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German-Austrian Recommendations for HIV-therapy in Pregnancy and in HIV-exposed Newborn – Update 2005

Common Declaration*

of

The German AIDS-society (DAIG)
The Austrian AIDS-society (OEAG)
of the HIV-AIDS competence network
as well as

The Robert-Koch Institute Berlin (RKI)
The German Association of Physicians specialized in HIV Care (DAGNAE)
The German Society of Pediatric and Youth Medicine (DGKJ)
The German AIDS Pediatric Association (PAAD)
The German Society of Obstetrics and Gynecology (DGGG)
The National Reference Center for Retroviruses (NRZ)
German AIDS Assistance (DAH)

Updated by

Dr. med. Bernd Buchholz (Mannheim University Pediatric Clinic), Dr. med. Matthias Beichert (Mannheim, Gynecology and Obstetrics Practice), Dr. med. Ulrich Marcus (Robert Koch Institute, Berlin), Dr. med. Thomas Grubert, Dr. med. Andrea Gingelmaier (Gynecology Clinic of the Ludwig Maximilians University of Munich) Dr. med. Annette Haberl (HIV-Department, J. W. Goethe-University Hospital, Frankfurt), Dr. med. Brigitte Schmied (Otto-Wagner Spital, Vienna) and Prof. Dr. med. Norbert Brockmeyer (Clinic for Dermatology, Ruhr University, Bochum).

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The participants at this conference included (in alphabetical order):

Bogner J (München)
Buchholz B (Mannheim)
Cordes C (Berlin)
Feiterna-Sperling C (Berlin)
Funke A-M (Köln)
Gingelmaier A (München)
Graefe K (Hamburg)
Gröger S (Hamburg)
Grosch-Wörner I (Berlin)
Grubert T (Ravensburg)
Gürtler L (Greifswald)
Haberl A (Frankfurt)
Hien S (Mannheim)
Hollwitz B (Hannover)
Kästner R (München)
Königs C (Frankfurt)
Korn K (Erlangen)
Kremer H (Miami)
Marcus U (Berlin)
Niehues T (Düsseldorf)
Öttinger A (Linz)
Schafberger A (Berlin)
Scheld A ?
Schleehauf D (Berlin)
Sonnenberg-Schwan U (München)
Stögerer M (Graz)
Vocks-Hauck M (Berlin)

Abstract

German-Austrian recommendations for HIV-therapy in pregnancy - Update May 2003

Bernd Buchholz (Mannheim University Pediatric Clinic), Matthias Beichert (Mannheim, Gynecology and Obstetrics Practice), Ulrich Marcus (Robert Koch Institute, Berlin), Thomas Grubert, Andrea Gingelmaier (Gynecology Clinic of the Ludwig Maximilians University of Munich), Dr. med. Annette Haberl (HIV-Department, J. W. Goethe-University Hospital, Frankfurt), Dr. med. Brigitte Schmied (Otto-Wagner Spital, Wien), Norbert Brockmeyer (Clinic for Dermatology, Ruhr University, Bochum).

In Germany during the last years about 200-250 HIV infected pregnant women delivered a baby each year, a number that is currently increasing. To determine the HIV-status early in pregnancy voluntary HIV-testing of all pregnant women is recommended in Germany and Austria as part of prenatal care. In those cases, where HIV infection was known during pregnancy, since 1995 the rate of vertical transmission of HIV was reduced to 1-2%.

This low transmission rate has been achieved by the combination of anti-retroviral therapy of pregnant women, caesarean section scheduled before onset of labour, anti-retroviral post exposition prophylaxis in the newborn and refraining from breast-feeding by the HIV infected mother. To keep pace with new results in research, approval of new anti-retroviral drugs and changes in the general treatment recommendations for HIV infected adults, in 1998, 2001 and 2003 an interdisciplinary consensus meeting was held. Gynaecologists, infectious disease specialists, paediatricians, pharmacologists, virologists and members of the German AIDS Hilfe (NGO) were participating in this conference to update the prevention strategies. A third update became necessary in 2005. The updating process was started in January 2005 and was terminated in September 2005. The guidelines provide new recommendations on the indication and the starting point for therapy in pregnancies without complications, drugs and drug combinations to be used preferably in these pregnancies and updated information on adverse effects of anti-retroviral drugs. Also the procedures for different scenarios and risk constellations in pregnancy have been specified again.

With these current guidelines in Germany and Austria the low rate of vertical HIV-transmission should be further maintained.

Key words: Pregnancy, HIV-therapy, HIV-status, HIV-testing, anti-retroviral drugs, recommendations

Introduction

The German-Austrian recommendations for HIV therapy in pregnancy reflect the current international knowledge and the experience of German clinical settings specialized in the treatment of HIV-positive pregnant women.

Even though all constellations, scenarios and contingencies of a pregnancy can not be considered within the scope of these recommendations, they are designed as scientifically-based guidelines. The most important and most frequent questions and problems which doctors, who treat HIV positive expectant mothers are facing, irrespective of whether they are experienced in the care for such pregnancies or not, are covered in these guidelines.

The medical measures recommended in these guidelines are helpful for every health care professional, who advises a HIV-positive pregnant woman. **Therefore these recommendation should be available in every delivery room.** In case of obstretic emergencies the tables of these recommendations can be used as emergency plan.

Therapeutic recommendations can never replace extensive experience with patients and their specific problems. Therefore antenatal care of HIV positive expectant mothers, considering the many uncertainties associated with pregnancy, should be performed in - or in cooperation with specialized centers.

All measures necessary for the prevention of vertical HIV transmission can only be employed, if the HIV infection status of the expectant mother is known. Risk factors for an HIV-infection such as origin from a an HIV epidemic region, current or previous intravenous drug abuse or sexual intercourse with an HIV-infected partner, can not always be identified amongst all pregnant HIV-infected individuals. **For that reason an HIV antibody test should be offered to every pregnant women** together with competent personal counseling in regard to possible consequences in the case of a positive test result. If necessary this must be carried out with a interpreter and cultural mediation, even if the patient needs to be referred to a specialized center for this purpose. By German law the explicit approval of the pregnant mother is required for HIV-testing, which routinely consists of an ELISA screening test. A positive test result must be confirmed by Western Blot [1, 2]. If the patient is counseled by her gynecologist alone, addresses and telephone numbers of additional experts should be made available to the expectant mother. The personal and medical consequences of any positive test result for the woman should also be discussed in the counseling. Furthermore a competent pediatrician should contribute to the counseling about transmission risks, follow-up tests and the course of an HIV infection in a child.

As with many other problems in pregnancy, the welfare of the child must be weighed up against that of the mother when deciding for therapeutic/prophylactic measures against HIV.

The goals of interdisciplinary co-operation between general practitioners, obstetricians and pediatricians in the treatment of HIV-infected expectant mothers and HIV-exposed newborns are: 1) the prevention of mother to child transmission, and 2) the optimal treatment of pregnant women combined with minimal adverse effects in the expectant mother and in the unborn child.

Mothers with a high viral load and/or low t-helper cell numbers transmit HIV more frequently to their children [3, 4, 5], therefore successful therapy of the mother is also beneficial for the child. Risks for the child that might arise from intrauterine exposure to anti-retroviral combination therapies are still uncertain since data regarding pharmacokinetics, pharmacody-

namics, embryotoxicity and fetotoxicity of these drugs are lacking [6, 7, 8, 9, 10, 11, 12]. The vertical transmission rate without intervention is approximately 16%, therefore it should also be considered that 84% of the children are treated unnecessarily to reach a HIV-transmission rate of <2%. Up to now no reliable prognostic factors are known to select the pregnancies at greatest risk for HIV-transmission. From a pediatric standpoint this point was already discussed with concern back in 1995 [13].

