

# Recommendations of the Swiss Federal Commission for Sexual Health (FCSH) for Medical Care of HIV-Infected Women and their Offspring

## 1. BACKGROUND AND AIM

Reduction of HIV mother-to-child transmission (MTCT) to virtually zero due to implementation of prevention strategies is one of the greatest medical successes in fighting the HIV epidemic [1]. Widely recommended measures to prevent HIV MTCT include most importantly (i) combined antiretroviral treatment (cART) of the pregnant women leading to fully suppressed plasma HIV viral load (pVL), (ii) elective caesarean section (ECS), (iii) neonatal post-exposure prophylaxis (nPEP) with Zidovudine (AZT) or Nevirapine (NVP), and, in industrialised countries, (iv) mothers are widely advised to refrain from breastfeeding.

Nowadays, improved cART results in a full suppression of HIV replication in most infected individuals. This was convincingly evidenced by cessation of molecular HIV evolution in a treated host [2]. In the Swiss HIV Cohort Study (SHCS), 96% of appropriately treated individuals achieve full suppression of HIV plasma viral load [3]. Most notably, pregnant HIV-infected women show comparable results [4]. This is confirmed in the period 2012–2016 by a total of 229 pregnancies registered in the SHCS whereof 95.9% women reached full suppression of HIV pVL prior to delivery (data on file).

As exposure to any intervention involves risks, re-evaluation of the necessity of ECS, nPEP, and avoidance of breastfeeding is crucial in the light of suppressed HIV pVL during pregnancy, labour and lactation. The overarching aim is to avoid harm for mother and child while ensuring optimal quality of life.

This document is a guide for clinicians in Switzerland to provide best-practice

medical care to HIV-infected women and their offspring with the main focus on the prevention of HIV MTCT as well as of unnecessary harm. Here, we provide a short summary of the recommended principles. Additional information, in particular regarding antiretrovirals during pregnancy and peripartum, can be found in the supplement.

## 2. METHODS

### 2.1 Development Procedures

The Swiss Federal Commission for Sexual Health (FCSH) [5] appointed an ad-hoc group of ten experts from MoCHIV (Mother and Child HIV Cohort Study) and mandated them to re-evaluate the last recommendations from 2009. This group includes two obstetricians, five paediatricians, and three HIV specialists for adult patients. The step-wise working process of the ad-hoc group included (i) the *review of four existing international guidelines* [6–9] followed by (ii) defining a *list of priority issues* to be addressed, and (iii) *examination of essential publications* listed in PubMed.

For the search of the essential publications we used the following search term expressions filtered for *Publication date since 2009/01/01, Core clinical journals*: (i) “Mother to child transmission” HIV and (ii) “HIV vertical transmission”, additionally filtered to *Infant: birth-23 months*. Moreover, we identified additional literature by PubMed PICO search [<https://pubmedhh.nlm.nih.gov/nlmd/pico/piconew.php>] with *Population*: pregnancy HIV, *Intervention*: prevention with *Comparison* and *Outcome* blank.

We defined four priority issues: (i) treatment during pregnancy, (ii) mode of delivery, (iii) nPEP, and (iv) breastfeeding. Two to three members of the ad-hoc

group focussed on a single of the four priority issues and reviewed the pertinent literature identified with the aim to present a consensus to the whole ad-hoc group. Subsequently, decision by consensus for each priority issue was taken by the whole ad-hoc group after discussion in a face-to-face meeting as well as during three telephone conferences. In addition, there were e-mail dialogues and discussions in the working group 1 “Clinical and Therapy HIV & STI” of the FCSH as well as with international experts. Finally, the proposed new consensus recommendations were approved by the FCSH full commission.

### 2.2 Clinical Equipoise and Patient's Autonomy

The decision to implement any clinical intervention ought to be based on balancing its risk and benefit. If published evidence is available, an obvious distinction of risk and benefit is possible. However, if the evidence becomes less clear or, more importantly, when the clinical potential risk as well as the benefit of an intervention tend towards zero, balancing risk and benefit is utmost challenging, or even impossible. Such a clinical situation is usually defined as *clinical equipoise* [10]. We encountered this situation specifically for breastfeeding.

An important improvement in modern clinical medical practice is the consideration of patient's autonomy when it comes to medical decisions. The concept of patient's autonomy is based on ethical principles and has only recently found its appreciation, as described by Hurst [11]. For the decision on implementation of elective caesarean section in HIV-infected pregnant women, it was recently proposed to consider not only the individual risks and benefits but also the autonomy of women [12].

### 3. NEW RECOMMENDATIONS IN A NUTSHELL

#### 3.1 Optimal Scenario for the Prevention of HIV MTCT

Assuming maternal HIV infection has been diagnosed<sup>1</sup>, the situation for most HIV-infected pregnant women in Switzerland is a low-risk scenario for HIV MTCT. Recommendations for any intervention discussed here distinguish an “optimal scenario”, in which

- regular follow-up of treatment during pregnancy (e.g. every 2–3 months) by a physician with expertise in the field of HIV is ascertained
- HIV pVL is <50 copies/ml ideally throughout pregnancy, but at least at the last two consecutive measurements before birth (minimal interval of 4 weeks and the last measurement after week 36 of pregnancy)

from a “suboptimal scenario”

- with elevated risk for HIV MTCT, where all prevention measures known to reduce HIV MTCT should be implemented. It is strongly recommended that physicians (obstetrics, paediatrics and infectious diseases) with expertise in the field of peripartur HIV be involved in the decisions on the prevention measures taken.

