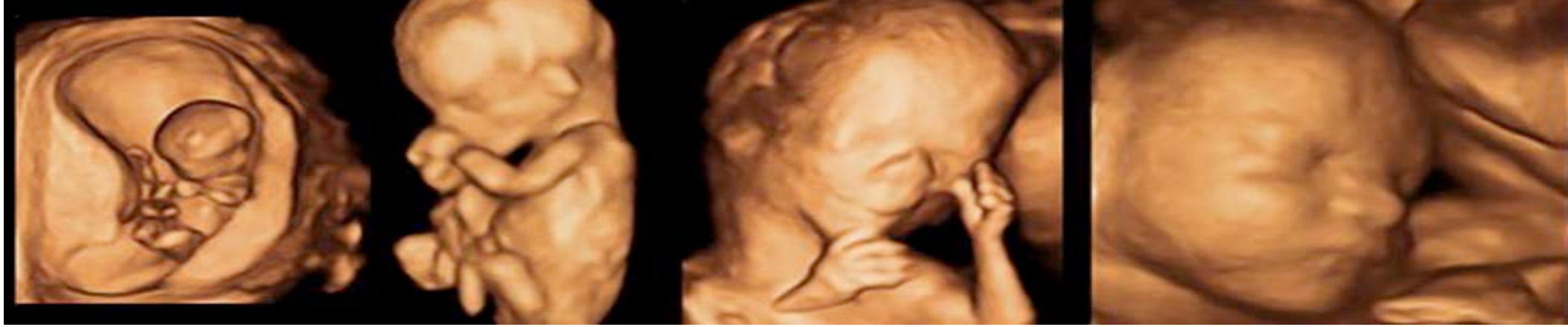

Guidelines for HIV in pregnancy: Dilemmas from an obstetrician`s point of view

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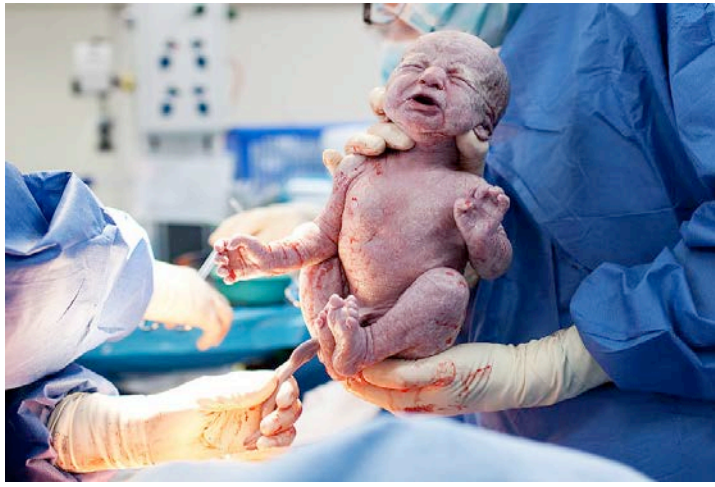


No disclosures in regard to this talk

Where is Switzerland?

Switzerland is a small country known for its cheese and chocolate

Outline

Dilemma 1: When to start
Dilemma 2: What to start
Dilemma 3: Invasive procedures, amniocentesis
Dilemma 4: Rupture of membranes
Dilemma 5: Procedures during vaginal delivery
Dilemma 6: Breastfeeding, adherence

Guidelines mentioned:

Europe: BHIVA (British HIV Association) 2018 and EACS (European Aids Clinical Society) guidelines 2017
US: Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States Nov 2017
Canada: SOGC Clinical Practice Guideline 2014

Case notes: Anna

Profile

- 33 year old woman presents in the antenatal clinic in Bern

History

- Migrant from Kenya
- History of sexual assault
- She had a C-Section 3 years ago with 28 weeks gestation in her home country, baby did not survive
- She is today 9 weeks pregnant, complaining about nausea and vomiting
- Her partner left the country

HIV Pos
- **CD4 380/mm^3**
- **VL 36,000 copies/ml**

- **HCV positive**
- **HbsAg negative**

Annual number of deliveries to women living with HIV in the Euro Region

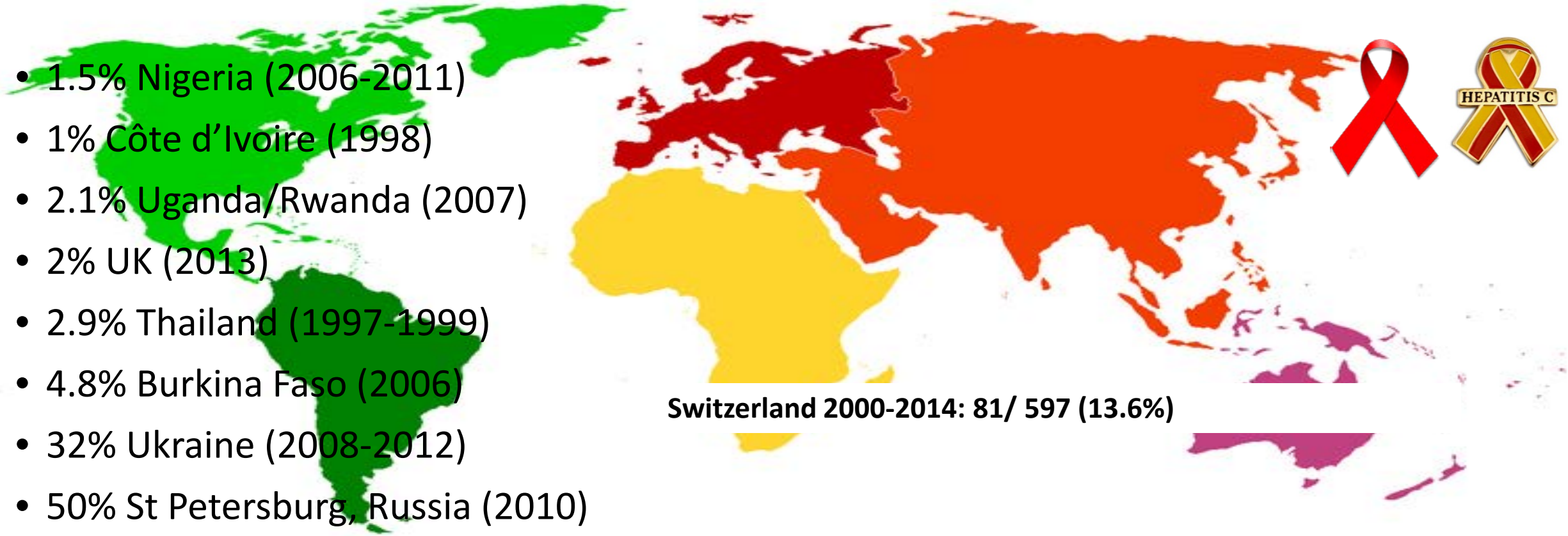
>27,000 deliveries per year across the Region

