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

8th International Workshop on HIV & Women
2 - 3 March 2018, Boston, MA, USA

Karoline Aebi-Popp MD MSc
Consultant Obstetrician/ Gynecologist
Department of Infectious Diseases
University Hospital Bern
Switzerland
mail@aebi-popp.com
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/mm³
• VL 36,000 copies/ml

• HCV positive
• HbsAg negative
### Annual number of deliveries to women living with HIV in the European Region

<table>
<thead>
<tr>
<th>Deliveries</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>Armenia, Albania, Bulgaria, Georgia, Lithuania, Latvia, Serbia, Slovakia</td>
</tr>
<tr>
<td>&lt;200</td>
<td>Estonia, Kyrgyzstan</td>
</tr>
<tr>
<td>&lt;200 to &lt;500</td>
<td>Azerbaijan, Moldova</td>
</tr>
<tr>
<td>&lt;500</td>
<td>Belarus, Tajikistan</td>
</tr>
<tr>
<td>&lt;500 to &lt;1000</td>
<td>Uzbekistan</td>
</tr>
<tr>
<td>≈3,500</td>
<td>Ukraine</td>
</tr>
<tr>
<td>≈16,000</td>
<td>Russian Federation</td>
</tr>
</tbody>
</table>

Approximately 7,500 deliveries to HIV+ women annually in the EU.
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)
- Switzerland 2000-2014: 81/ 597 (13.6%)
- 32% Ukraine (2008-2012)
- 50% St Petersburg, Russia (2010)

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 frequent 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

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternate</th>
<th>Not recommended or insufficient data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir/Lamivudine TDF/ FTC or 3TC</td>
<td>Zidovudine/Lamivudine</td>
<td>Didanosine Stavudine TAF/FTC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Efavirenz Rilpivirine</td>
<td>Etravirine Nevirapine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protease Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/r Darunavir/r</td>
<td>Lopinavir/r</td>
<td>Nelfinavir Tipranavir/r Fosamprenavir/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Dolutegravir</td>
<td>Enfuvirtide Maraviroc Elvitegravir/c/TDF/FTC or TAF/FTC</td>
</tr>
</tbody>
</table>
What to start: Europe
European Aids Clinical Society (EACS) Guidelines 2017

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
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
EFV is a 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 recommended

Late presenting: add INSTI

If VL>50 c/mL add iv Zidovudine
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)
**Dolutegravir:** Data from the Antiretroviral Pregnancy Registry (APR) and from EPPICC (European Pregnancy and Paediatric HIV Cohort Collaboration)

128 life births, no still births
- 1st trimester exposure: 2/77 birth defects
- 2nd/3rd trimester exposure: 2/56 birth defects
- 10.9% preterm deliveries
  (background birth defect rate: 2.7 %, background preterm rate: 12.3%)

Data on DTG safety during pregnancy are reassuring but remain inconclusive due to small sample size.

- 82 life births, 60% first trimester DTG exposure
- 13.8% preterm deliveries
- Birth defects in 4/81 infants (4.9% 95% CI 1.4-12-2%)
Anna

- 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 transmission 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

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

<table>
<thead>
<tr>
<th>Year of publication of national recommendations for vaginal delivery</th>
<th>1999</th>
<th>2001</th>
<th>2002</th>
<th>2004</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moldova</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ukraine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany/Austria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Viral load thresholds for recommendation of vaginal delivery

- <50 HIV RNA copies/ml
- <400 HIV RNA copies/ml
- <1000 HIV RNA copies/ml

Countries:
- Germany/Austria
- Italy
- Norway
- Poland
- Portugal
- Spain
- Sweden
- Switzerland
- The Netherlands
- UK
- France
- Ireland
- Denmark
- Lithuania
- Moldova
- Ukraine
- Russia

Aebi-Popp K. et al. EJPH 2013
Point Zero: year of publication of guidelines recommending vaginal delivery in women with undetectable viral load

n= 3013 deliveries from 10 countries

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

Aebi-Popp et al JAIDS 2013
Anna

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?

1. Await lung maturation (24 hours) with steroids and induce labour if cervix suitable
2. Perform an emergency c-section
3. Take no action and monitor her progress for 24 hours
4. Allow labour to go ahead and treat baby with post-exposure prophylaxis
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

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
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...)

Anna
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

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*

<table>
<thead>
<tr>
<th></th>
<th>Low and middle income countries</th>
<th>High income countries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusive Bf v non-Bf</td>
<td><strong>Strong effect</strong> ↓88%</td>
<td>↓SIDS 36% (CI 19-49)</td>
</tr>
<tr>
<td>Any Bf</td>
<td>↓50%</td>
<td>↓NEC 58% (CI 4-82)</td>
</tr>
<tr>
<td>Never Bf</td>
<td>↑x3-4 times</td>
<td></td>
</tr>
<tr>
<td><strong>Acute Morbidity</strong></td>
<td>Diarrhoea ↓ 50%, RTI ↓ 33%</td>
<td>↓Otitis for &lt;2yrs</td>
</tr>
<tr>
<td><strong>Chronic Diseases</strong></td>
<td>‘Suggestive’ re obesity &amp; DM</td>
<td></td>
</tr>
<tr>
<td>IQ</td>
<td>‘Consistent positive effect’</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No protection vs Allergy, Eczema, Asthma</td>
<td></td>
</tr>
</tbody>
</table>
Anna read the EACS guidelines 2017:

*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.*

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

**DEFENSES**
- Effective connection to ongoing supportive services
- Flexible appointment/reminder systems
- Friendly and supportive clinical environment
- Peer navigation/support
- Effective treatment adherence strategies
- Provider/patient support

**Cheese: Supportive services and clinical environment**

**Gaps:**
- Patient priorities
- Lack of support

*Consumer priorities/challenges (housing, work, childcare, transportation, insurance, financial concerns)*
- Lack of provider/program follow-up on those lost to care
- Appointment scheduling and provider availability
- Unfriendly clinic environment or “just a bad day today”
- Lack of supportive services for mental health, substance abuse
Example combined clinic in Dublin/Ireland

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

K. Aebi-Popp¹, S. Murphy¹, R. Moore¹, F. Lyons¹, M. O’Connell², O. Cunningham², F. Mulcahy¹

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.

EACS Conference Bruxelles 2013
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
HIV in menopausal women:

- Increased menopausal symptoms
  - Experience of menopause at an earlier age, with greater symptomatology

- Menopausal women with HIV should be educated about behavioural strategies to help reduce the risk of cardiovascular disease, and screened for osteoporosis and cancer

- Further work is needed to define the benefits of hormone replacement therapy (HRT) in women with HIV


Cross-sectional study of Brazilian women > 40 years of age

HIV+ n= 289

HIV– n= 247

Cross-sectional study of middle-aged women living in New York

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

Acknowledgements:

Andri Rauch, Anna Hachfeld University Hospital, Bern, Switzerland
Claire Thorne, UCL Institute of Child Health, London UK
Fiona Mulcahy, St. James`s Hospital, Dublin, Ireland
Catriona Waitt, University of Liverpool, UK
Mona Loufty, Women`s College Hospital, Toronto, Canada