#### 3.2 Specific Recommendations to Prevent MTCT of HIV

Table 1.

### 4. NEW RECOMMENDATIONS IN DETAIL

The overall aim of medical care is to firmly assure an “optimal scenario” (see 3.1) to all HIV-infected pregnant women in Switzerland. Only differences to standards of medical care in non-HIV-infected pregnant women or non-HIV-exposed children are mentioned hereafter.

#### 4.1 Antiretroviral Treatment during Pregnancy

cART is recommended for every HIV-infected individual, particularly in pregnant women and beyond pregnancy with the aim to reduce AIDS-related events, non-AIDS-related events, and all-cause mortality as well as HIV transmission [13, 14]. cART initiation and follow-up should be provided by a physician with expertise in the field of HIV [15] to assure standards of medical care, including potency and safety of the treatment. cART is the most important measure to attain the “optimal scenario” (see 3.1). Any pVL measurement >50 HIV RNA copies/ml should be followed by a second measurement within four weeks to ascertain viral suppression and exclude treatment failure. There are insufficient data to recommend an ideal cART regimen during pregnancy. Table 4 in the supplement offers an overview of antiretroviral drugs licensed for treatment during pregnancy and listed in four international guidelines [6, 7, 16, 17]. Recently, the challenges of cART during pregnancy have been revisited [18]. With the exception of Darunavir (where twice-daily dosing may be considered), drug dosages in pregnancy are the same as for standard adult dosing and therefore therapeutic drug monitoring is only requested on an individual basis.

For certain drugs, a possible association with birth defects has been reported in the Antiretroviral Pregnancy Registry (APR) [19]. This should be considered particularly for cART during the first trimester. The supplement (see Table 4) provides a detailed overview on the risk of birth defects and preterm birth associated with ART.

Recently, an unplanned analysis of an ongoing study revealed an increased risk of neural tube defects (NTD) in newborns exposed to Dolutegravir (DTG) at the time of conception and in the first trimester, prompting the European Medicines Agency (EMA) [20] and others to recommend that DTG should not be used until this issue is resolved. Interestingly, very recent results of the same study do not describe an increased risk compared to Efavirenz-based cART [21]. However, until the final disposal of the ongoing EMA review, DTG should currently only be prescribed for women of childbearing age if pregnancy has previously been ruled out and an effective contraception has been implemented. Because NTD occurs in the first four weeks of gestation, treatment with DTG during the second and third trimesters is likely to be safe.

Table 1:

**Swiss 2019 recommendations to prevent HIV MTCT. Changes from 2009 are highlighted (yellow), major changes are in bold.**

Prevention measures	Optimal Scenario	Suboptimal Scenario
1. cART during pregnancy	most important prevention measure and highly recommended for all HIV-infected individuals <sup>1</sup>	
2. Mode of delivery	vaginal birth, if no obstetrical contraindications are present <sup>2</sup>	caesarean section, if possible prior to ROM (= ECS) <sup>3</sup>
3. nPEP	<b>none</b>	neonatal cART <sup>4</sup>
4. breastfeeding	<b>shared decision-making</b> <sup>5</sup>	contraindicated

pVL = maternal HIV plasma viral load, cART = combined antiretroviral treatment, nPEP = neonatal post-exposure prophylaxis, ECS = elective caesarean section, ROM = rupture of membranes

<sup>1</sup> standard cART regimen, preferentially with drugs with long-standing experience in pregnant women

<sup>2</sup> hepatitis C co-infection is NOT a contraindication anymore

<sup>3</sup> discuss intravenous AZT if maternal pVL is > 1000 copies/ml and neonatal cART is not available (see 5.3.4)

<sup>4</sup> daily triple cART, for the dosing see 4.3.2

<sup>5</sup> see Table 2 and Table 3 to support shared decision-making and specify the follow-up

<sup>1</sup> In Switzerland, HIV testing is strongly recommended and considered standard of care for all pregnant women at the first obstetrical visit and at each pregnancy since 2003 [Bulletin FOPH, 24.02.2003].

In case HIV is diagnosed only during the third trimester of pregnancy, cART should be commenced prior to obtaining the results of resistance testing with a combination that guarantees rapid reduction of HIV viremia and takes into account the potential for pre-existing resistance-associated mutations. In such situation, pVL testing should be requested at two-weekly intervals to allow for optimal birth planning.

The use of cART in different clinical scenarios is considered in the supplement (see chapter 5.3).