Approximately 7,500 deliveries to HIV+ women annually in the EU

<100	Armenia, Albania, Bulgaria, Georgia, Lithuania, Latvia, Serbia, Slovakia
<200	Estonia, Kyrgyzstan
<200 to <500	Azerbaijan, Moldova
<500	Belarus, Tajikistan
<500 to <1000	Uzbekistan
≈3,500	Ukraine
≈16,000	Russian Federation

HCV seroprevalence in pregnant women with HIV

- 1.5% Nigeria (2006-2011)
- 1% Côte d'Ivoire (1998)
- 2.1% Uganda/Rwanda (2007)
- 2% UK (2013)
- 2.9% Thailand (1997-1999)
- 4.8% Burkina Faso (2006)
- 32% Ukraine (2008-2012)
- 50% St Petersburg, Russia (2010)



Switzerland 2000-2014: 81/ 597 (13.6%)

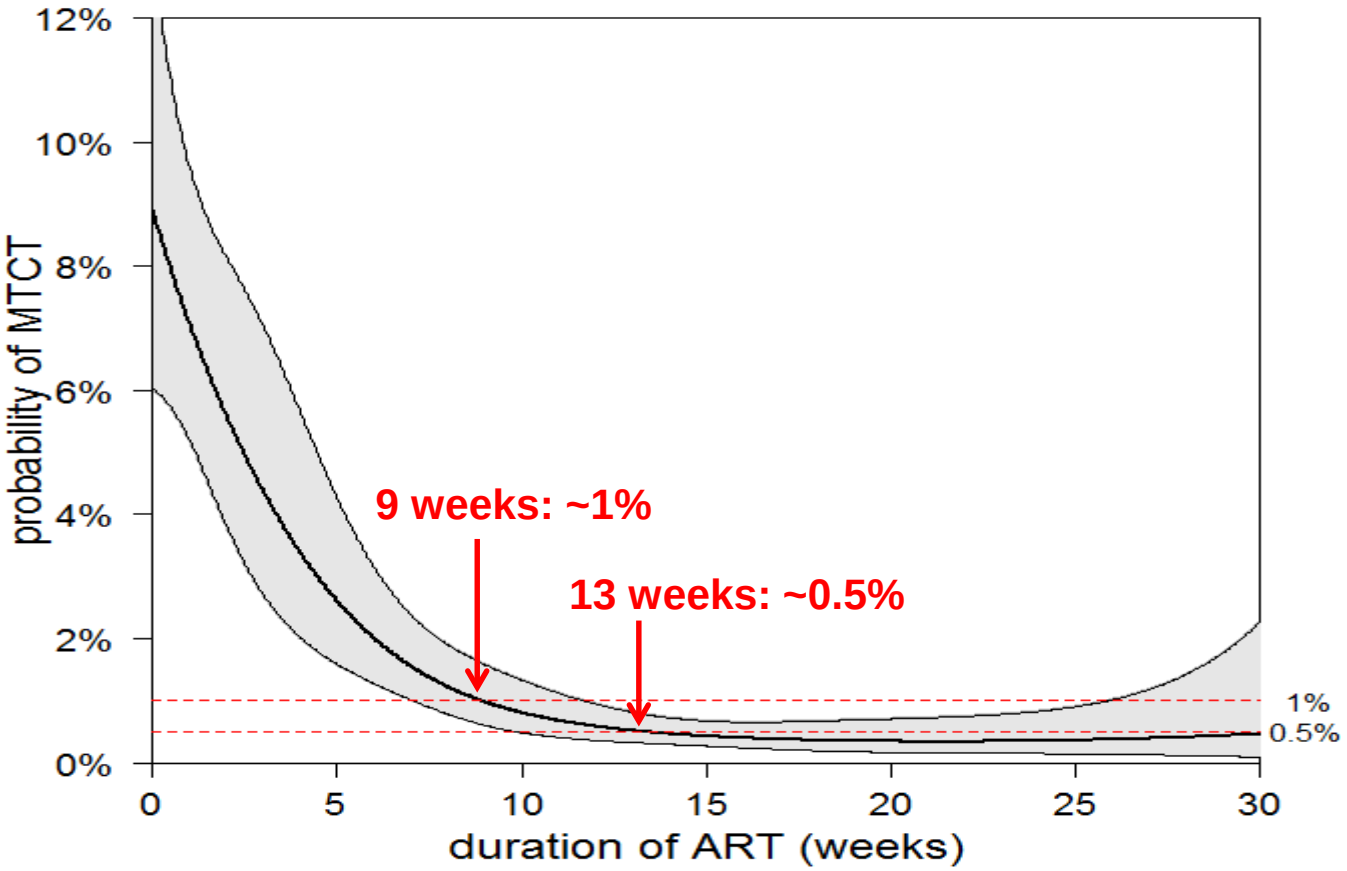
Data from UK NSHPC, Ukraine European Collaborative Study, EPPICC; Floridia et al 2010 Epidemiol Infect, Ezechi et al 2014 Pan Afr Med J ; Rouet et al 2004 J Med Virol; Kissin et al 2010 BMC Inf Dis; Simpore et al 2006 J Med Virol; Pirillo et al 2007 J Med Virol; Ngo-Giang-Hong et al 2010 Int J Infect Dis

Would you start her on treatment for HIV today (9 weeks pregnant) ?

