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National Guidelines for the prevention of mother-to-child transmission of HIV across Europe – how do countries differ?

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Objectives: The aim was to summarize national prevention of mother-to-child transmission (PMTCT) guidelines across Europe and to identify differences between these. **Methods:** A survey was conducted using a structured questionnaire sent to experts in 25 European countries from January to March 2012, requesting a copy of the national guidelines. Responses were received from 23 countries. **Results:** Twenty-two (96%) countries supported a policy to recommend antenatal HIV screening for all pregnant women (15: opt-out strategy; 8: opt-in strategy). For HIV-positive women in whom the only indication for antiretroviral therapy (ART) was PMTCT, the recommended gestational age for commencing ART varied from 12 to 28 weeks: initiation before 19 weeks gestation was recommended in guidelines from nine countries; in France, the UK and the Netherlands, there was a wide range, from 14 to 24 weeks, whereas the Swiss and Ukrainian guidelines recommended starting at 24–28 weeks and the German/Austrian and Lithuanian at 28 weeks. Six national guidelines recommended inclusion of Zidovudine in antenatal ART regimens, and seven (37%) allowed continuation of Efavirenz for women conceiving on this drug. According to nine guidelines, zidovudine should always be used intrapartum. Eighteen national guidelines stated that HIV-positive women on successful ART can have a vaginal delivery. Viral load thresholds for vaginal delivery were <1000 copies/ml in 5 countries, <400 copies/ml in 3 and <50 copies/ml in 11 countries. **Conclusion:** There are important differences across Europe in national PMTCT guidelines, with most variation seen where the evidence-base remains limited. Such differences should be considered when interpreting research and surveillance findings.

Introduction

HIV infection remains of major public health importance in Europe, with a continued increase in the reported diagnosed HIV cases. According to the UNAIDS (Joint United Nations Programme on HIV/AIDS) estimates, there were 820 000 people living with HIV in Western and Central Europe and 1.4 million in Eastern Europe and Central Asia in 2009, whereas together, the Russian Federation and Ukraine contribute >80% of all HIV infections in this region.[1] In the European Union and European Economic Area (EU/EEA), 27 116 new HIV infections were diagnosed in 2010 and the highest rates of new infections in EU/EEA were reported by Estonia (27.8), Latvia (12.2), Belgium (11.0) and the UK (10.7).[2]

More than one-third of HIV-infected women in Europe are of childbearing age, but there are relatively limited data on antenatal HIV prevalence across Europe. In the UK, estimated HIV prevalence in women delivering is ~0.4% in London, 0.1% elsewhere in England and 0.05% in Scotland,[3] whereas this figure was 0.17% in 2009 in Catalonia, Spain[4] and 0.7% in St Petersburg, Russia in 2010.[5] Advances in prevention of mother-to-child transmission (PMTCT) of HIV and improved survival and quality of life owing to antiretroviral therapy (ART) have led to increasing numbers of women with HIV deciding to have children.[6–8] Strategies for PMTCT are therefore highly important.

The development of clinical guidelines for the management of pregnant women with HIV and their infants has become an important and effective tool for implementation of effective

PMTCT services. Guidelines for PMTCT have been developed at a national level across most of Europe and are adapted to the country's specific needs, and human and economic capacities are mainly available in the national language.

During the past decade, widespread use of antenatal combination ART (cART) has been associated with mother-to-child transmission rates below 1–2% on a population level in many European countries.[9–13] Consequently, most recent European national guidelines have changed to include the recommendation of vaginal delivery instead of elective caesarean section (CS) for women with undetectable or very low HIV viral load (VL) and after exclusion of other potential risk factors.[14,15]

Although PMTCT policies have recently been compared between some countries in Central and Eastern Europe,[16] and antenatal HIV screening policies have been assessed across Europe several times during recent years,[17–19] to date there has been no attempt to contrast and compare national PMTCT policies across Europe as a whole. The aim of this study was to ascertain and summarize national PMTCT guidelines across Europe, with a main focus on temporal and geographical patterns of antenatal ART and mode of delivery and to identify international variability. This should facilitate the interpretation of research findings from different countries and the identification of areas with limited evidence.