## 4.2 Mode of Delivery

### 4.2.1 Optimal Scenario

As introduced in the 2009 recommendations and in the absence of obstetric contraindications, planned vaginal delivery is recommended for term and preterm deliveries. In women for whom a vaginal delivery has been recommended and labour has commenced, obstetric management should follow the same principles as for the uninfected population. There is no evidence to support any additional risk of any type of operative vaginal delivery [22]. Any technique the operator feels most appropriate should be used as in the non-HIV population. Peripartum AZT infusion is no longer recommended for women with suppressed pVL.

### 4.2.2 Suboptimal Scenario

ECS prior to rupture of membranes (ROM) between weeks of gestation 38 and 39 is recommended. The earlier timing reflects the importance of avoiding onset of labour with rupture of membranes which is an additional risk for HIV MTCT in women with HIV pVL > 1000 copies/ml in term babies and for preterm babies likely even < 1000 copies/ml. In case of pre-labour spontaneous ROM at term, birth should be expedited. In preterm ROM (< 37 weeks of gestation), interdisciplinary planning including provision of steroids, mode and timing of delivery should be based on standard medical care, taking into consideration the risks of premature birth and an increased risk of HIV MTCT, which should lead to an optimisation of maternal therapy until birth if possible (see 5.3.3 and 5.3.4 in the supplement).

### 4.2.3 Hepatitis C Co-Infection

There is no indication to perform ECS if the pregnant woman is eligible for vaginal delivery, as the literature does not support additional benefit of ECS in case of HIV/HCV co-infection [6].

## 4.3 Neonatal Post-exposure Prophylaxis

### 4.3.1 Optimal Scenario

nPEP has been abandoned in Switzerland since 2016 (Bulletin FOPH, 25.1.2016) under the conditions mentioned in 3.1. Thus, in optimal scenario neither nPEP with AZT nor NVP is recommended for term or preterm newborns. Currently, this differs from guidelines in all other countries where treatment with AZT is still recommended for – depending on the country – two to six weeks. The reasons to abandon nPEP in Switzerland were:

1. No randomised controlled trial is available to support nPEP with AZT as a single prevention measure in the optimal scenario.
2. nPEP with AZT was introduced in the mid-1990s (PACTG-076) [23]. Since, the landscape of cART has undergone revolutionary changes in terms of effectiveness and tolerance not only for pregnant women but also for neonates. As an example, combined prophylaxis with AZT plus three doses of Nevirapine was twice as effective in preventing HIV MTCT in untreated pregnant women and non-breastfed children (PACTG-1043) [24] compared to the currently recommended nPEP with AZT alone. But if we assume a risk for HIV MTCT, why not take the most effective treatment? Also, a shorter duration with three days of AZT to the neonate born to women with AZT monotherapy starting at 28 weeks of gestation seems not inferior in preventing HIV MTCT compared to six weeks of nPEP with AZT (PHPT-1) [25]. However, if there is a relevant transmission risk, are three days of AZT truly effective? That this is not the case was confirmed in the same study as three days of AZT were not sufficient when mothers had been treated with AZT monotherapy for a shorter duration before birth (starting at 35 weeks of gestation). Finally, the

follow-up study of the same study (PHPT-2) highlights the minimal effect of neonatal therapy compared to maternal therapy. The additional effect of a single dose of Nevirapine (sdNVP) for mother and child was compared to placebo. AZT treatment was implemented for pregnant women (during third trimester) and children (one week). Whereas sdNVP to the mother showed a clear reduction in vertical transmission, sdNVP to the child did not.

3. nPEP with AZT shows measurable toxicity in all studies, mainly neutropenia and anaemia (e.g. PACTG-1043 [24], appendix 3 and 4). Thus, if there is no clear preventive effect, this intervention should be avoided.

4. In the following situations, prevention measures including post-exposure prophylaxis (PEP) have been abandoned because the transmission risk was considered negligible if HIV pVL was undetectable: (i) ECS in HIV-infected mothers, (ii) PEP after needle stick injury with HIV-positive source, (iii) condom use during sex with an HIV-infected person and (iv) PEP after unprotected sex with HIV-infected person. ECS was able to halve HIV MTCT, and was therefore significantly more effective, compared to nPEP with AZT [26] but has been abandoned some years ago. Discontinuation of all other prevention measures was reflected in many international guidelines including the Swiss and the European 2016 guidelines. The statement: *undetectable equals untransmittable* (U=U); this is now broadly supported by many countries and organisations.

### 4.3.2 Suboptimal Scenario

cART is recommended for the term or preterm newborn. Availability of drugs for this specific situation is extremely restricted and therefore all attempts should have been done during pregnancy to intensify maternal treatment (see 5.3.4). As first line cART **initially during the first week**, zidovudine (AZT) 2 × 4 mg/kg (2 × 2 mg/kg in preterm < 34 weeks of gestation) in combination with lamivudine (3TC) 2 × 2 mg/kg and Nevirapine (NVP) 2 × 4 mg/kg are recommended (no dosing recommendation is available < 34 weeks of gestation).