1. **Yes**

2. **No**

UK & Ireland data: probability of MTCT by duration of cART



Unadjusted model including 6507 women who started cART in pregnancy, 2000-2011

MTCT probability declined rapidly during first 9 weeks of cART

Then declined more slowly, levelling off at around 0.5% after around 13 weeks

Townsend et al 2014, AIDS

Dilemma 1: When to start cART

- immediately **(EACS)**, after 1st trimester, latest 24 weeks **(BHIVA)**

Commence as soon as women are able to do so. Discuss deferring treatment start to second trimester if nausea/ vomiting. Start immediately if VL >100 000 copies/ml **(BHIVA)**

- ART should be initiated as soon as HIV is diagnosed without waiting for the results of resistance testing **(US)**

Determinants of the probability to suppress HIV VL:
baseline viral load, time to achieve this target
(eg history of preterm delivery)

Case notes: Anna

Which antiretroviral therapy would you start ?

What to start: US

Public Health Service Task Force ARVs in Pregnant HIV-Infected Women; Update 2017

Preferred	Alternate	Not recommended or insufficient data
NRTI		
Abacavir/Lamivudine TDF/ FTC or 3TC	Zidovudine/Lamivudine	Didanosine Stavudine TAF/FTC
NNRTI		
	Efavirenz Rilpivirine	Etravirine Nevirapine
Protease Inhibitors		
Atazanavir/r Darunavir/r	Lopinavir/r	Nelfinavir Tipranaivr/r Fosamprenavir/r
Other		
Raltegravir	Dolutegravir	Enfuvirtide Maraviroc Elvitegravir/c/TDF/FTC or TAF/FTC

Public Health Service Task Force, Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States, 2017

What to start: Europe
European Aids Clinical Society (EACS) Guidelines 2017

- Same as non-pregnant, EFV is suitable alternative
- If on RAL, DTG, RPV or DRV/r could be continued, if on EVG/c consider VL and drug level monitoring
- Among PI/r prefer ATZ/r, TAF/cobi not reommended
- Late presenting: add INSTI
- If VL>50 c/mL add iv Zidovudine

SCENARIO	
	1. Maintain ART, unless taking some contraindicated regimen during pregnancy (ddI + d4T, triple NRTI combinations)
	2. Maintain ART, unless taking some contraindicated regimen during pregnancy (ddI + d4T, triple NRTI combinations)
	3. Starting ART as soon as possible is highly recommended NEW!
	4. Start ART immediately and consider INSTI as the preferred choice to obtain rapid HIV-VL decline and to ensure the HIV-VL is undetectable by the time of delivery
	5. Perform resistance testing and consider changing to or adding INSTI if not on this class to obtain rapid HIV-VL decline
	Same as non-pregnant NEW!
	If on RAL, DTG, RPV or DRV/r: could be continued. Women on EVG/c need to be informed that more monitoring of HIV-VL and drug levels may be necessary during pregnancy
	Among PI/r, prefer ATV/r NEW!
	EFV is a suitable alternative for pregnant persons needing to start treatment. It can be continued if already started before pregnancy
	NVP not to be initiated, but continuation is possible if started befor pregnancy NEW!
	Limited experience with TAF and COBI in pregnancy: not recommended in initial regimen
	ddI + d4T, triple NRTI combinations
	Only if HIV-VL > 50 copies/mL at week 34-36
[illegible] during labour	Not recommended
Caesarean section	Only if HIV-VL > 50 copies/mL at week 34-36 NEW!
Breastfeeding	We advise against breastfeeding. In case a woman insists on breastfeeding, we recommend follow-up with increased clinical and virological monitoring of both the mother and the infant

Dilemma 2: What to start

- Dual nucleoside reverse transcriptase inhibitor combination (abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine or lamivudine)

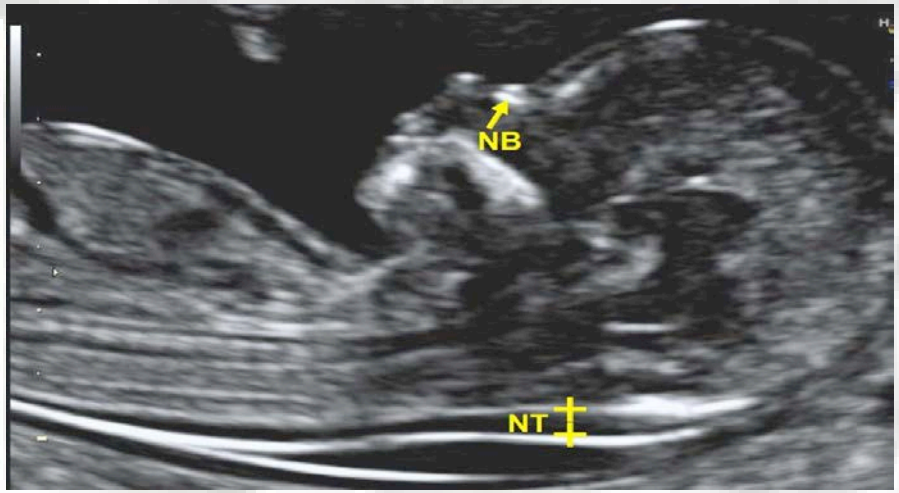
- PLUS ritonavir-boosted protease inhibitor (atazanavir/ritonavir or darunavir/ritonavir)

  or an integrase strand transfer inhibitor (raltegravir)

Insufficient data about 1st trimester exposure: Cobicistat, **Dolutegravir**, Elvitegravir, Tenofovir alafenamide, Maraviroc, Etravirine

(http://www.apregistry.com/forms/interim_report.pdf)

Anna



Risk:1:10

- Anna started ART at 10 weeks with tenofovir disoproxile fumarate with emtricitabine and darunavir/ritonavir

- Combined screening test shows an elevated risk for Trisomy 21 at 12+4 weeks of gestation (1:10)

Would you allow to perform an amniocentesis ?