Basic and clinical research data suggest multiple risk factors which contribute to vertical HIV-transmission [3, 4, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25]. Combined interventions as described in the following chapters can reduce the HIV-transmission rate below 2% [16, 26, 27, 28].

The recommendations for diagnostic and therapeutic procedures given here are based on published study results wherever these were available. Such study results, however, are not available for all practical problems and questions, so that often clinical experience and expert opinions must be resorted to.

Even if the goal of these recommendations is the optimal treatment of mother and child based on the most recent findings, it should be stressed that the decision for the recommended diagnostic and therapeutic measures ultimately must be made in agreement with the expectant mother. This means that a refusal of a recommended diagnostic and/or therapeutic measure must also be respected wherever the consent of an expectant mother can not be acquired despite adequate counseling.

After a detailed analysis of data and publications, a number of procedures were developed for specific situations. Most common situations and scenarios were considered. For all other situations however, individual decision on a case-by-case basis are necessary.

The following situations were discussed and consensus recommendations were made:

1. Prenatal care

2. Indication for anti-retroviral treatment and therapeutic regimens during pregnancy

2.1 Indication for anti-retroviral treatment
2.2 Resistance testing
2.3. Initial therapeutic regimen
2.4. Interruption of anti-retroviral therapy during the 1st trimester of the pregnancy

3. HIV transmission prophylaxis with standard risk profile

4. Risk-adapted transmission prophylaxis
4.1 Multiple pregnancy, premature labor and premature infants 33rd (+0)- 36th (+6)GW and duration of maternal ART/prophylaxis <4 weeks before birth
4.2 Amnion infection syndrome/amnionitis, (premature) rupture of membranes > 4h, premature birth <33rd (+0)GW and viral load increase at the end of pregnancy >10 000HIV copies/ml
4.3 Incision injury of the child/ aspiration and/or ingestion of blood contaminated amniotic fluid
5. Procedures with incomplete transmission prophylaxis
5.1 With verified HIV-infection
5.2. Situations with unclear HIV infection status

6. Mode of delivery

7. Postnatal care in the delivery room

8. Postnatal treatment of the child

9. Refraining from breast-feeding

10. Postnatal care of the HIV-exposed child and preparation of a surveillance register

11. Phone-Hotline, notification of unexpected observations and experiences

The recommendations were graded as outlined in the German-Austrian guidelines for the anti-retroviral Therapy of HIV infection [29]. Unless the results of voting are indicated, the recommendation was agreed upon unanimously.

Table 1. Grading of the therapeutic recommendations.

	I On the basis of at least one randomized study with clinical end points *	II On the basis of surrogate marker studies	III According to expert opinion
A Unambiguous recommendation	A I	A II	A III
B In general advisable	B I	B II	B III
C Justifiable	C I	C II	C III
D In general not recommended	D I	D II	D III
E Unambiguously not recommended	E I	E II	E III

* Clinical end point studies for new substances are no longer carried out due to the fact that conditions for licensing by the FDA and the EMEA have changed.

1. Prenatal care

Upon diagnosis of HIV in a pregnant women, an interdisciplinary center specialized in HIV care should be contacted immediately. From that point onwards the woman should be treated in close cooperation with the gynecologist familiar to the pregnant women. The gynecologist, who usually treats the women, is primarily recommended to carry out the conventional prenatal care for HIV-positive pregnant women, according to current antenatal care guidelines, to preserve the bond with the patient's familiar environment. Any other additional care measures should also be fitted in this setting. With the help of a well-planned time scheduling a closely-knit monitoring can be ensured.

Psychosocial care should be provided to each HIV-positive expectant mother, at the latest in the HIV-specialized centers, and the opportunity to contact women's AIDS self-help groups should also be offered. In the HIV-specialized centers the patients should be fully counseled regarding maternofetal transmission risks, current therapeutic options, the possibility to reduce mother-to-child HIV transmission rates, existing residual risks, potential short - and long-term effects of intrauterine exposure to anti-retroviral therapy for the child as well as the necessity of postnatal prophylaxis in the child and of avoiding breast-feeding. [30, 31, 32]. Considering the rapidly developing state of knowledge regarding HIV, up to date information is only warranted in such specialized centers. To overcome language barriers the help of interpreters should be obtained wherever necessary to ensure that all information reach the patients.

In co-operation between the general practitioner, the gynecologist, the obstetrician, the pediatrician and the patient, an individual risk-adapted anti-retroviral treatment or prophylaxis concept corresponding to current German-Austrian guidelines for therapy in pregnancy should be set up. The general practitioner/ infectious disease specialist should be consulted to adapt this therapeutic plan to ongoing therapies or prophylaxes against opportunistic infections. A switching of the treatment regime during pregnancy or the initiation of new therapeutic measures should only be undertaken upon consultation with a physician or center specialized in anti-retroviral therapy.

In the case of therapy-refractory morning sickness/emesis gravidarum all anti-retroviral medications should be stopped simultaneously (NNRTI wherever appropriate in a staggered manner a few days previously) and reintroduced simultaneously if the symptoms start to improve again in order to prevent the development of resistance anti-retroviral drugs (AIII).

Concurrently with the therapy, a monthly monitoring of blood counts is also recommended (AIII). Changes in blood counts are particularly significant because of the possibility of zidovudine-induced anemia and thrombocytopenia. If the hemoglobin-values drop to less than 10mg/dl in the expectant mother, it must be decided in close cooperation with the general practitioner whether waiting with closely-knit controls is possible or if the anti-retroviral regimen must be changed.

An oral glucose tolerance test is recommended between the 23rd (+0) and 27th (+7) weeks of gestation (GW) to screen for pregnancy-related diabetes, particularly if the expectant mother is treated with protease inhibitors (under protease inhibitor therapy diabetes mellitus occurs approximately three times more frequently) [33] (AIII). Measurements of blood lactate, liver enzymes, amylase, lipase and LDH should be carried out at the beginning of the pregnancy, after starting a therapy or prophylaxis, with suspicious clinical symptoms (signs of lactate acidosis such as nausea, severe vomiting, abdominal pain, fatigue, raised liver values) and particularly in the 3rd trimester because of the increased risk of lactate acidosis at the end of pregnancy (AIII).

Immunological and virological parameters (lymphocyte subsets, HIV viral load) should be checked at least bimonthly (AIII). The last measurement of HIV-viral load before birth should be performed in time (2-4 weeks before birth), that the result is known at the latest at birth. In the case of an increased HIV-viral load of the mother it is possible to intensify the anti-retroviral prophylaxis of the HIV-exposed newborn to reduce the increased risk of vertical HIV-transmission.

The expectant mother should be informed about any possible side effects and symptoms of the anti-retroviral therapy and should also be requested to inform their general practitioner immediately of any suspicious complaints [34, 35, 36]. Furthermore, she should also be requested to consult her general practitioner before taking any other prescribed or OTC medications during the pregnancy because of potential interactions with the anti-retroviral therapy (e.g. benzodiazepines).

Especially HIV-positive pregnant women on methadone substitution or with drug abuse should be informed in detail about drug interactions between these drugs and anti-retroviral therapy/prophylaxis. Without continuous medical evaluation anti-retroviral therapy can lead to withdrawal syndrome, which jeopardize success of anti-retroviral therapy due to lack of adherence.

