HIV mother-to-child transmission, as identified in National Registry of HIV pregnant women and perinatally exposed children in Romania.* 8th International workshop on HIV&Women, 2-3 March, 2018, Boston, MA, USA.