Amniocentesis in the cART era

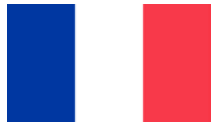
Italian study

- 2065 pregnancies, 113 (5.5%) invasive antenatal tests 2001-2015: no HIV transmisison in those on cART

UK/ Ireland HSHPC

- 27 (1%) of deliveries with invasive prenatal procedures 2012-2016: no MTCT

French study



- 166 invasive tests, 25% transmissions in untreated and 6% in AZT mono, no MTCT in 81 women on cART 1985-2006

Floridia et al 2017 BJOG, Peters et al 2017 EJOG, Mandelbrot et al. AJOG 2009

Dilemma 3: Screening for aneuploidies and invasive procedures

- Screening (11-13+6 weeks of gestation):

  nuchal translucency, beta HCG and PAPP-A (bloods)

- Amniocentesis: VL should be < 50 copies/mL **(BHIVA, US)**
- **If VL>50 copies/mL: - include raltegravir and give nevirapine 2-4 hours before procedure** **(BHIVA)**

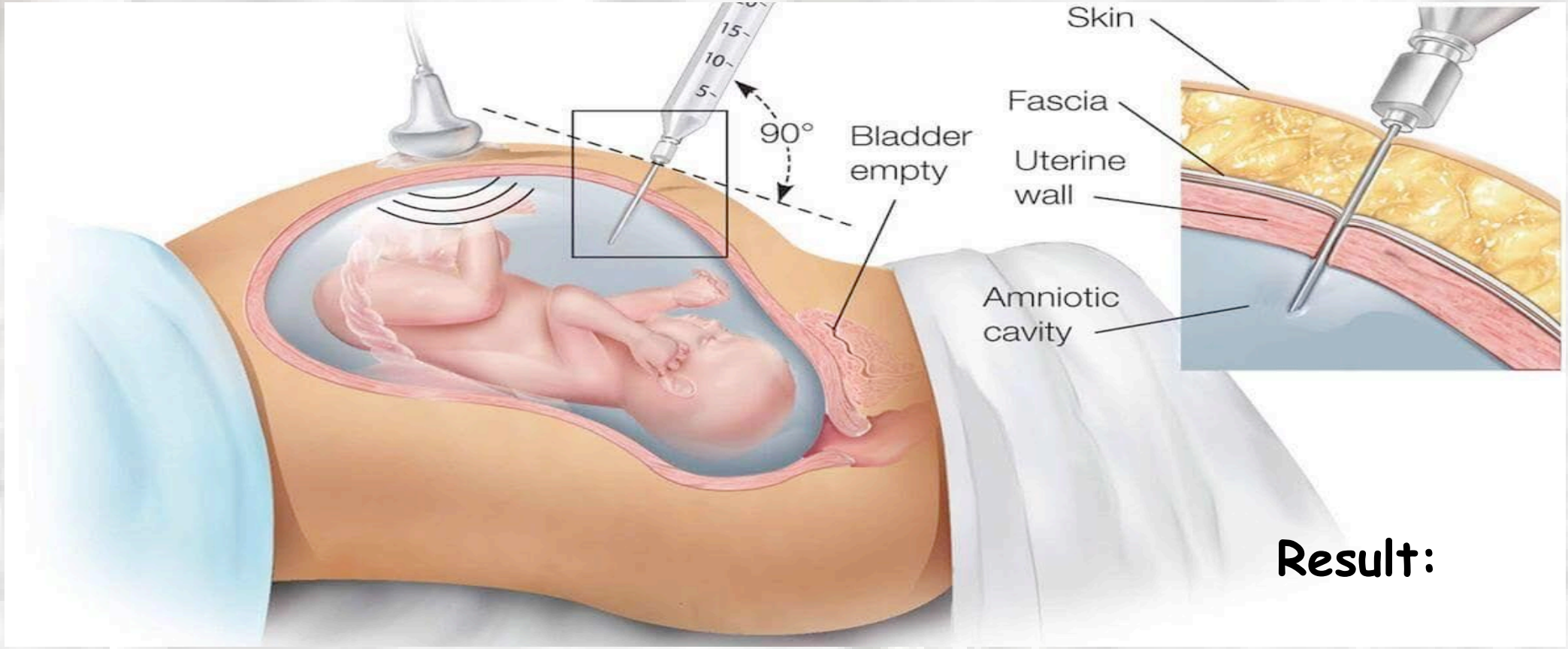
  - consultation with an expert **(US)**

Non invasive prenatal test (NIPT): test for fetal chromosome anomalies in maternal blood (no MTCT risk)

Anna

Amniocentesis at 16 weeks

VL< 50 copies per mL (6 weeks on ART)



Result:

46 XY

Case notes: Anna states that she plans not to breastfeed as she is afraid of HIV transmission.
But she asks you if she can have a vaginal delivery:

1. Yes, if she is at term and fully suppressed
2. No, as she had a c-section before
3. No, as she is HCV positive
4. You do not know yet.

HCV coinfection does not necessitate cesarean delivery **(BHIVA, EACS, US, Canada)**