A comprehensive diagnostic evaluation and therapy for genital infections is also important. Local co-infections such as chlamydiasis, trichomoniasis and bacterial vaginosis amongst others correlate with higher HIV transmission risks, especially due to potential induction of premature labor [24]. The following examinations are obligatory: determination of vaginal secretion pH; sampling of a native preparation and microbiological culturing; STD diagnostics; toxoplasmosis screening at the start of therapy and in the second and third trimester to exclude a reactivation and/or new infection at the end of the pregnancy; a complete hepatitis serology. Urinary tract infections should be excluded e.g. by Uricult examinations.

Up to 30% of HIV-infected women display vulvar, vaginal and cervical dysplasias, which can progress more rapidly to carcinoma as a result of the HIV-induced immune suppression [37]. For this reason a colposcopic examination should be carried out at the onset of pregnancy in addition to pap smear testing of the cervix and HPV-testing for high-risk-HPV-subtypes. If the colposcopic examination and HPV-testing yield normal results, the next control examination can

be scheduled in a postnatal appointment. Any abnormalities must be controlled colposcopically and if necessary histologically (AIII). The perianal region should be examined in addition to the vulva, vagina and cervix, as also recommended for non-pregnant HIV-infected women.

For all HIV-infected expectant mothers nuchal translucency/transparency of fetus should be measured between the 10th (+6) and 13th (+6) weeks of gestation to estimate risks of aneuploidy. Fetal sonography (at least DEGUM stage 2) should be carried out between the 19th (+6) and 22nd (+6) weeks of gestation to screen for fetal malformations.

Invasive prenatal diagnostics should be avoided whenever possible. If there is an urgent indication, it should be performed with consideration of viral load and **only under the protection of anti-retroviral therapy/prophylaxis** because of the risk of contamination of the amniotic fluid [110, 111] (AIII).

If the HIV-status of the mother is unknown and invasive prenatal diagnostic is indicated, an HIV-test should be offered again.

Table 1. (Additional) Diagnostic measures during a uncomplicated HIV pregnancy:

Diagnostic measure	**Timepoint/ frequency**	**Reason**
HIV screening and if necessary HIV confirmative test	- routinely in the 1st trimester in case of unknown HIV1-status; - at the start of the 3rd trimester after negative initial test but continuous risk of infection	Precondition for therapeutic measures to reduce the risk of vertical HIV1-transmission
CD4 cell count + viral-load	At least every two months	Monitoring the course of the HIV infection; Initiation of ART or switchover of ART in case of therapeutic failure Control of the efficacy of the (HA)ART to prevent a high HIV viral load at birth
HIV resistance test	1. As early as possible before the onset of prophylaxis 2. In case of virological therapy failure during an ART 3. With detectable viral load towards the end of an HIV prophylaxis 4. 2-6 weeks after application of a prepartal NVP ultra-short prophylaxis	1. Exclusion of a primary ZDV resistance [38, 39, 40, 41] 2. According to general therapeutic recommendations for optimizing a therapeutic switchover [29] 3. Registration of any possible resistance induction that might have implications for a future therapy [42] 4. Registration of a potential resistance induction [43, 44]
Blood count (Hemoglobin value)	Monthly	Detection of anemia, thrombopenia related to the use of ZDV in particular
Oral glucose tolerance test	Between 23rd (+0) and 27th (+6) weeks of gestation	Detection of gestation diabetes
Lactate level + liver values + γGT + LDH + amylase + lipase	1. At the start of pregnancy 2. After onset of therapy/prophylaxis 3. In case of clinical symptoms 4. Monthly in the third Trimester	Recommended for detecting lactic acidosis (raised incidence in the 3rd trimester). Discussion of raised lactate and other values in cooperation with clinicians experienced in carrying out and analyzing lactate measurements.
pH measurement in the vaginal secretion Native preparation Microbiological culture STD-diagnostics: Chlamydia, gonorrhea, trichomonas, syphilis hepatitis serology		Recognition and timely treatment of local co-infections that can increase the risk of HIV1 transmission
Toxoplasmosis screening	At the start of a pregnancy as well as in the 2nd and 3rd trimesters	For the diagnosis of a new infection or a toxoplasmosis reactivation
Colposcopy, cytological controls for vulvar, vaginal and cervical dysplasias, HPV-testing	Colposcopy, cytological examination and HPV-testing at the start of a pregnancy; If abnormalities are revealed, colposcopic controls and wherever necessary histological clarification (biopsy)	Increased risk of dysplasia with HIV infection [37]
Measurement nuchal translucency	10th (+6) – 13th (+6) week of gestation	Estimation of the risk of aneuploidy
Sonography, at least DEGUM stage 2	19th (+6) – 22nd (+6) week of gestation	Exclusion of malformations

2. Indication for anti-retroviral treatment and therapeutic regimens during pregnancy

2.1 Indication for anti-retroviral treatment

Treatment indications [30] for adult HIV patients also apply to pregnant women (but check 3.1b!!), i.e. in clinically asymptomatic women the immunological threshold for treatment is reached at a CD4-cell count between 200 and 350 CD4+ cells/mm^3. It should be noted here that a certain degree of immunosuppression is induced physiologically by a pregnancy [20,47] so that the CD4-values drop by around 10-20% during every pregnancy. In an HIV infected woman, this effect is may be even more pronounced (up to 40%). (AIII)

2.2 Resistance testing

In order to ensure the efficacy of anti-retroviral prophylaxis/ therapy during pregnancy, testing for pre-existing resistance is generally indicated for every treatment naive pregnant woman before the start of anti-retroviral therapy or - prophylaxis [38, 39] (AIII).

For women who become pregnant during anti-retroviral treatment, German-Austrian guidelines for HIV therapy in adults recommend resistance testing (AIII) whenever a virological treatment failure is diagnosed.

If at the end of anti-retroviral HIV transmission prophylaxis (determined just before - or directly at the time of birth) viral load is detectable in pregnant women, resistance testing should also be performed in order to document the eventual development of resistance under prophylaxis so that this can be taken into account if the woman requires anti-retroviral therapy at a later timepoint [41] (AIII).

If nevirapine ultra-short prophylaxis (single maternal dose immediately before birth) is given, resistance testing should be carried out 4-6 weeks after the anti-retroviral medication was stopped (see points 4 and 5) in order to determine whether resistance against nevirapine has been induced.

2.3. Initial therapeutic regimen

Apart from the inhibition of viral replication in the mother, a major objective of an optimized initial therapeutic regimen during pregnancy is to combine an effective prophylaxis against HIV-transmission with the highest possible degree of compatibility for mother and fetus. Restriction of subsequent maternal therapeutic options e.g. because of development of drug resistance should also be avoided.

A standard therapeutic regimen (usually a triple combination including either one – if necessary boosted - protease-inhibitor, or one NNRTI, but not efavirenz[!] due to the report of cerebral malformations in the newborns of efavirenz-treated pregnant monkeys [45]) is recommended as an initial maternal therapeutic regimen (AI,II). In addition, nucleoside analogues of particularly high mitochondrial toxicity (i.e. dideoxycytidine (ddC), stavudine (D4T) and didanosine(DDI)) should not be given in combination with one another wherever possible because of the raised risk of a potentially fatal lactate acidosis in the expectant mother [46] (AIII).

It has to be considered that with the exception of zidovudine, no anti-retroviral drug has been approved for therapy during pregnancy and that the limited experience until now has not permitted any definitive evaluation of the risks and benefits. When choosing anti-retroviral drugs one must also keep in mind that the pharmacokinetics of each drug group (NRTI, NNRTI+PI) can be altered during pregnancy [48,49,50]. Therefore during use of PI and NNRTI in pregnancy drug monitoring is compulsory.

Table 2. Comments on the initial anti-retroviral combinations/substances.