Methods

We conducted a survey between January and March 2012 using a short structured questionnaire sent by email with a letter, requesting collaboration, to experts (mainly infectious diseases specialists or obstetricians at university hospitals) in 25 European countries, chosen to represent all European regions (as defined by United Nations) and with those countries with the greatest HIV burden included. Those experts were identified through established clinical HIV networks: PENTA (Paediatric European Network for Treatment of AIDS) and EPPICC (European Pregnancy and Paediatric HIV Cohort Collaboration in EuroCoord) and SHE (Network of Strong, HIV positive, Empowered women, www.shetoshe.org). Additionally, we asked for a copy of the national guidelines to validate the survey responses. Those were reviewed in terms of the correlation to the expert's answers. The questionnaire was designed to obtain descriptive information about national policies regarding pregnancy and mode of delivery in HIV-infected women.

The survey included specific questions on the following issues: antenatal HIV testing strategies, recommended timing of ART initiation during pregnancy for women only requiring this for PMTCT, substitution of Efavirenz if treatment containing this drug was on-going at conception and during pregnancy, vaginal delivery in HIV-infected women and the applicable HIV ribonucleicacid threshold, recommended mode of delivery with hepatitis C virus (HCV) co-infection, option of Zidovudine (ZDV) monotherapy during pregnancy, use of intrapartum ZDV and duration and composition of infant prophylaxis. Experts who did not respond within one month were reminded by email. Following non-response after a reminder, an alternative expert from that country was contacted in two cases.

We obtained answers from 23 of 25 countries with a response rate of 92%. Survey responses were available for the following 23 countries: Belgium, Denmark, Estonia, Finland, France, Germany/Austria (conjoint guidelines), Greece, Hungary, Ireland, Italy, Lithuania, Moldova, Norway, Poland, Portugal, Russia, Slovakia, Spain, Sweden, Switzerland, The Netherlands, UK and Ukraine. No response was received from contacted experts from Bulgaria or Romania. Of the 23 countries for which questionnaires were returned, 19 had national written guidelines, published between 2007 and 2011. No official country-specific guidelines existed in Belgium, Estonia, Finland and Slovakia (confirmed by the appropriate national experts). As antenatal HIV testing policies are a component of national antenatal care policies (i.e. not HIV-specific), we present results on policies for HIV testing in pregnancy for all 23 countries. All other results are restricted to the 19 countries with national written guidelines.

Results

Testing strategies for HIV during pregnancy

In all but one (22 of the 23) countries, there was a policy to recommend antenatal HIV screening for all pregnant women; the exception was in 'Hungary', where testing was performed only if requested by the mother. Of the 22 countries with universal recommendation of HIV testing in pregnancy, in the majority ($n = 16$, 73%), there was an opt-out screening strategy (table 1); under this approach, pregnant women are told that a HIV test will be included in the standard routine prenatal tests and that they may decline the test. Unless they decline, they will undergo HIV testing. In the remaining seven (32%) countries, there was an opt-in policy, whereby HIV testing is offered by the physician or other health care professional and can only be carried out with specific informed consent from the woman. In Russia, pregnant women are in general asked to sign an informed consent for HIV testing during pregnancy. The year when the current national recommendations for antenatal HIV screening were adopted are shown in table 1 where available and varied between 1987 in Sweden and Norway to 2010 in Denmark, where a universal opt-out strategy was introduced following a previous policy of selective screening (i.e. of specified risk groups).

Start of ART during pregnancy in women not requiring treatment for their own health

Use of antiretroviral treatment or prophylaxis during the antenatal period was recommended for all HIV-infected pregnant women, regardless of plasma HIV ribonucleicacid level or CD4 cell counts in all national guidelines reviewed ($n = 19$). The recommended gestational age for commencing ART during pregnancy varied between 12 and 28 weeks of gestation for HIV-infected women in whom the only indication for ART was PMTCT (table 2). In nine (47%) of the countries surveyed, there was a policy to advise initiation of prophylactic ART at circa 14 weeks of gestation. Although the German/Austrian guidelines had the recommendation to routinely start prophylaxis at 28 weeks of pregnancy, they did advise an earlier