New guidelines: Vaginal delivery as option in women with HIV

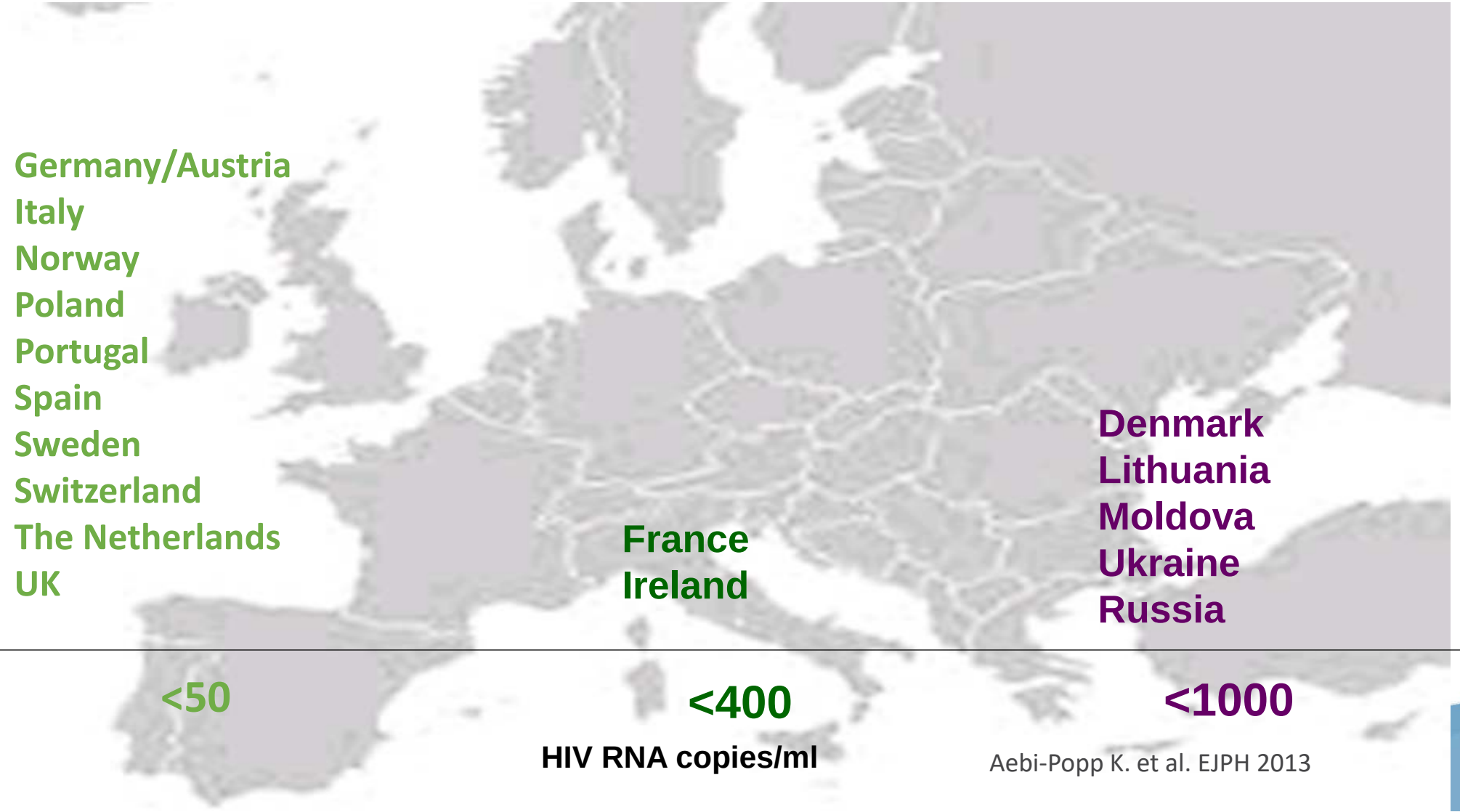
National guidelines 1999 - 2010 recommending vaginal delivery for women with undetectable or very low viral load

Year of publication of national recommendations for vaginal delivery

1999	2001	2002	2004	2007	2008	2009	2010
Netherlands	Ireland	France	Moldova	Denmark Lithuania Spain Ukraine	Germany/Austria Poland UK	Norway Portugal Switzerland	Italy Sweden

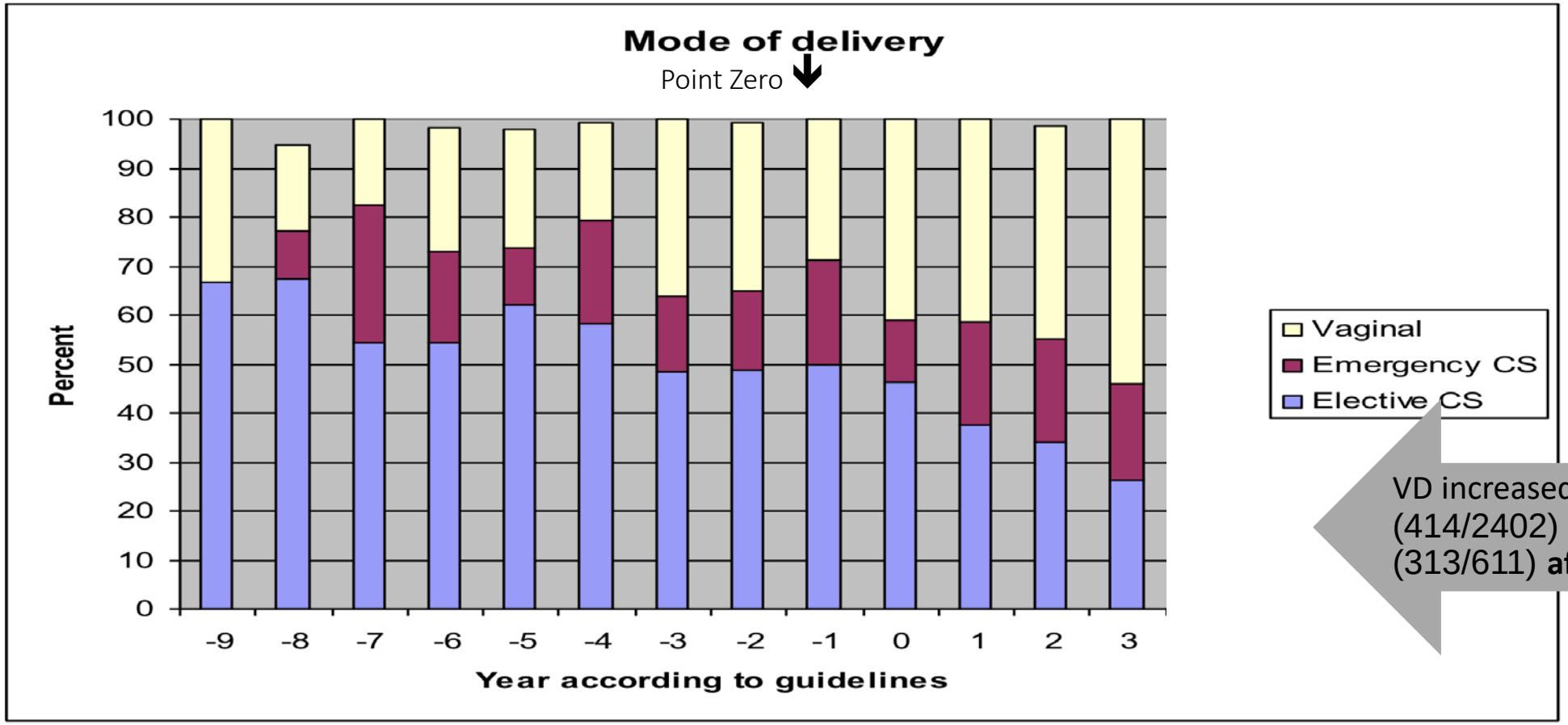
Aebi-Popp K. et al. EJPH 2013

Viral load thresholds for recommendation of vaginal delivery



Aebi-Popp K. et al. EJPH 2013

Mode of delivery by time before/after guidelines publication (Europ. Data)



VD increased **from 17%** (414/2402) before to **52%** (313/611) **after guidelines**