Initial combinations and substances		**Comment**
Nucleoside analogs for which most experience has been gained	Zidovudine + Lamivudine (also as Combivir®) Zidovudine + Didanosine	Most clinical experience has been gained with the use of these substances. One additional rationale for application of zidovudine is the metabolization of this drug in the placenta which might contribute to the transmission preventing effect [51,52]. Some cases of lethal mitochondriopathies were reported in non-infected children after maternal zidovudine/lamivudine-therapy [7, 8]. Data about long term toxicity especially carcinogenicity/ genotoxicity as a matter of incorporation of nucleoside analogs into DNA [112] are lacking. In case of therapeutic failure changed pharmacokinetics of nucleoside analogs because of pregnancy must to be taken into consideration [113].
Alternatives	Stavudine + Lamivudine Didanosine + Lamivudine Abacavir Tenofovir:	Less clinical experience in pregnancy. Increased attention relating to potential side effects. In animal studies where Tenofovir was applied in higher doses than usual in humans reduced bone density and renal damage were observed.
NNRTI	Nevirapine:	Caution: raised liver enzymes, more allergic reactions since pharmacokinetics are altered during pregnancy [49]. Increased liver toxicity in pregnancy especially with CD4-counts >250/µl. With longer administration enzyme induction of the cytochrome P450 system and therefore accelerated metabolization of nevirapine not only in the expectant mother but also in the newborn [53]. A single dose applied before birth and to the newborn is therefore not sufficient for prophylaxis of HIV1-transmission if nevirapine has already been given over a longer period during the course of the pregnancy.

Table 2. (continued)

Initial combinations and substances		Comment
Protease inhibitors, for which most experience has been accrued [50]:	**In common:**	Because of the poor ability of most PIs to cross the placenta (no or poor data: Fos-Amprenavir [57, 113, 125], Atazanavir [28, 57, 113]), no therapeutic levels are to be expected in the fetal compartment [54,55,56]. As such, no relevant adverse effect frequency is to be expected amongst the fetuses, but it is still unclear whether therapeutic drug-levels in the fetus are necessary to inhibit vertical HIV1-transmission.
	Nelfinavir	Up to now most experiences in pregnancy have been accrued for Nelfinavir [57,113, 126] but an anti-retroviral therapy with an unboosted PI is no more recommended as optimal therapeutic regimen in adults.
	Lopinavir + Ritonavir (=Kaletra®) **or** Saquinavir (Fortovase®) + Ritonavir	Until now rare published studies about the use in pregnancy [54, 57, 113, 126] but no incidence for unusual or unexpected adverse effects [57, 126].
Alternatives:	Ritonavir	Contraindicated as a mono-PI because of poor compatibility; can be applied at low doses to boost plasma levels of other PI's.
	Indinavir + Ritonavir	High number of tablets, relevant side effects. With Indinavir there is an increased need for water uptake to prevent the formation of kidney stones in the mother.
	Other boosted PI's, double PIs:	Hardly any results published concerning safety during pregnancy.
	Fos-Amprenavir, Atazanavir	No or poor data about use in pregnancy: Fos-Amprenavir [57, 113, 125], Atazanavir [28, 57, 113].
	Saquinavir (Invirase®), Amprenavir(Agenerase®)	These drugs will be no more available in future, because production is stopped.
New substances:	T-20 (fusion inhibitor)	Should only be used in heavily pretreated pregnant women as part a of anti-retroviral salvage therapy based on resistance testing. Because of the high molecular weight a transplacental passage is not expected. Some case reports show no adverse effects [57, 127].
	Emtricitabin	No results published regarding use and safety during pregnancy.

2.4. Interruption of anti-retroviral therapy during the 1st trimester of the pregnancy

The decision to interrupt maternal anti-retroviral therapy in the 1st trimester of pregnancy depends on the individual clinical, immunological and virological status of the pregnant woman as well as the anti-retroviral treatment case history. If the patient was clinically symptomatic before the start of anti-retroviral therapy, or if immunological and/or virological parameters showed an advanced state of immune deficiency and/or a very high risk for rapid disease progression, interruption of therapy is fraught with greater risks for the pregnant women than it is for a clinically asymptomatic woman, whose laboratory parameters might justify the start of an anti-retroviral therapy, but whose clinical status is stable and whose laboratory parameters are no cause for major immediate concern.

Vertical HIV-Transmission occurs very rarely during the first 12 weeks, and is most common at the end of pregnancy and during birth. Therefore an effective HIV-transmission prophylaxis does not require anti-retroviral therapy during the entire pregnancy. Since currently adverse side effects (especially during the phase of organogenesis) can not be excluded, particularly with application during the first trimester, an at most 3 month interruption of maternal anti-retroviral therapy should be taken into consideration. The decision to interrupt anti-retroviral therapy in the first trimester of pregnancy should be made individually and according to individual risk profiles with the informed consent of the mother. If therapy is interrupted, monitoring intervals should be short (at least monthly measurement of t-helper cell number and the virus load) (AII, III).

Up to now, no results of controlled trials have been published regarding the risks associated with interruption of anti-retroviral therapy during pregnancy, and inadequate data exist to allow any estimation of the risk that anti-retroviral combination therapy during the 1st pregnancy trimester entails for the child [12, 57].

From an embryo-toxicological standpoint, no drugs with unclear human teratogenic potential should be applied in the first trimester until the 11th completed week of gestation + 0, (after the last regular menstruation) due to their potential effects on organogenesis [58, 59, 60].

If a decision is made in favor of therapy interruption, **all** anti-retroviral medications should be ceased. In regimes consisting of 3NRTI or 2NRTI +PI the simultaneous interruption of all drugs can be managed without problems.

In contrast, because of a possible long half-life up to 3-4 weeks of NNRTI with a high interindividual variability, simultaneous interruption of an anti-retroviral combination therapy with 2NRTI+1NNRTI (such as efavirenz and nevirapine) results in an temporary monotherapy with a high risk of development of NNRTI-resistance. At present the most safe management of this problem in non-pregnant individuals is to replace the NNRTI by a (boosted) PI and cease this new anti-retroviral treatment after 4 weeks. As an al-

Table 3.1. Prevention of maternofetal HIV infection during a normal course of pregnancy.

<table>
<tr><th>Status of expectant mother:</th><th colspan="3">No ART before pregnancy
Therapy indication according to German-Austrian guidelines for the therapy of HIV infection (30)</th><th>ART before pregnancy</th></tr>
<tr><td>Indication:</td><td>CD4 >200-350/µl
and
HIV-RNA < 10 000 HIV copies/ml (RT-PCR/bDNA)</td><td>CD4 >200-350/µl
and
HIV-RNA > 10,000 HIV copies/ml (RT-PCR/bDNA)</td><td>A) Clinical disease category B + C or
B) CD4 <200-350/µl or
C) CD4 >350-500/µl and
HIV-RNA >50,000-100,000 HIV copies/ml (RT-PCR/bDNA)</td><td>Women is getting pregnant while receiving an anti-retroviral combination therapy</td></tr>
<tr><td>Maternal treatment indication</td><td>NO</td><td>NO</td><td>YES</td><td>YES</td></tr>
<tr><td>Fetal indication for prophylaxis</td><td>YES (prophylaxis with standard risk)</td><td>YES (prophylaxis with raised maternal transmission risk)</td><td>YES</td><td>YES</td></tr>
<tr><td rowspan="4">Therapy: 1st -13th week of gestation</td><td colspan="4">Resistance testing to exclude primary ZDV resistance</td></tr>
<tr><td colspan="4">Invasive prenatal diagnostics only under anti-retroviral therapy/ prophylaxis
(perform only if absolutely indicated)</td></tr>
<tr><td colspan="2">No ART

At least bimonthly monitoring of CD4 + VL

Start of ART in case of urgent maternal treatment indication (see above)

Invasive prenatal diagnostics (strictly indicated !) only under anti-retroviral therapy/ prophylaxis</td><td>A) Immediate initiation of ART

At least bimonthly monitoring of CD4 / VL

Switch of ART in case of therapeutic failure
or
B) Initiation of ART after week 13, depending on the urgency of the maternal treatment indication (see below).