Table 1 HIV-testing strategies recommended for pregnant women in 22 countries with policy of universal recommendation for antenatal HIV testing (years when national recommendations were adopted)

Opt-in strategy	Opt-out strategy
France (1992)	Belgium
Germany/Austria (1989)	Denmark (2010)
Greece (1996)	Estonia (1991)
Moldova (2004)	Finland (1998)
Poland	Italy (2001)
Russia	Ireland (1999)
	Lithuania (2002)
	Norway (1987)
	Portugal (1996)
	Slovakia (1991)
	Spain (1995)
	Sweden (1987)
	Switzerland (2003)
	The Netherlands (2004)
	UK (England 2000)
	Ukraine

start (24 gestational weeks) in cases of high maternal HIV VL or risk factors for preterm delivery.

Use of ZDV and Efavirenz

In the majority ($n = 14$, 74%) of countries surveyed, there was not an explicit recommendation that ZDV should be included in all antenatal ART regimens for women in receipt of combined ART. However, this was the case in five (26%) countries (table 3). In eight (42%) countries, there was a recommendation for intrapartum use of oral (if not available intravenously) or intravenous ZDV for all HIV-positive women (table 3). ZDV monotherapy coupled with an elective CS was considered to be an appropriate management option for a selected group of women with low VL in three countries (UK below 10 000 c/ml, Lithuania below 1000 c/ml, Ireland undetectable; table 3). In 13 (68%) countries, it was recommended that Efavirenz-containing regimens should be avoided in women who are planning a pregnancy, and that women on such regimens at conception should be switched to a different drug (table 3).

Table 2 Recommended timing of ART start during pregnancy in women without indication for therapy for their own health

Gestational weeks				
12–14 weeks	**14–18 weeks**	**20–24 weeks**	**24–28 weeks**	**28 weeks**
Italy	Sweden	Ireland	Switzerland	Germany/Austria
Poland	Norway	Moldova (22–24)	Ukraine	Lithuania
Portugal	Denmark			
Greece	Spain			
	Russia (16–18)			
	Hungary (16–18)			
	14–24 weeks			
	France			
	UK			
	The Netherlands			

Vaginal delivery in HIV-infected women

In most ($n = 18$, 95%) countries surveyed, national guidelines included the recommendation that HIV-positive women on successful cART with a very low or undetectable VL can have a vaginal delivery. Countries incorporated this recommendation into their national guidelines at different times (table 4). Experts reported that practice changes proceeding policy change were common regarding vaginal deliveries. In Greece, the national guidelines continue to recommend elective CS as the preferred mode of delivery in HIV-infected women without mentioning the option of vaginal delivery.

Maternal VL at 36 weeks of pregnancy was an important factor when deciding on mode of delivery in most (12, 63%) countries, whereas experts of the Netherlands suggest that women without an undetectable HIV VL at 36 weeks can still be considered for a vaginal delivery if they achieve an undetectable VL at term. In Moldova, the decision about mode of delivery is made on the basis of VL measurement at 38 weeks of gestation. In contrast, the Swiss guidelines recommend having an undetectable HIV VL for three consecutive measurements before delivery, whereas the Italian guidelines recommend that decision making regarding mode of delivery is made between 30 and 34 weeks of gestation. The Lithuanian guidelines suggest that vaginal delivery should be available on maternal request, if the VL was undetectable during several measurements for 4–6 weeks before the estimated date of delivery. Danish guidelines showed that elective CS is the preferred mode of delivery in any HIV-infected women, but the mother can opt for vaginal delivery if the VL is below 1000 copies/ml at 36 weeks of pregnancy. In Russia, the national policy is to perform an elective CS if the VL at 38 weeks is above 1000 copies/ml. There are countries, where the guidelines would allow vaginal delivery under certain circumstances if requested by the mother (e.g. Denmark, Lithuania and Poland), whereas elsewhere, the national guidelines encourage women to favour vaginal delivery under optimal circumstances.