Point Zero : year of publication of guidelines recommending vaginal delivery in women with undetectable viral load

n= 3013 deliveries from 10 countries

Aebi-Popp et al JAIDS 2013

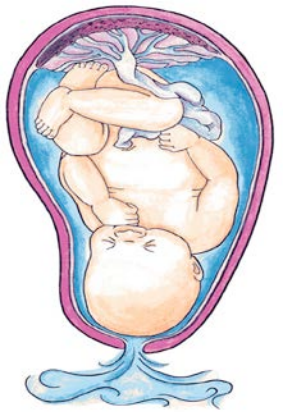
Telephone call from Anna:
She thinks she has rupture of membranes (ROM), she is 32 weeks pregnant

Reported gastroenteritis and adherence issues over the last 2 weeks

- **HIV RNA VL = 360 copies/ml**
- **No laboratory signs of other infection**
- **No signs for pre-eclampsia (normal blood pressure, no proteinuria, LFT normal)**

What delivery plan would you recommend if ROM is confirmed?

Dilemma 4: Pre-labour rupture of membranes (ROM) >37 weeks



- VL > 1000 copies/mL:

  add intravenous Zidovudine (ZDV) until delivery **(BHIVA, US),** add ZDV if VL>50 c/mL **(EACS),** always add ZDV during delivery **(Canada)** + urgent C-Section

- VL 50-999: consider immediate CS, take into account the VL, adherence and obstetric factors **(BHIVA)**

- < 50 copies/mL **(BHIVA)** or < 1000 copies **(US)**

  duration of ROM not associated with MTCT, vaginal delivery is recommended

Dilemma 4: Preterm ROM < 37 weeks

- If < 34 weeks: Intramuscular steroids (lung maturation, 24 hours delay in induction)
- Virological control should be optimized (eg add Raltegravir) **(EACS; BHIVA)**
- Individual decision about timing and mode of delivery: Other infections (pyrexia)? Pre-eclampsia?

Group B Streptococci (GBS) antibiotic prophylaxis if < 37 weeks to prevent GBS disease

Special concern in regard to preterm delivery (< 37 weeks)

- Preterm baby less

  likely to tolerate oral therapy.

- Loading the infant through the transplacental route with maternal therapy:

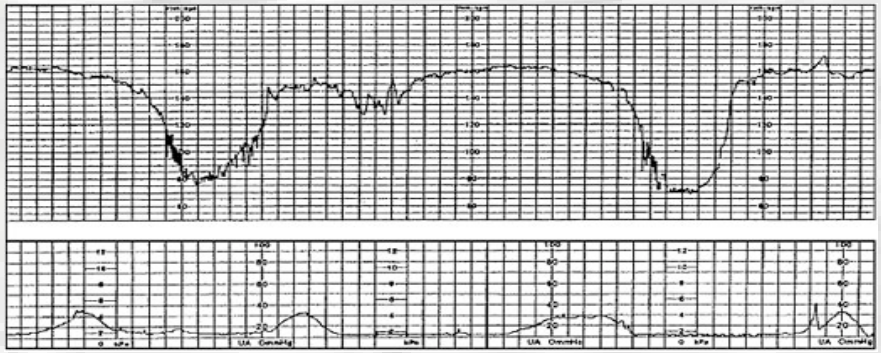
  Single dose Nevirapine? **(BHIVA yes, EACS ,US + Canada no)**

  Intravenous Zidovudine ? **(EACS, BHIVA, US, Canada)**

Anna

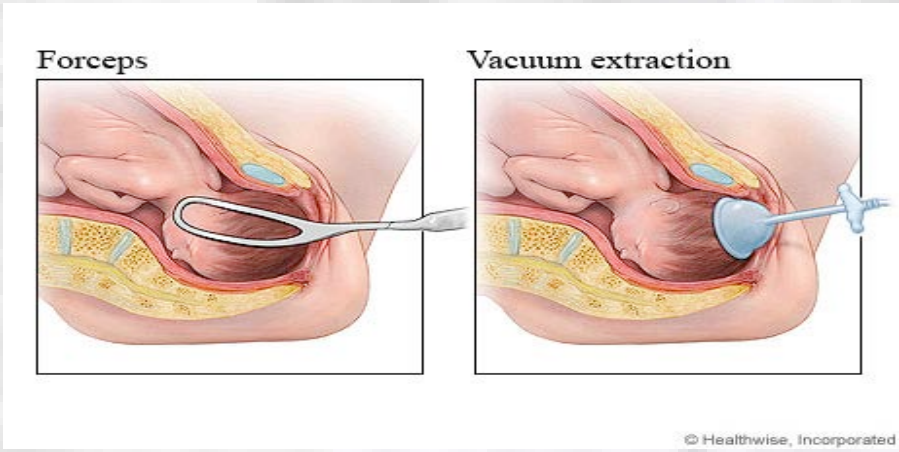
- ROM NOT confirmed at 32 weeks, but hospitalized
- VL < 50 copies/ml (34 weeks)
- 35+2 weeks: rapid progress in labor

- Full cervix dilatation, fetal head + 2
- Pathologic CTG with late decelerations indicating fetal distress



Episiotomy?

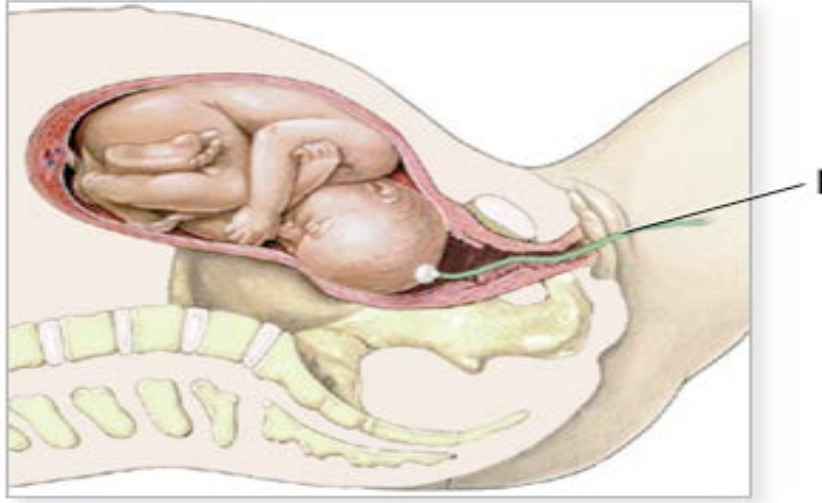
Forceps or Vacuum?