At least bimonthly monitoring of CD4 +VL

Start of the ART before week 13 in case of urgent maternal treatment indication</td><td>A) Interruption of ART if clinical, immunological and virological status of the mother allows (CAVE: Interruption of NNRTI with long half-life !!!)

At least bimonthly monitoring of CD4 and VL

Immediate restart of ART in case of urgent maternal treatment indication
or
B) Otherwise continuation of ART, if necessary substitution of efavirenz; substitution of stavudine or didanosine if given in combination

At least bimonthly monitoring of CD4 and VL</td></tr>
<tr><td>Therapy: 14th - 32nd week of gestation</td><td colspan="2"></td><td colspan="2">Beginning/ restart of ART e.g. with ZDV + 3TC/ ddI + PI / NVP or premedication,
if possible without EFV or d4T+ddI,

At least bimonthly monitoring of CD4 and VL,

Change of ART if therapeutic failure occurs</td></tr>
<tr><td>Therapy: 32nd - 37th (+0) / 37th (+6) week of gestation</td><td>A) ZDV (AI)
2 x 250 mg/d p.o.
B) HAART (BI) e.g. with ZDV + 3TC/ddI + PI / NVP; if possible without EFV or d4T+ddI</td><td>HAART e.g. with ZDV + 3TC/ddI + PI / NVP if possible without EFV or d4T+ddI</td><td colspan="2"></td></tr>
<tr><td>37th (+0) – 37th (+6) week of gestation</td><td colspan="4">Primary cesarean section
+ 1 mg/kg i.v. ZDV from 3h before cesarian until separation,
during the first hour a doubled loading-dose, i.e. 2 mg/kg
no ZDV if d4T is a component of the maternal therapy</td></tr>
<tr><td>Newborn with a complication-free birth process</td><td colspan="4">A): ZDV 4 x 2mg/kg/d p.o. for 2-4 weeks
B): ZDV 4 x 1.3 mg/kg/d i.v. for 10 days

Refraining from breast-feeding</td></tr>
</table>

ZDV, zidovudine; ART, anti-retroviral combination therapy with usually three medications: two nucleosidal reverse transcriptase inhibitors + a protease inhibitor (PI) or nevirapine; 3TC, lamivudine; ddI, didanosine; d4T, stavudine; NVP, nevirapine; EFV, efavirenz; VL, virus load

Table 3.2. Prevention of vertical HIV transmission in case of pregnancy - and birth complications.

Pregnancy : complication	**Complication-free multiple pregnancy with prophylaxis >4 weeks**	**Duration of maternal ART/ prophylaxis <4 weeks before birth**	**Premature labor, premature birth in ≥33rd (+0) - 36th (+6) GW**	**AIS/amnionitis (premature) rupture of membranes >4h, premature birth < 33rd (+ 0) GW**	**Viral load increase at the end of pregnancy >10 000 HIV copies/ml**	**Lacking prepartal prophylaxis**
HIV trans-mission risk	Normal	Raised	Raised	Very high	Very high	Very high
Measures in the 24th (+0) – 37th (+0-6) week of gestation	Prophylaxis onset brought forward with ZDV or ART after GW 29 (+0) because of the risk of premature birth		- Tocolysis, - if necessary antibiotics. - RDS-prophylaxis - **HAART** e.g. with ZDV + 3TC/ddI + PI/NVP if possible no EFV or d4T+ddI			
Birth: 37th (+0) – 37th (+6) week of gestation	(Elective) CS + 1 mg/kg i.v. ZDV starting 3 h before cesarean until birth, during the first hour a doubled loading-dose, i.e. 2 mg/kg			If still possible (decision dependent of obstetrical situation) cesarean within 4h after rupture of membranes; + 1 mg/kg i.v. ZDV from 3 h before cesarean until birth, during the first hour a doubled loading-dose, i.e. 2 mg/kg Prepartal 1x 200mg NVP° in addition to the ongoing ZDV prophylaxis or ART	Elective CS + 1 mg/kg i.v. ZDV starting 3 h before CS until birth, during the first hour a doubled loading-dose, i.e. 2 mg/kg Prepartal 1x 200 mg NVP° in addition to the ongoing ZDV prophylaxis or ART	
Postnatal prophylaxis of the newborn (108):	**4 weeks:** **Dosing with newborns:** ZDV 4x 2mg/kg/d p.o. Refraining from breast-feeding	**6 weeks:** **A) Dosing with newborns + premature babies ≥ 33rd (+0) GW:** ZDV 4x 2mg/kg/d p. o. **B) Dosing with premature babies < 33rd (+ 0) GW (109):** 2x 2mg/kg/d p.o. (or 2x 1.5mg/kg i.v.) **Dosing with premature babies > 28th (+0) GW: from 3rd week of life:** increase to 3x 2mg/kg/d p.o. **Dosing with premature babies ≤ 28th (+0) GW: from 4th week of life:** increase to 3x 2mg/kg/d p.o. Refraining from breastfeeding	**6 weeks:** ZDV 4x 2mg/kg/d (note premature born dosing) + 3TC 2x 2mg/kg/d* A) with successful prenatal NVP application ° a further NVP dose with the newborn (2mg/kg) at an age of between 48-72h B) If NVP° is not given prepartally, two NVP doses (each 2mg/kg) postnatally to the newborn: 1st Dose as soon as possible after birth, 2nd Dose on the 3rd day of life (no NVP, if NVP is a component of the maternal therapy during pregnancy) Refraining from breast-feeding		

Table 3.2. (continued)

Birth complications:	**- Incision injury to the child** **- Oral intake of bloody amniotic fluid into gastrointestinal or respiratory tract of the newborn**
HIV-transmission risk	Very high
Postnatal measures in the newborn:	**6 weeks:** ZDV 4x 2mg/kg/d (check premature born dosing wherever necessary) + 3TC 2 x 2mg/kg/d* **Two** postnatal **NVP doses°** (each 2mg/kg) to the newborn: 1st Dose as soon as possible after birth, 2nd Dose on the 3rd day of life (no NVP, if NVP is a component of the maternal therapy during pregnancy) Refraining from breast-feeding

*** Beware: Presently only a few clinical results have been published regarding the application and dosing of lamivudine with (extreme) premature infants.**
° Beware: if the HIV1-positive expectant mother has been treated for a longer period of time with nevirapine during pregnancy, an enzyme induction may occur that may lead to a more rapid breakdown of nevirapine in the newborn.
ZDV, zidovudine; ART, anti-retroviral combination therapy usually with three medications: two nucleoside reverse transcriptase inhibitors + one protease inhibitor (PI) or nevirapine; 3TC, lamivudine; ddI, didanosine; d4T, stavudine; NVP, nevirapine; EFV, efavirenz;
AIS, amnion infection syndrome

ternative the 2NRTI are continued over 4 weeks after stopping NNRTI (if possible under monitoring the NNRTI-level via therapeutic drug monitoring). Because a pregnancy is usually observed not before some weeks after conception an additional 4 weeks lasting procedure to interrupt an regimen with 2NRTI +NNRTI interferes with the avoidance of these drugs during organogenesis. Therefore a prompt interruption of NNRTI-containing regimens can hardly be arranged in the first 6-8 weeks of gestation (where most organs develop) and therefore can not be recommended. Nevertheless an interruption of a combination with NNRTI in the remaining weeks should be guided by an HIV-experienced infectious disease specialist to minimize the development of drug resistance.