Table 2:

**Breastfeeding in HIV-infected mothers fulfilling the “optimal scenario with a strong wish to breastfeed”****Pro and con arguments****1) List of potential RISKS associated with breastfeeding**

- HIV transmission to the child (MTCT) cannot be ruled out:
  - i) Transmission through breastfeeding in the range of 0.3–0.9% (6 months to 24 months of breastfeeding, PROMISE Study) has been observed when women were under effective combined antiretroviral therapy (cART) during pregnancy and the breastfeeding period but viral load measurement (pVL) data during the breastfeeding period from this study is yet missing.
  - ii) There is no formal study evaluating the risk of MTCT by HIV-infected mothers who are under cART with undetectable HIV pVL.
  - iii) Even if we did not identify HIV MTCT in the “optimal scenario” we cannot exclude that such a case did or might happen with lifelong consequences for the child.
- Postpartum is a vulnerable period (e.g. irregular sleep, elevated risk for mood disorders) for women with the risk of impaired adherence and consequential increased pVL. In this period particularly, support of adherence to cART is important.
- Longer exposure to maternal antiretroviral drugs; although breast milk concentrations are low, toxicity cannot be absolutely excluded.
- Episodes of mastitis might increase the risk of transmission.
- An increased risk of HIV MTCT was observed through breastfeeding if the HIV-infected mothers were untreated and when breastfeeding was accompanied by solid food (=mixed feeding). There is currently no data to support any such additional risk in the “optimal scenario” but it cannot be excluded. Exclusive breastfeeding during the first 4 months is generally recommended for all children in Switzerland.
- The role of cell-associated virus in breast milk as an additional possible risk is not fully understood.

**2) List of potential BENEFITS arguing for breastfeeding**

- Recommendations to breastfeed during the six months postpartum exist in many European countries including Switzerland.
- Parents consider breastfeeding a simple, easy and free way of providing nutrition to the infant AND/OR psychologically essential for infant care and development.
- Breastfeeding has the following beneficial effects for the child (though formally not proven for children of HIV-infected mothers), among others:
  - i) The human microbiome is established normally with possible beneficial health consequences; e.g. lower risk to develop allergies, overweight and diabetes;
  - ii) Anti-inflammatory and anti-infective components in breast milk might have beneficial effects for immune response and immune tolerance which are important to prevent the development of allergies or infectious diseases.
- Beneficial effects of breastfeeding for the mother:
  - i) Improved postpartum recovery: stimulates involution of the uterus and reduces postpartum depression
  - ii) Reduction of the future risk to develop breast cancer and of glucose homeostasis with protection against type 2 diabetes

Dosing of NVP is based on current US guidelines [9] but considers a lead-in dosing during the first week for all newborns as recommended in preterm infants. As alternative (e.g. maternal NVP resistance or HIV-2 infection) Raltegravir (RGV) 1 × 1.5 mg/kg is available. For dosing beyond the first week of life and for the duration of infant cART, please contact your local paediatric service, if available a paediatric infectious disease specialist.

#### 4.4 Breastfeeding by HIV-positive Mothers

##### 4.4.1 Optimal Scenario

In our literature review, we were unable to identify a single case of HIV MTCT via breastfeeding in women who fulfilled the criteria of an optimal scenario. Nevertheless, this does not prove absolute absence of transmission risk. But the risk of breastfeeding must at the maximum be very low. This is supported by the most recent data from the PROMISE

Study [27] with an overall HIV MTCT at ages 6, 9, 12 and 24 months of 0.3% (95% confidence interval [CI] 0.1–0.6), 0.5% (95% CI 0.2–0.8), 0.6% (95% CI 0.4–1.1) and 0.9% (95% CI 0.6–1.5) in 2416 breastfed infants with mothers receiving antiretroviral treatment. Analysis of the HIV RNA for the whole breastfeeding period is currently not yet available. However, a very recent study from Tanzania did not identify a single case of HIV MTCT among 214 mothers who

Table 3:

**Guidance for a shared decision-making process to decide on breastfeeding in HIV-infected mothers with a strong wish to breastfeed their children****Guidance****1) Prerequisite conditions to minimise HIV MTCT risk ("optimal scenario")**

- Suppressed HIV pVL (< 50 RNA copies/ml) throughout pregnancy
- Regular follow-up of treatment (e.g. every 2–3 months, initially in postpartum period every month) is accepted by the pregnant woman to ensure maintained suppression of pVL.
- All health care providers involved should agree on an open, non-judgemental and unbiased approach towards breastfeeding.
- Inform the woman that the whole HIV care team accepts whatever the decision is and this will not affect the quality of care offered to her.

**2) Shared decision-making**

- Interdisciplinary process with patient and HIV care providers (including adult HIV specialist, paediatrician and obstetrician/gynaecologist)
- Start as early as possible during pregnancy but (re-)discussion required prior to delivery
- Discuss pro and con arguments of breastfeeding including open questions and admit limitations of medical knowledge (see Table 2)
- The final decision should be documented in the patient notes of the mother and distributed to all care providers involved.