Dilemma 5:Vaginal delivery HIV MTCT risk ?

Procedures: amniotomy, fetal scalp electrodes

blood sampling, instrumental delivery, episiotomy



Internal fetal monitoring

If VL is fully suppressed, all those procedures seem not to be associated with increased MTCT **(BHIVA)**

If VL detectable avoid ROM, avoid fetal scalp electrodes for fetal monitoring and operative delivery if possible **(US)**

If vaginal delivery was recommended follow the same guidelines as for HIV negative women

Anna

A baby boy is born by forceps extraction
2600 grams, Apgar 8-8-9 umbilical cord ph 7.18

- Anna wishes to breastfeed, she refuses to take Cabergolin tablets (her mother might find out her HIV status, she thinks it is the best way of feeding…)

What would you do if Anna insists on breastfeeding ?

1. Inform authorities about her decision
2. Explain that even with undetectable VL there is a risk of breast milk transmission of HIV
3. Advise if she must breastfeed, it should be exclusive and not for more than 6 months
4. Advise prolonged infant prophylaxis
5. Provide advice on how to explain bottle feeding to her community

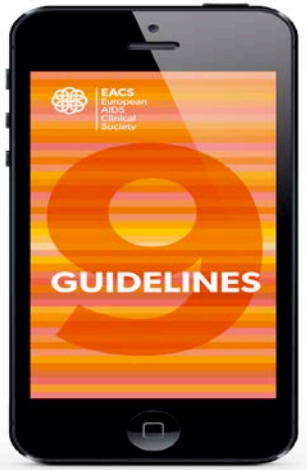
Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect

Lancet 2016; 387: 475–90

Cesar G Victora, Rajiv Bahl, Aluísio J D Barros, Giovanny V A França, Susan Horton, Julia Krasevec, Simon Murch, Mari Jeeva Sankar, Neff Walker, Nigel C Rollins, for The Lancet Breastfeeding Series Group*

	Low and middle income countries	High income countries
Mortality Exclusive Bf v non-Bf Any Bf Never Bf	**Strong effect** ↓88% ↓50% ↑x3-4 times	↓SIDS 36% (CI 19-49) ↓NEC 58% (CI 4-82)
Acute Morbidity	Diarrhoea ↓ 50%, RTI ↓ 33%	↓Otitis for <2yrs
Chronic Diseases	'Suggestive' re obesity & DM	
IQ	'Consistent positive effect'	
No protection vs Allergy, Eczema, Asthma		

Anna read the EACS guidelines 2017:



We advise against breastfeeding.

In case a woman insists on breastfeeding, we recommend follow-up with clinical and virological monitoring of both the mother and the infant.

What does that mean?

How often to monitor? Monthly, weekly....?

Adherence post partum:
“All they wanted was a baby”

- **UK**: 6% of women conceiving on ART and 27% of those starting ART in pregnancy had viral rebound by 3 months after delivery (supressed at delivery)

Huntington et al AIDS 2015

- **Switzerland:** 22% of women were LTFU 6 months after delivery, 12% over 1 year