The anti-retroviral treatment should not be resumed before the 13th (+0) week of pregnancy in order to take into account the uncertainties in the exact time of conception.

If a woman under anti-retroviral therapy has planned for a child, a pregnancy test (HCG) should be undertaken very early on. The pregnancy test becomes positive 6-8 days after conception, thus a decision to interrupt anti-retroviral therapy can be made accurately in time. On the other hand because the time until conception cannot be calculated and can last very long an anti-retroviral therapy should never be stopped before conception even when the pregnancy is planned.

If a HIV-positive women plans to get pregnant, if possible no Efavirenz containing ART should be started or Efavirenz containing regimes should be changed to regimens with other components (for example boosted PI ,Nevirapine) in time.

After interruption in the first trimenon therapy with the same drugs can be restarted (exceptions: efavirenz, combination of stavudine + didanosine, provided that therapeutic alternatives are available)[45, 46], since resistance development is not to be expected [32, 33] (AII,III).

These recommendations also apply if pregnancy is first diagnosed during the course of the 1st trimester.

3. HIV transmission prophylaxis with standard risk profile (see Table 3.1)

Prophylactic scheme (= no maternal treatment indication, criteria see Table 3.1!!!!):

3.1a) Viral load in the expectant mother < 10,000 genome copies/ml:

In this situation two alternative regimens can be used:

I. Zidovudine application from the completed 32nd (+0) GW at an oral dose of 2x250 mg.
II. Temporary antiretroviral combination therapy with 3 drugs (HAART, but if possible no Efavirenz) from week of gestation 32+0 until immediately after birth

Comments to oppurtunity I:
Provided that there is no primary resistance to zidovudine, a reduction of viral load at birth can be achieved under a zidovudine monoprophylaxis from a low initial virus load. This suffices - particularly in combination with a planned cesarean birth - for minimizing the risk of transmission to the child. The advantage in comparison with HAART is the lower risk of prophylaxis-associated toxicity for mother and child. Because of the short duration of this monoprophylaxis and of the comparatively high resistance barrier of zidovudine the risk of developing a resistance against zidovudine should be very low [68, 115]. In comparison to HAART the risk in monoprophylaxis (provided a good adherence to both regimens) is higher that viral load is not reduced sufficiently until birth.

Comments to oppurtunity II:
Under a temporary standard antiretroviral therapy (HAART) from week of gestation 32+0 until immedi-

ately after birth the low viral load can be decreased under limit of detection at birth with a high probability. Because of the long half life (which can induce resistance during an cessation after birth) and increased toxicity in patients with CD4-cells higher than 250/µl, this prophylactic HAART should not contain Nevirapine. Ideal for prophylaxis are regimens with a (boosted) PI. Provided a good adherence the risk of induction of a drug resistance is lower than in a monoprophylaxis with zidovudine. Disadvantage of a prophylaxis with HAART is the higher drug burden for mother and child, which can lead to more adverse effects and toxicities than in a monoprophylaxis. These complications can reduce adherence and then result in development of drug resistance [114]. On the other hand changed pharmacokinetics of antiretrovirals in pregnancy (published for Indinavir; for many other antiretroviral drugs no pharmacokinetic data in pregnancy exist) can induce drug resistance [61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 114].

In the decision to use a monoprophylaxis with zidovudine or HAART in pregnant women with a viral load < 10,000 genome copies/ml also the increased rate of prematurity under HAART must be taken into account [12, 132].

3.1b) viral load in the expectant mother >10,000 genome copies /ml:

The risk of vertical transmission is directly proportional to the viral load in the pregnant women. If there is not yet a distinct maternal indication for treatment (CD4 cell count >200-350/µl), but the viral load is higher than 10,000 virus copies/ml, a temporary antiretroviral standard combination prophylaxis (without efavirenz !) is recommended from GW 32 (+0) to immediately after delivery , since a zidovudine monoprophylaxis is not able to reduce the viral load with adequate certainty (raised risk of transmission with VL > 10,000 [5, 62, 71, 72, 73, 74]) (AI,II).

3.2 Primary cesarean section, utilizing an operation technique which avoids excessive bleeding, performed rapidly by the most experienced obstetrician available between 37 (+0) to 37 (+6) gestational week [75, 76]. The benefit of the elective cesarean section for transmission prophylaxis in patients under an anti-retroviral combination therapy or prophylaxis with a low viral load in the plasma, is not evidenced and is still a matter of dispute (see point 6 for a detailed discussion of the mode of birth) (AI,II).

3.3 Pre- and intra-operative intravenous zidovudine application starting 3 hours before cesarean section (2 mg/kg as a loading-dose for 1 hour followed by 1 mg/kg until the delivery of the child according to the original ACTG 076 protocol), even if zidovudine is not a component of the maternal therapy/ prophylaxis during the pregnancy [77] (AI,II).

3.4 Postnatal zidovudine application for the child over 2-4 weeks orally (2 mg/kg every 6 hours) or 10 days i.v. (1.5 mg/kg every 6 hours)[78] (AI, II, III).

Since a higher prevalence of zidovudine-resistant HIV-strains can be expected in the future [40], the presence of wild-type HIV should be confirmed genotypically in the expectant mothers before zidovudine is applied (exclusion of genotypic resistance).

4.Risk-adapted transmission prophylaxis
(see Table 3.2)

For birth-related HIV transmission risks, HIV transmission prophylaxis should be escalated in a risk-adapted manner.

4.1 Multiple pregnancy, premature labor and premature infants > 33rd week of gestation, duration of maternal ART/prophylaxis < 4 weeks before birth

Because of the increased risk of premature birth in multiple pregnancies, prophylactic zidovudine application should already be started from the 29th (+ 0) week of gestation (AIII).

In case of premature labor, anti-retroviral combination prophylaxis should be started immediately (with e.g. zidovudine + lamivudine + PI), if the pregnant women is not yet receiving a combination therapy, if a cesarean birth is not indicated because of immaturity of the baby and if labor can still be stopped (AIII).

If a premature birth is unavoidable, the procedure described in 4.2 should be followed.

The recommended mode of birth is cesarean section (AI/III).

If the prenatal part of the anti-retroviral prophylaxis regimen is considerably shorter than 4 weeks due to premature birth, the postnatal prophylaxis should be prolonged according to the ACTG 076-study protocol where zidovudine is applied over 6 weeks orally [14, 63]. The newborn should be closely monitored during this prolonged prophylaxis. If problems such as anemia, neutropenia or lactate acidosis occur, benefits and risks of continuing the prophylaxis should be carefully weighed, and in doubt prophylaxis should be discontinued.

4.2 Amnion infection syndrome/amnionitis, (premature) rupture of membranes >4h, premature birth <33rd + 0h GW and viral load increase at the end of pregnancy > 10,000 HIV copies/ml.

In these obstetric emergency situations the transmission risk is greatly increased [3, 15, 16, 79]. The prepartal part of the prophylaxis should (as long as a standard combination therapy/prophylaxis is not already being given) be intensified by an (additional) dose of nevirapine* as long as this is still possible.