**3) Follow up mother and child**

- Obtain a cord blood sample at birth to identify or exclude intrauterine infection of the newborn whenever possible. Previous concern about contamination by maternal HIV RNA is irrelevant in the "optimal scenario" but the unlikely event of a HIV-positive RNA result should be confirmed.
- Women deciding to breastfeed should be followed up initially monthly (during postpartum period with elevated risk of impaired adherence), afterwards every 2–3 months during the full breastfeeding period.
- Women who breastfeed should contact their obstetricians in case of signs and symptoms of mastitis. The decision to continue or to stop breastfeeding in this situation will be taken individually based on its severity, maternal compliance for cART, antibiotic treatment and the wish of the informed mother. The same holds true for hematemesis and melena in infants, where breastfeeding is the leading cause.
- HIV pVL (> 50 RNA copies/ml) must result in a stop of breastfeeding.
- All HIV-exposed children will have HIV testing as standard of care at month 1 and 6 by PCR as well as at months 18–24 by serology, if possible by a paediatric infectious disease specialist, until maternal antibodies are confirmed negative in the child. In breastfed infants the follow-up is similar, except that 1 or 2 additional follow-up visits (e.g. month 2 and/or month 4) should be considered to assure the "optimal scenario" is still granted. Additionally, HIV testing 3 months after weaning of breastfeeding is recommended.

were retained in care and had suppressed pVL [28].

Since breastfeeding itself has established health benefits for mother and child and is widely recommended during the first six months of life for all infants (see chapter 1), it is currently challenging to balance the additional risks and the potential benefits of breastfeeding in the "optimal scenario". Most of the risks are suspected on theoretical grounds, and the beneficial values of breastfeeding need to be judged individually. In consequence and based on the considerations mentioned in chap-

ter 2.2., the ad-hoc group encountered for breastfeeding a situation of equipoise [10]. Here, any recommendation to implement prevention measures should be based on a preceding process of shared decision-making.

This process requires comprehensive and unbiased information to the HIV-infected pregnant woman that empowers her to understand the risks and benefits of each decision. The health care provider's role in this process is to supply all the required information for the decision-making process in an unbiased manner, and to understand and respect the woman's

preference and autonomy. Ideally, after exchanging this information and discussing all potential risks and benefits, a decision is made that can be shared by all the involved partners. This decision process should take place before delivery. Table 2 summarises the competing arguments. The lists can be considered as a minimal set of arguments to be discussed with the HIV-infected mother. Over time, this list should be adapted or extended, whenever new information becomes available.

In summary, breastfeeding still should not be actively recommended for

HIV-infected mothers in Switzerland until more robust safety data is available. A recent viewpoint article compiled the research priorities for still unanswered questions [29]. However, until this data is available, a strong wish of a HIV-positive woman to breastfeed the child must be respected and should be supported in case the conditions of the

optimal scenario are fulfilled and the decision is the result of a shared decision-making among physician and mother or parents. Additional and enhanced information with in-depth argumentation of pros and cons within our group has been provided elsewhere [30]. To support the process, the proceedings including the follow-up of

mother and child are proposed on page 6 (see Table 3). In order to identify feasibility and results of this new recommendations a research project by the SHCS has been established (SHCS817).

#### 4.4.2 Suboptimal Scenario

HIV-infected mothers should be strongly discouraged to breastfeed.

## 5. SUPPLEMENT

### 5.1 Table 4

Table 4:

#### Overview of antiretroviral drugs available for treatment during pregnancy

Antiretroviral substances – official FDA pregnancy category	APR, July 2017 – category – recorded congenital defects (CBD)/live births – prevalence of CD (95 % CI)	Other guidelines: European Guidelines (EACS) Version 9.0 – October 2017 British Guidelines (BHIVA), Version 2018 American NIH Panel, November 2017 WHO 2016	Recommendations for Switzerland: ART treatment in pregnancy	
			Maintenance of existing ART through pregnancy	Starting ART in pregnancy
<b>Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (N(t)RTIs)</b>				
Abacavir (ABC) <sup>1</sup> – C	APR-1.5 30/1088 2.8 % (1.9 %, 3.9 %)	EACS: maintain or start BHIVA: maintain or start NIH: maintain or start	yes <sup>1</sup>	yes <sup>1</sup>
Didanosin (ddl) – B	APR-2 20/427 4.7 % (2.9 %, 7.1 %)	EACS: ddl not recommended anymore as first or alternative regimen in any HIV+ person. ddl in combination with d4T explicitly contraindicated in pregnancy. BHIVA: not recommended as ARV anymore in general. Combination with d4T contraindicated in pregnancy. Signal of increased rate of congenital anomalies if 1st trimester exposure. NIH: not recommended	ddl is no longer recommended as a first-line or alternative antiretroviral.	
Emtricitabine (3TC) – B Lamivudine (FTC) – C	APR-1.5 Lamivudine: 149/4880 3.1 % (2.6 %, 3.6 %) Emtricitabine 60/2614 2.3 % (1.8 %, 3.0 %)	EACS: maintain or start BHIVA: maintain or start NIH: maintain or start	yes	yes
Stavudine (d4T) – C	APR-2 21/811 2.6 % (1.6 %, 3.9 %)	EACS: d4T not recommended anymore as first or alternative regimen in any HIV+ person. d4T in combination with ddl explicitly contraindicated in pregnancy. BHIVA: not recommended as ARV anymore in general. Combination with d4T contraindicated in pregnancy. NIH: not recommended	d4T is no longer recommended as a first-line or alternative antiretroviral. The use of Stavudine is strongly discouraged.	
Tenofovir disoproxil fumarate (TDF) – B	APR-1.5 76/3342 2.3 % (1.8 %, 2.8 %)	EACS: maintain or start BHIVA: maintain or start NIH: maintain or start	yes	yes
Tenofovir alafenamide (TAF) – B	insufficient data	EACS: maintain; not recommended in initial regimen BHIVA: insufficient data to make recommendations NIH: insufficient data to make recommendations	yes	no <sup>3</sup>