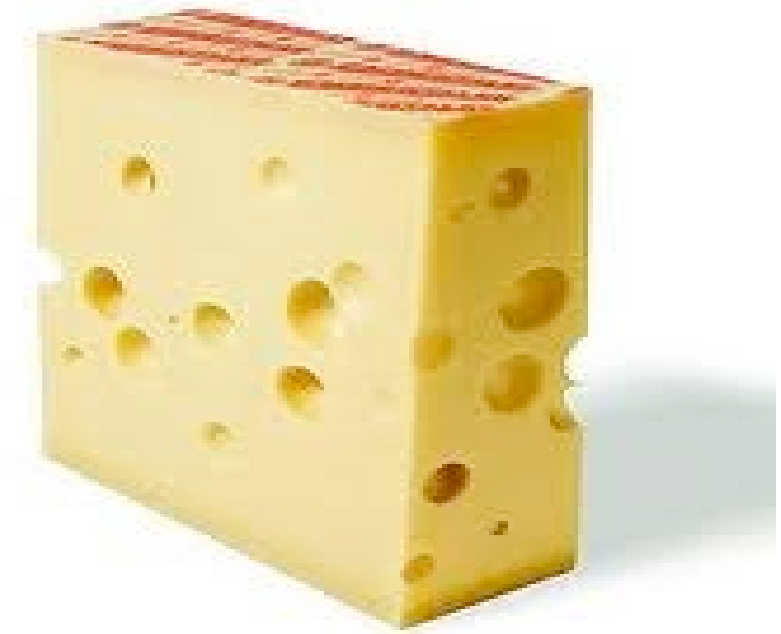
Aebi-Popp HIV Med 2016

- **France:** 14% less than 2 visits in 2 years, 11% less than once per year

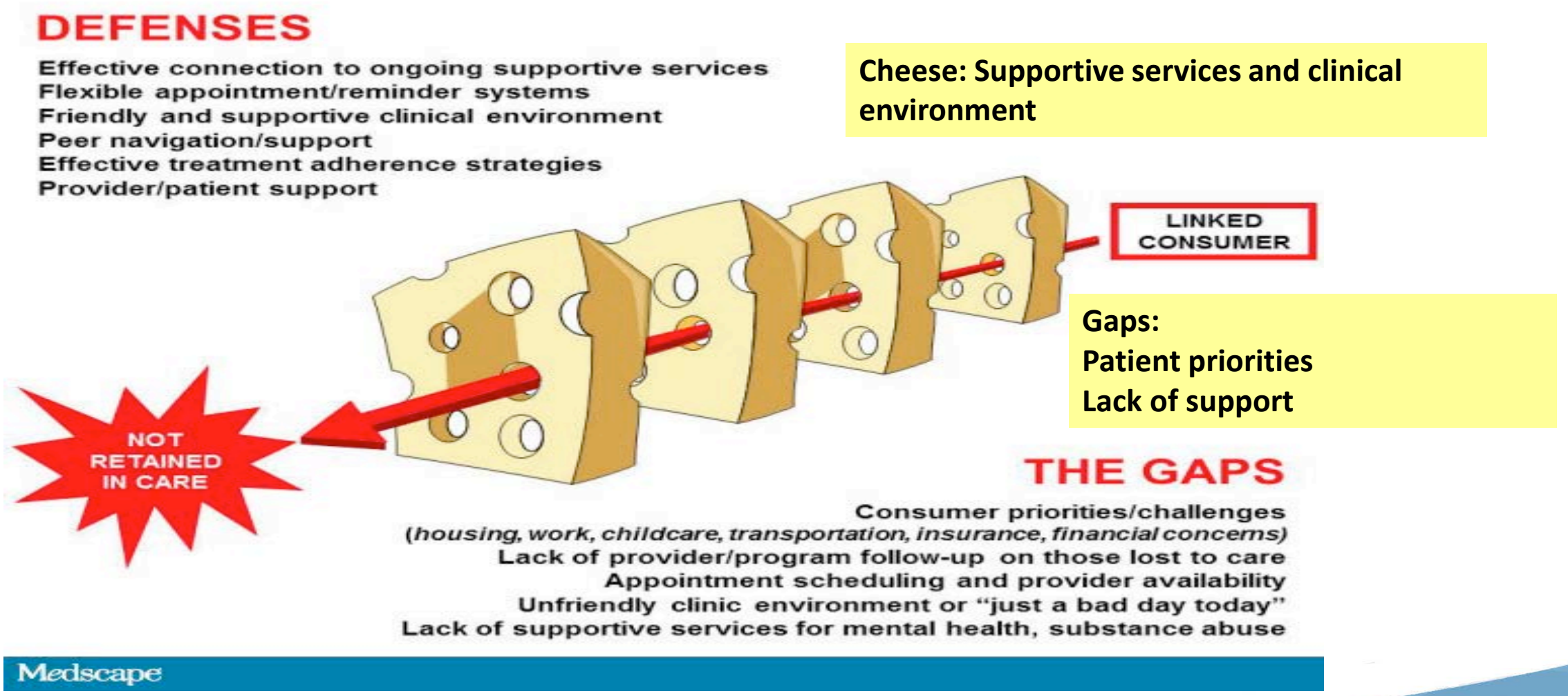
Lemly et al AIDS Care. 2007

Poor adherence = viral rebound = increased MTCT risk if breastfeeding

How can the gaps in Swiss cheese help to understand the problem of women lost to follow up after delivery?



„Swiss Cheese Effect“ and LTFU



Cheese: Supportive services and clinical environment

Gaps:
Patient priorities
Lack of support

Example combined clinic in Dublin/Ireland

THE GUIDE CLINIC

Coombe Women & Infants University Hospital

A Combined Obstetric/ HIV Clinic: a model for engagement in antenatal and HIV care for women with HIV during and after pregnancy

K. Aebi-Popp [1], S. Murphy[1], R. Moore[1], F. Lyons[1], M. O`Connell[2], O. Cunningham[2], F. Mulcahy[1]

1. St. James's Hospital, GUIDE Clinic, Dublin, Ireland. 2. Coombe Women & Infants University Hospital

75/98 (77%) women attended all antenatal visits, 9 missed one, 7 missed 2 or 3 and 7 missed >3 appointments

53 (54%) women returned for postpartum visit at 6 weeks
87% women were retained in HIV care after 6 months.

Irish Cheddar is better…

No gaps ！

Dilemma 6: Does U=U also apply for breastfeeding?

- Women might choose to breastfeed for personal, social or cultural reasons or because of stigma
- Risk of MTCT through breastfeeding is very low if on cART (Flynn et all JAIDS 2017)
- Risk-benefit in low-income settings (mortality) is **much different** than in high income settings
- Balancing 'any risk' of MTCT with the benefits of breastfeeding, needs patient centered approach

Frequency of clinical and virological monitoring?
What to do in an event of viral rebound ?

We need to collect more data to answer those questions.

Case notes: Anna

- Anna is breastfeeding
- Baby boy stays HIV PCR negative, tested monthly for the duration of breastfeeding and at 8 weeks after cessation of breastfeeding
- Contraception advice
- Evaluation for HCV treatment

The End

Pharmacokinetics of ART in breastmilk:
We know, what we do not know…

THE LANCET
HIV

www.thelancet.com/hiv Published online June 27, 2018 http://dx.doi.org/10.1016/S2352-3018(18)30098-5

Does U=U for breastfeeding mothers and infants? Breastfeeding by mothers on effective treatment for HIV infection in high-income settings

Catriona Waitt, Nicola Low, Philippe Van de Perre, Fiona Lyons, Mona Loutfy, Karoline Aebi-Popp

Factors influencing drug transfer into breast milk and exposure of the newborn

1. Maternal factors

   Dose and frequency of therapy, drug clearance

2. Infant factors

   Age, extent of breastfeeding (quantity, frequency, solid foods), timing of feeds in regard to drug intake

3. Drug factors

   Lipid solubility, protein binding, molecular weight

PK STUDIES : ART and breast milk transfer

- NNRTI breast milk concentrations are lower than plasma, and consistent between studies
- PI reach very low concentrations in breast milk (related to high degree of protein binding)
- NRTI breast milk concentrations can be considerably higher
- Breastfed infant exposed to **less than 10% of the weight- adjusted pediatric ARV dose** (except NVP and 3TC): Which consequences in regard to toxicity, MTCT and resistance?

Waitt *et al.* JAC 2015

Unanswered questions: Breastfeeding on cART

Questions about transmission risk:

- Does U=U in breastfeeding?
- What is transmission risk outside trial settings?
- What is significance of cell-associated DNA?
- What is the optimal frequency of VL monitoring?

Optimisation of Regimens

- **Are any regimens safer in breastfeeding mother-child pairs ?**

Key Unanswered Questions And Research Perspective

Newer Drugs

- **PK of DTG, RAL, EVG, TAF and others?**
- **Timely design of lactation studies**

Pharmacovigillance Systems

- **Are there any subtle/ developmental risks?**
- **Collaboration to design data collection tools**

Waitt *et al*, Lancet HIV 2018

What did we learn ?

Guidelines are great, but they cannot replace interdisciplinary discussion in „real life“

Thank you very much for your attention

mail@aebi-popp.com

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