Postnatally, transmission prophylaxis can also be escalated in the newborn through application of nevirapine in addition to a combination prophylaxis with zidovudine + lamivudine [82, 83, 84]. In this case one dose of nevirapine should be given to the newborn after 72h if the mother has already received one dose prepartally. Two doses should be given if the mother did not receive a prepartal dose or if less than two

* *Birth risks:* Twin pregnancy, birth obstacles, repeated vaginal infections; possible birth complications: prolonged delivery, intrauerine bleeding.

hours have elapsed between nevirapine application to the mother and birth [80, 81]. If two doses are given, the first should be given immediately -and the second within 72h after birth (AI,III). If the HIV-positive expectant mother was treated with nevirapine during the pregnancy for a longer period of time, an enzyme induction might result in the newborn so that a more rapid breakdown of nevirapine occurs [53]. For this reason, with longer nevirapine therapy of expectant mothers during pregnancy, the drug must be applied at higher doses to the newborns (4 mg/kg).

The preferred mode of delivery is immediate cesarean section if the rupture of membranes does not already date back longer than 4 hours. For intervals >4 h after (premature) rupture of membranes, no advantage of cesarean section regarding transmission risks can be expected [85]. However, the decision to implement this must be based on obstetric considerations.

Rupture of membranes between the 24th and 28th gestational weeks represents a particularly problematic special case. Steroid induced pulmonary maturation in the unborn is not effective before 24 hours after application and therefore contradicts measures required for preventing HIV transmission. In this case the high risk of permanent damage to the child due to lacking pulmonary maturation and the increased HIV transmission rate must be carefully weighed up.

4.3 Incision injury to the child/ aspiration and/or ingestion of bloody amniotic fluid

With an incision injury to the child during caesarian section, or if bloody amniotic fluid can be aspirated from the stomach and/or the lungs, a percutaneous inoculation or a mucosal exposure to virus-containing body fluids must be assumed [23]. This justifies an intensification of the usual standard pediatric prophylaxis to a combination prophylaxis consisting of two NRTI-s consistent with post-exposure prophylaxis recommendations for adults [86] (AIII). An extended application of nevirapine (exceeding the ultra-short prophylaxis) for post-exposure prophylaxis can not be recommended at this time because of the lack of data regarding pharmacokinetics and safety.

Because of the lack of experience and formal approval of protease-inhibitors and NNRTIs for the therapy of newborns, and because of the dearth of comparative studies on the efficacy of double NRTI and triple drug post-exposure prophylaxis regimens, the recommendations for treatment escalation are limited to measures that have been proven effective and tolerable within the context of mother-to-child transmission prophylaxis.

5. Procedures with incomplete transmission prophylaxis

5.1 With verified HIV-infection

If despite of a known HIV-infection no transmission prophylaxis has been carried out until the time of birth, this should be done at the latest during delivery and postnatally. A benefit for the newborn can even be expected with incomplete transmission prophylaxis [63, 64, 87, 88, 89]. A combination of a nevirapine ultra-short prophylaxis (one dose prepartally for the mother, one dose postnatally for the newborn or 2 doses postnatally) with a six-week zidovudine or zidovudine + lamivudine application for the newborn is then recommended (AI).

According to data from the HIVNET 012 study, a single dose of nevirapine shortly before birth combined with a single dose given to the newborn within 72 hours of birth is more effective in preventing vertical transmission than the immediate pre- and intrapartal administration of zidovudine combined with a week long postnatal administration of zidovudine to the newborn [87]. (Measures of maternal short time nevirapin prophxlaxis see also 4.2/footnote)

Zidovudine therapy started within 48 hours of birth according to the ACTG 076 protocol (application over 6 weeks) can still lower the HIV transmission rate. In a retrospective US study a transmission rate of 9.3 % has been reported with initiation of zidovudine therapy in the first 48 hours after vaginal delivery, as compared to a rate of 18.4% for a later onset of therapy (>48 h). Without any therapy, 26.6 % of the children became infected.

5.2. Situation with an unclear HIV infection status

If a patient presents late in her third trimester without HIV-Test and sufficient time remains to perform a screening test (and if necessary a confirmatory test), this should be offered without delay, so that intrapartal and postpartal transmission prophylaxis can be carried out whenever the test proves positive [64].

The HIV-antibody test should be accompanied by competent personal counseling, provided if necessary by an appropriate institution [1, 2]. The refusal to undergo HIV-antibody testing must be respected.

In cases when the HIV status of the pregnant women is unknown and there is no time to carry out regular testing and counseling, the experts were unable to reach a consensus on the recommendations to be made (no expert consensus !).

In this case, there are three possible options:

- No prophylactic measures, as long as no HIV test results are available(CIII)
- With unambiguous anamnestic risk factors, prophylactic measures should be offered (such as cesarean birth, application of medications). Cessation of measures, as soon as HIV infection is ruled out by testing (CIII).
- An HIV rapid test can be offered and prophylactic measures can be instituted with positive rapid test results, but this should be ceased if the confirmation test proves negative (CIII).

Attention to the predictive value of rapid HIV-tests: The HIV prevalence in pregnant women in Germany is estimated to be 0.5 to 06 per 1,000 in bigger cities and 0.1 to 0.2 per 1 000 in the remaining areas [90]. Even with the high specificity of the two rapid tests approved in Germany (99,7 %, 3 false-positive results per 1,000 tests), the predictive value of a positive rapid

test is small in the absence of other anamnestic risk factors (in an unselected population it would be expected that only approximately a fifth to a third of the rapid test positives are true positive!). This must of course be considered when the expectant mothers are being counseled and informed of the findings.

An opportunity to further increase the specificity arises from controlling a positive rapid test finding with a second rapid test procedure. If the second test reports a negative finding, the probability is high that the first test result was false positive.

6. Mode of delivery

Delivery by elective cesarean section (before the onset of labor) results in a reduction of the vertical transmission risk by approximately 50%, i.e. in a 8.2% vs.16.8% risk associated with vaginal birth [76]. Elective Cesarean section should therefore represent an essential component of every prophylactic HIV-transmission regimen (AI, II). Preliminary and still unpublished studies have shown no measurable additional protective effect of cesarean birth amongst expectant mothers with very low (VL < 1000 copies/ml) or not detectable VLs and a complication-free birth process [91]. The expectant mothers should be informed about these findings when being counseled about the optimum mode of birth, although it should also be pointed out that the risks of birth complications and/or of a low/ local viral load at birth are lower with a cesarean section [21, 23, 92, 93, 94, 95, 96, 119, 120, 121]. Up to now experience suggests that a raised complication rate on cesarean section compared to non-HIV1 positive expectant mothers is not to be expected [97, 98, 99, 100]. But a new, big prospective study showed higher rates of peritonitis, and anemia after caesarian section in HIV1-positive - than after caesarian section in HIV1-negative pregnant women as well as in HIV1-positive women after vaginal birth [117]. In comparison to HIV1-positive pregnant women with vaginal birth that HIV-positive women with cesarian section had more often fever, hematomas and complications in healing of her section wound (even when they were treated with HAART) [118].

Preoperative/ intra-operative i.v. zidovudine therapy of the mother at a dose of 1 mg/kg/h after a loading-dose of 2 mg/kg over 1 hour until delivery also represents a prophylactic measure (AI, AII).The elective, primary cesarian section should be carried out by the most experienced obstetrician available utilizing an operation technique which avoids excessive bleeding, performed between 37 (+0) to 37 (+6) gestational week on a labor-free uterus under i.v. application of zidovudine.

Because of lower maternal complications (pneumonia/fever) and the possible early bonding in delivery room a local anesthetic procedure (f.e. spinal anesthesia) is preferably recommended [97].

It should be noted that an increased rate of premature birth has been documented on several studies in mothers treated with an anti-retroviral combination therapy [101]. However, two large American studies [5, 36] failed to find an increased rate of premature birth under HAART. Considering these contradictory findings, special attention must be paid towards women with anti-retroviral combination therapy or other risk factors for premature birth in the last trimester so that a premature birth or other emergency mode of birth under unfavorable conditions can be avoided. This is warranted by frequent antepartum controls in the third trimester and ,under certain conditions, early hospitalization.