Antiretroviral substances – official FDA pregnancy category	APR, July 2017 – category – recorded congenital defects (CBD)/live births – prevalence of CD (95% CI)	Other guidelines: European Guidelines (EACS) Version 9.0 – October 2017 British Guidelines (BHIVA), Version 2018 American NIH Panel, November 2017 WHO 2016	Recommendations for Switzerland: ART treatment in pregnancy	
			Maintenance of existing ART through pregnancy	Starting ART in pregnancy
Zidovudine (AZT) – C	APR-1.5 134/4160 3.2% (2.7%, 3.8%)	EACS: maintain or start in pregnancy. However, AZT not recommended anymore as first or alternative regimen in any HIV+ person. BHIVA: maintain or start NIH: maintain or start. Disadvantage of twice-daily administration and increased potential of hematologic toxicity.	AZT is no longer recommended as a first-line or alternative antiretroviral.	
<b>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</b>				
Efavirenz (EFV) – D	APR-2, c 22/990 2.2% (1.4%, 3.4%)	EACS: maintain. Is a suitable alternative for pregnant persons needing to start treatment. BHIVA: maintain or start NIH: maintain. No restriction of use in pregnancy, but only an alternative agent for starting (no increase of birth defects in observational studies).	yes	(yes) <sup>2</sup>
Etravirine (ETV) – B	insufficient data	EACS: maintain or start BHIVA: maintain or start NIH: maintain. Not recommended for start.	yes	no <sup>3</sup>
Nevirapine (NVP) – B	APR-1.5 32/1135 2.8% (1.9%, 4.0%)	EACS: maintain, but not to be initiated during pregnancy BHIVA: maintain or start NIH: maintain. Not recommended as a starting regimen because of greater potential for adverse events.	yes	no
Rilpivirine (RPV) – B	APR-2 3/263 1.1% (0.2%, 3.3%)	EACS: maintain or start BHIVA: maintain. Rather start with other options NIH: maintain (monitor pVL more frequently). Still little experience with use in pregnancy.	yes	no <sup>3</sup>
<b>Protease Inhibitors Pharmacologically Boosted with Ritonavir (PI/r)<sup>4</sup></b>				
Atazanavir/r (ATV/r) – B	APR-1.5 27/1235 2.2% (1.5%, 3.2%)	EACS: maintain or start BHIVA: maintain or start NIH: maintain or start	yes	yes
Darunavir/r (DRV/r) – C	APR-2 9/425 2.1% (1.0%, 4.0%)	EACS: maintain or start BHIVA: maintain. Rather start with other options. Twice-daily dosing to be considered if starting DRV in pregnancy and to be recommended if known resistance. NIH: maintain or start. Twice daily 600 mg DRV + 100 mg RTV recommended in pregnancy.	yes	yes
Lopinavir/r (LPV/r) – C	APR-1.5 29/1290 2.3% (1.5%, 3.2%)	EACS: maintain or start. LPV only part of alternative regimen for starting ART in any patient. BHIVA: maintain or start NIH: maintain or start. Once-daily LPV/r is not recommended for use in pregnant women.	yes	(yes) <sup>2</sup>

Antiretroviral substances – official FDA pregnancy category	APR, July 2017 – category – recorded congenital defects (CBD)/live births – prevalence of CD (95% CI)	Other guidelines: European Guidelines (EACS) Version 9.0 – October 2017 British Guidelines (BHIVA), Version 2018 American NIH Panel, November 2017 WHO 2016	Recommendations for Switzerland: ART treatment in pregnancy	
			Maintenance of existing ART through pregnancy	Starting ART in pregnancy
<b>Integrase Strand Transfer Inhibitors (INSTI)</b>				
Dolutegravir (DTG) – B (?)	insufficient data	see 4.1	no	no
Elvitegravir/cobicistat (EVG/c) – B	insufficient data	EACS: maintain or start (more frequent monitoring of viral load; TDM of EVG) BHIVA: maintain. Rather start with other options. NIH: maintain, but EVG exposure is significantly reduced during pregnancy. Therefore in case of EVG/c use, TDM for EVG is recommended and pVL should be strictly monitored. Starting EVG/c in pregnancy is not recommended.	(yes)	no <sup>3</sup>
Raltegravir (RGV) – C	APR-2 8/2078 2.9% (1.3%, 6.0%)	EACS: maintain or start BHIVA: maintain. Starting strongly recommended in woman presenting late (> 28 weeks) if a) pVL unknown or b) pVL > 100,000 c/ml (as part of 3- or 4-drug regimen) or c) untreated woman presents in labour together with stat single dose NVP 200 mg plus AZT/3TC plus iv AZT during labour. NIH: maintain or start	yes	yes
<b>Entry-Inhibitor</b>				
Enfuvirtide (T-20) – B	insufficient data	EACS: not listed as first or alternative drug choice in any HIV+ patients BHIVA: insufficient data to give recommendation. T-20 does not cross placenta. In general population there is only a role for T-20 if extensive drug resistance (triple-class failure) NIH: not recommended for drug-naïve pregnant women	no <sup>5</sup>	no
Maraviroc (MVC) – B	insufficient data	EACS: not listed as first or alternative drug choice in any HIV+ patients BHIVA: insufficient data to give recommendation. Only listed as switch option in general population. NIH: few case reports of use in pregnancy	no <sup>5</sup>	no