In case of HIV/HCV co-infection, elective CS was recommended as the most appropriate mode of delivery in 10 (53%) countries (France, Greece, Hungary Ireland, Italy, Lithuania, Moldova, Norway, Sweden and Switzerland). In the remaining nine countries, the guidelines specified the option of vaginal delivery in

Table 3 Recommendations regarding use of ZDV and Efavirenz

ZDV	Antenatal cART should contain ZDV	Greece, Hungary, Lithuania, Russia, Spain, Ukraine
	Intrapartum use for all women	Greece, Italy, Lithuania, Moldova, Portugal, Russia, Spain, Ukraine
	Intrapartum use only for specific scenarios	Denmark, France, Germany/Austria, Hungary, Ireland, Norway, Poland, Sweden, Switzerland, The Netherlands, UK
	ZDV monotherapy plus elective CS for selected groups	Ireland, Lithuania, UK
Efavirenz	Stop Efavirenz if pregnant	Denmark, France, Germany/Austria, Greece, Hungary, Italy, Lithuania, Poland, Portugal (if <10 weeks), Russia, Spain, Switzerland, Ukraine
	Continue Efavirenz if virologically stable	Ireland, Moldova, Norway, Portugal (if >10 weeks), Sweden, UK, The Netherlands

Table 4 Year of published guidelines including recommendation for vaginal delivery in HIV infected women with suppressed VL. Table does not include Belgium, Estonia, Finland and Slovakia (no written guidelines) and does not include Greece (recommend CS) and Russia [vaginal delivery (VD) if VL < 1000 c/ml]

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

HIV/HCV co-infected women, if HIV VL was completely suppressed.

Infant prophylaxis

ZDV monotherapy as a suspension two to four times daily for 4–6 weeks for the infant was the recommended prophylaxis in most situations (14 of the 19 countries, 74%). In countries with capacity to do those analyses ZDV monotherapy was advised provided that supressed maternal VL and no resistance to ZDV was shown. Guidelines of Moldova and Ukraine advised 1 week ZDV prophylaxis. Of note, in the remaining countries, most ($n = 12$, 63%) national guidelines recommended shorter durations of $\leq$4 weeks. In the Netherlands, the recommendation was for 4 weeks of neonatal prophylaxis with dual therapy [ZDV and 3TC (Lamivudine)].

Discussion

Written national guidelines for the management of HIV-infected pregnant women and their infants existed in 19 of the 23 European countries participating in our survey. Although these guidelines largely agreed on general management of pregnant women, they differed in some important aspects. Reasons for this are likely to be multiple, but a major explanation is the lack of randomized clinical trial (RCT) data to answer specific management questions in HIV-positive pregnant women resulting in a reliance on observational data and expert opinion for some management issues. In some cases, there is RCT evidence, but this may be 'historic' and less relevant for the contemporary population of HIV-positive pregnant women in Europe, of whom >90% use cART.[10]

Identification of HIV-positive pregnant women is the critical entry point to PMTCT services, as reflected in universal antenatal HIV testing policies throughout Europe, which is a cost-effective strategy.[20–22] Opt-out strategies, adopted by most countries here, have led to remarkable increases in antenatal testing rates [23,24] and have the added benefit of encouraging 'normalisation' of HIV testing in the general population and reducing stigma associated with testing. However, it is important that pregnant women are aware of the system in place and how to opt out, to avoid involuntary testing.[25] Increasing proportions of pregnant women with HIV are already aware of their status before conception, in many cases following antenatal diagnosis in a previous pregnancy.[26] Not all diagnosed women will be on ART at conception, and recent studies have demonstrated some concerning findings regarding this group of women, including an increased risk of late initiation of antenatal ART, possibly reflecting disengagement from HIV care after their earlier pregnancy.[27,28]

In 2009, rapid advice from the World Health Organization (later incorporated into the 2010 World Health Organization guidelines for use of antiretroviral drugs in pregnancy) recommended that prophylaxis should start as soon as possible in the second trimester in women only needing antiretroviral drugs for PMTCT.[29] Although there was no RCT evidence behind this advice, the expert group determined that the body of observational evidence was sufficient to make this recommendation. The current US Department of Health and Human Services (DHHS) guidelines suggest starting antiretroviral prophylaxis at 10–12 weeks of pregnancy, regardless of maternal VL, reflecting findings that early control of HIV replication in pregnancy is associated with decreased transmission in women with undetectable VL at delivery.[30] However, the European AIDS Society recommends start of prophylaxis at 28 weeks in women without treatment indication, or earlier with high VL,[31] which is considerably later than most national guidelines evaluated here, with the majority recommending start before 24 weeks.