It is urgently recommended that an HIV post-exposure prophylactic emergency set be kept in stock by the hospital and that all medical personnel involved is informed about indications and procedures related to HIV post-exposure prophylaxis after occupational HIV exposure (e.g. following needle prick or knife injuries to the operating surgeon).

7. Care of the newborn in the delivery room

Amniotic fluid can be contaminated with HIV-1 by the opening of the amniotic sac during both a spontaneous delivery and a cesarean section. With a vaginal delivery there is also the possibility that virus-containing vaginal secretions or maternal blood gain access to the body openings of a child [23, 93]. Unlike adults, the mucous membranes of the respiratory and gastrointestinal tracts do not represent barriers to HIV in the newborn, and the still anacidic stomach can fail to inactivate the virus. Higher transmission rates from HIV-infected mothers to breast-fed (as opposed to bottle-fed) children confirm that the oral uptake of virus-containing fluids plays a considerable role in vertical transmission [102].

Practical procedure in the delivery room:
The use of sterile gloves is recommended for initial treatment. Before suction of the mouth, the oral cavity and the nostrils should be cleaned of any potentially HIV-1 contaminated amniotic fluid using sterile swabs soaked in 0.9% physiological saline. After stabilization of vital functions, all body openings (ears, eyes, anus and genitals) should be cleaned in the same way.

Before the final severance of the umbilical cord, gloves must be changed in order to avoid any HIV-contamination of the umbilical stump (AIII).

8. Postnatal transmission prophylaxis in case of standard risk

The recommendation of oral zidovudine application over 6 weeks to the child at a dose of 2 mg/kg every 6 hours results from the findings of the ACTG 076 study [14]. After oral zidovudine application during pregnancy, intravenous zidovudine infusion during birth, and elective cesarean section, this represents the fourth component of HIV transmission prophylaxis. A de-escalation of the six-week postnatal component (according to the ACTG-076 protocol) of the transmission prophylaxis is justified by the results of a study carried out in Thailand involving a shortened zidovudine regimen and considering experience gained in Germany until now. The Thai study showed that the six week therapy produced an additional benefit as compared to a three day postnatal zidovudine dosing when the duration of prepartal prophylaxis was very

short (from the 36th week of gestation with spontaneous delivery as the predominant mode of birth) [63]. In Berlin, satisfactory results (no transmissions) have been achieved (involving a small number of cases, n = 57 [78]) with an i.v. dosing of 1.3 mg/kg every 6 hours over 10 days if the prepartal prophylaxis was started in the 32nd week of gestation. The majority of experts conclude from this that postnatal zidovudine should be given to the child, although they consider a reduction of the duration of postnatal zidovudine transmission prophylaxis to 2 to 4 weeks (2 mg/kg orally every 6 hours) as usually sufficient (AI, III). Exceptions to this rule include pregnancy and birth complications as well as failure to implement a maternal prophylaxis (see 4.2, 4.3 and 5.1).

9. Refraining from breast feeding

Breast-fed children of HIV-1-positive mothers are infected twice as frequently as formula-fed children of HIV-1 infected mothers. The HI viruses and HIV infected lymphocytes detectable in breastmilk as well as inflammation/injuries of the nipple or the mammary gland involving exudation of infectious wound secretion/ blood contribute to this raised infection rate. The WHO therefore recommends that babies of HIV-infected mothers should be fed with formula food in industrialized countries with clean drinking water. All HIV-positive mothers should therefore be urged to avoid breast feeding [103, 104, 105] (AI,II).

10. Postnatal care of the HIV-exposed child and preparation of a surveillance register

From the 32nd week of gestation IgG antibodies, including also IgG antibody against HIV-1, are transmitted from the mother to the fetus across the placenta. Since the conventional HIV-1 test is an antibody test, all, i.e. even non-infected children of HIV-1-infected mothers, are serologically HIV-1 positive until the maternal antibodies disappear.

Detection of HIV-1 during the first two years of life must therefore be completed using HIV1-PCR based methods. It is possible to detect either HIV-1 DNA or HIV-1 RNA. Up to now it is unclear which test procedure is the more sensitive with respect to the special situation of neonatal infection diagnostics. All positive HIV-1 test results should be confirmed as rapidly as possible by a second blood test.

It should be noted that commercially available HIV-PCR kits do not cover all HIV-1 subtypes or mosaic viruses (not subtype B) and may provide false negative results [106]. With an HIV-1-positive parent that might be infected with a subtype other than B (especially if the patient originates from outside Western Europe or North America), the maternal blood must always be analyzed as a positive sample in addition to the child's blood (if possible before the onset of an anti-retroviral therapy/ prophylaxis of the mother!).

If the maternal blood is unambiguously HIV-1-positive in the PCR, the result of the HIV-1-PCR of the child should also be utilized. If the detection of HIV-1 nucleic acids fails with maternal blood (negative or borderline findings), the HIV-1 PCR analysis of the child's blood can not be relied upon. Then, either a special examination must be initiated using subtype-adapted PCR primers in specialized laboratories, or the disappearance of the maternal HIV-1 antibody at the end of the 2nd year of life must be waited for in order to reliably exclude an HIV-1 infection in the child.

If the HIV-1 antibodies in the HIV-1 exposed child persist, an HIV-1 infection must be assumed. As a matter of definition, HIV-1-exposed children are regarded as HIV-1 negative if an HIV-1 Western blot proves completely negative with normal immunoglobulin concentrations.

Amongst children of HIV-1 positive mothers, two negative HIV-1 PCR findings are required to exclude an HIV-1 infection. The first HIV-1 PCR should be performed one month after birth (in the age of 28 days: sensitivity 96%, specificity 99% [129]); the second one after the third month of life, because at this timepoint the sensitivity and specificity of the HIV-1-PCR is considered to be sufficiently high [107].

With the HIV-1-PCR test in the first month of life a high rate of HIV1-infected children can be diagnosed. This is important for starting prophylaxis against Pneumocystis carinii as early as possible (if possible 4-6 weeks after birth where HIV transmission has occurred) and the early-life anti-retroviral therapy in the first months of life.

With negative HIV-1 PCR findings as well, disappearance of maternal antibodies in HIV-1 exposed children should be documented at least once.

It must be stressed here that because of the intrauterine and postnatal exposure of a child to anti-retroviral substances with still unknown long-term consequences, clinical surveillance of the children is indispensable to get aware of any long-term damage.

11. Hotline, notification of unexpected observations and experiences

Honorary telephone hotline for problems regarding HIV infections during pregnancy and in HIV-exposed newborn:

Gynecologic problems: 0178 - 282 0 282
Pediatric problems: 0178 - 41 21 313

Further updating of the recommendations:

Since only little or even no results or information are available regarding the application of newer drugs or combinations of drugs during pregnancy or in newborns, all physicians involved in this work are urgently invited to inform us of any new or unexpected observations and results, e.g. by notifying us by e-mail at the address given in the "address for correspondence", or by notifying the "anti-retroviral Pregnancy Registry" (APR), the largest register for recording experiences with anti-retroviral substances during pregnancy:

Tel.: +1-910-256-0238
Fax: +1-910-256-0637 or +44 1895 825 005
Website: www.APRegistry.com

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Address for correspondence:
Dr. med. Bernd Buchholz
HIV-Ambulanz der
Universitätskinderklinik Mannheim
Theodor-Kutzer-Ufer 1-3
68135 Mannheim
Tel.: 0049-(0)621-383-2366
Fax: 0049-(0)621-383-3829
e-mail: bernd.buchholz@kikli.ma.uni-heidelberg.de