## APR categories

APR-2 – APR registry: “sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.”

APR-1.5 – APR registry: “sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a two-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date.”

c – advised not to start during pregnancy. However, maintain if pregnancy already in 2nd or 3rd trimester. Switch to another component if in 1st trimester.

<sup>1</sup> only for HLA-B\*5701-negative patients! Strict contraindication against use without prior testing for HLA-B\*5701 or with a positive HLA-B\*5701 allele.

<sup>2</sup> EFV and LPV/r are only recommended as an alternative option to start cART in the general population in EACS guidelines, therefore starting in pregnancy only if no other options.

<sup>3</sup> There is no signal for an increased rate of birth defects, however pregnancy data are still scarce. For this reason, starting is not recommended until more data is available.

<sup>4</sup> Following PIs not mentioned, as practically not in use anymore or withdrawn from the market: Fosamprenavir, Indinavir, Saquinavir, Tipranavir, Nelfinavir.

<sup>5</sup> If Enfuvirtide or MVC was commenced as salvage regimen for the mother, this treatment should not be modified if alternative effective drugs are not available.



Antiretroviral Pregnancy Registry (APR) [19]: records rates of congenital birth defects (CBD) in babies with 1st-trimester exposure to a specific antiretroviral in comparison to background rates of congenital birth defects and records of 2nd- and 3rd-trimester-only exposures to the same compounds. Reporting starts once a minimum of 200 prospective 1st-trimester exposures to an individual antiretroviral compound have been reported.

WHO guidelines [7] recommend the fixed-dose combination of TDF +FTC/3TC + EFV for all pregnant women and offer alternatives: AZT + 3TC + EFV / AZT + 3TC + NVP / TDF + 3TC (or FTC) + NVP. Second line options include ATV/r or LPV/r. The Swiss recommendations follow EACS guidelines: no specific combination is preferred when starting ART in pregnancy as long as contraindicated combinations are avoided such as ddI + d4T or any triple nucleoside reverse transcriptase inhibitor combinations.

## 5.2 Risk of Birth Defects and Premature Delivery Associated with Antiretroviral Drugs

The knowledge of the safety of ART exposure to the foetus/embryo in utero is increasing. The largest registry of antenatal exposure to ART is the Antiretroviral Pregnancy Registry (APR) [19], which has cumulatively collected data on a total of 18,660 live births with exposure to antiretrovirals at any time during pregnancy from January 1st 1989 through January 31st 2018. Birth defects were recorded in 516 neonates, corresponding to 2.8 birth defects per 100 live births (LB) (95 % confidence interval [CI] 2.5–3.0). This is not higher than reported in two population-wide cohorts in the USA, the CDC's birth defects surveillance system (MACDP) and the Texas Birth Defects Registry (TBDR) with 2.72 per 100 LB and 4.17 per 100 LB, respectively. There was also no specific type of birth defect registered nor an increase associated with a specific time of exposure to any antiretroviral drug during pregnancy. However, it must be considered that data are only reported once more than 200 pregnancies are recorded under a specific an-

tiretroviral compound – thus, newer drugs are not yet sufficiently represented. Birth defect rate at initial exposure in the first trimester was 2.7 per 100 LB (95 % CI 2.4–3.1) versus initial exposure during second or third trimester of 2.8 per 100 LB. Prevalence ratio was 0.99 (95 % CI 0.83–1.18). In summary: the Antiretroviral Pregnancy Registry does not find an increase in frequency of overall or specific birth defects compared to other pregnancy registries in the general population.

Systematic reviews [31, 32] and country-wide cohort studies [33–36] have been published to add to the increasing safety data for some of the antiretrovirals that have been used for several years [31–33]. In the country-wide studies different single antiretroviral drugs have been implicated to be associated with increased birth defects, though without consistent signal towards one specific drug.

Efavirenz (EFV) has been the most controversial antiretroviral drug with regard to birth defects. Since changing cART during pregnancy is associated with an increased risk of loss of viral suppression [37], all consulted guidelines advise to maintain EFV through pregnancy – even in first trimester – if part of a successful (viral suppression) and well tolerated regimen. The most recent WHO guidelines [7] regard EFV as a first-line drug at all stages of pregnancy and the British HIV Association guidelines [17] make no restrictions on the use of EFV (continue through or start in pregnancy). The European guidelines (EACS) have no objection to continuation of EFV, but regard starting EFV during pregnancy only as an alternative component [6]. The American guidelines of the National Institute of Health (NIH) [16] lifted their warning against starting EFV in pregnancy (any trimester) since November 14, 2017, acknowledging that the APR data do not confirm any excess rate of birth defects, specifically no accumulation of neural tube defects.

Since EFV is no longer a recommended first-line option in the EACS guidelines, we propose positioning EFV as suggested in the EACS guidelines: continue EFV

if part of a successful and well tolerated regimen, but only use as part of a starting regimen in first trimester if no other options are available; this should be an extremely rare situation.

There is data showing a moderately increased risk of premature delivery [38, 39, 37] following use of protease inhibitors during pregnancy. However, as they are one of the main drug classes for cART in pregnancy the advantages strongly outweigh potential doubts.

In 2017 a clinical practical guideline on ART in pregnancy [41] caused a stir by proposing that the AZT/3TC combination should be preferred over TDF/FTC, basing this conclusion mainly on one study [42]. In this study there were more severe adverse pregnancy outcomes (very preterm delivery <34 wks; early neonatal death through week 1) in the TDF/FTC-containing than in the AZT/3TC-containing cART (both plus Lopinavir/Ritonavir). Both the BHIVA Writing Group and the NIH guidelines do not support this recommendation since the conclusions were drawn from only one study that had methodological difficulties and given the robust evidence of the safety of TDF/FTC from other large cohorts and studies.

Dolutegravir – see section 4.1. on the new safety warning for use of Dolutegravir at the time of conception.

## 5.3 Use of cART in Pregnancy, Different Scenarios

### 5.3.1 Pregnant Women on cART Treatment

Women who are already treated for HIV infection with one of the available combinations of antiretroviral drugs should in principle continue with the same regimen.

Some of the available antiretroviral treatment, e.g. Lopinavir/Ritonavir and Nevirapine-based combinations with two nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTI) are well documented for the use in pregnant women and have an optimal pharmacokinetic profile. However, these regimens are no longer the preferred regimens for the treatment of HIV-infected adults.

The efficacy of a Lopinavir/Ritonavir-based ART may be jeopardized by reduced tolerance and the relatively high pill burden. Concerning Nevirapine, the risk of liver toxicity, severe rash and the low resistance barrier are among the issues that need to be taken into consideration. Therefore, starting NVP in pregnancy is not recommended, however there is no contraindication of continuing a well tolerated and virologically successful NVP-containing regimen. Table 4 in this supplement provides an overview on antiretroviral drugs available for treatment during pregnancy.

### 5.3.2 Women not on cART when Getting Pregnant

cART should be initiated in all women as soon as possible to achieve an undetectable HIV RNA in the third trimester. In the rare cases of HIV MTCT despite suppressed pVL at birth, the relevant factor was late start of cART, i.e. shorter duration of cART, during pregnancy [43, 44]. The dynamics of viral suppression under ART are dependent on initial plasma viremia and choice of antiretroviral combination. Time to suppression is markedly faster with an INSTI.

### 5.3.3 Women in Late Pregnancy (after Week 28) with High Viral Load (> 1000 Copies/ml) in HIV Primo-infection, Late HIV Diagnosis or Viral Failure

Fortunately, this situation is rare in Switzerland, but it requires a rapid reduction of viremia. Therefore, an INSTI should be part of the treatment combination. Most data on the use of INSTI during pregnancy are available for Raltegravir. Whilst awaiting results of resistance testing, and based on the patient's treatment history, we recommend to start with a quadruple combination therapy containing 2 NRTI, a boosted PI and Raltegravir. In analogy, women with treatment failure during the last trimester should be switched as fast as possible

according to prior treatment history and results of resistance testing and Raltegravir 2 × 400 mg should be added as fourth component according to a recent Thai study [45]. After delivery this intensified treatment combination should be changed back to a standard triple cART regimen taking into account resistance testing. It is strongly recommended to consult an experienced and if possible the treating infectious diseases physician.

### 5.3.4 Women Presenting In-labour or Premature Rupture of Membranes and not or Insufficiently Treated for HIV

It is recommended [17] to give a single dose of Nevirapine 200 mg to the mother, as NVP rapidly crosses the placenta and within two hours achieves effective concentrations in the neonate [46]. A single dose of NVP is tolerated well, even in women with high CD4 counts. Full triple cART should follow as soon as possible with two NRTIs and – ideally – Raltegravir (see 5.3.3). It has been shown that intrapartum intravenous (i.v.) AZT treatment in mothers with pVL > 1000 copies/ml at birth did not reduce the overall HIV MTCT if the neonate received full postnatal cART as nPEP [47]. Thus, implementation of i.v. Zidovudine (2 mg/kg at onset of labour followed by 1 mg/kg until delivery) should be discussed if maternal pVL is > 1000 copies/ml and if provision of nPEP immediately after birth is anticipated to be difficult, e.g. because of severe prematurity. Intrapartum i.v. AZT is no longer recommended in Switzerland in case of maternal pVL < 1000 copies/ml.

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