With respect to type of antenatal ART for PMTCT, cART predominates across Europe, with few women in Western Europe now receiving ZDV monotherapy[9] and only three national policies including recommendation for ZDV monotherapy in specific situations. In Ukraine, a lower-middle income setting, although national policy has recommended cART for PMTCT since 2007, ~40% of HIV-positive women delivering in 2010 received ZDV monotherapy, most likely reflecting limited availability of cART.[32] Such findings underscore the need to take into account factors such as health economics, as well as epidemiology; for example, the number of pregnancies in HIV-positive women per year ranges from ~5000 in Ukraine, to 1500 in the UK, to <20 in Hungary. Our finding regarding use of Efavirenz in pregnancy most likely reflects the fact that some experts remain concerned about the possibility of birth defects[33,34] associated with Efavirenz exposure, despite the Antiretroviral Pregnancy Registry having identified no increased risk.[35] The very low mother-to-child transmission rates in women on cART with very low or undetectable VL, irrespective of mode of delivery,[9,14,36,37] led to modification of mode of delivery policies in Europe, which previously recommended delivery by elective CS. A European study demonstrated national differences in mode of delivery practices (based on data up to 2007), for example, with higher elective CS rates in Italy and Spain than in Northern Europe in the cART era.[14] By the time of this survey in 2012, we found almost complete consensus on the recommendation of planned vaginal delivery for women on cART with low or undetectable VL; as expected, given the findings by the European Collaborative Study, a prospective cohort study of pregnant women with HIV, there was a wide time variation by country in the year of recommendation. Of note, a European pooled analysis and a single centre Spanish study both highlighted that obstetric practice does not always follow policy, with some women eligible for vaginal delivery undergoing CS.[15,38] Furthermore, in the HIV-infected pregnant population in Europe, there are missed opportunities to achieve full suppressed VL at time of delivery,[10,28,36] and therefore to deliver vaginally.

Although we show widespread use of ZDV monotherapy for neonatal prophylaxis in most situations, use of combination neonatal prophylaxis in situations where the infant is perceived to be at high risk of infection is increasing across Europe; in a recent pooled analysis of >5000 high risk mother–infant pairs, a quarter of neonates received combination prophylaxis.[39]

Our analysis of PMTCT policy approaches across Europe was cross-sectional, and it is important to consider that some guidelines have been updated more recently than others, with the oldest last updated 4–5 years ago. Clinical guidelines should reflect up-to-date knowledge, and most guidelines are therefore regularly updated.[40,41] The constantly expanding evidence base on HIV, pregnancy and PMTCT and the considerable time and effort needed to update guidelines explains the time interval between updated versions (e.g. British, 2008 and 2012; Spanish, 2007 and 2012; German, 2008 and 2011; Switzerland, 2004 and 2009). Thus, some examples of varying recommendations across countries may partly reflect the relative timing of the publication of new evidence versus the year of publishing the guidelines. Other factors behind differences in clinical guidelines may include different methods of evaluating the literature and the subsequent interpretation of this evidence.

This survey is limited by its cross-sectional nature, and interpretation needs to take account of the fact that we have described policies and not practices. We did not examine implementation of guidelines or different practices between or within countries. Furthermore, we restricted our synthesis of policies to those countries with a written national policy.

Conclusion

This is the first study comparing guideline recommendations for PMTCT across Europe. These findings are of interest to identify discordance in guidelines indicating areas where more research is

needed and to substantiate the difficulties in pooling data from different countries for research. At the same time, an understanding of different policies across countries facilitates interpretation of clinical and epidemiological studies. In the context of uncertainty regarding effectiveness of specific interventions, clinical heterogeneity may allow comparison of different management approaches in future research. This report could form the basis for discussion across Europe to share experience and expertise and to identify future research opportunities to provide the best care for HIV-infected pregnant women.

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Key points

- This is the first study to synthesize PMTCT guidelines across a broad range of European countries.
- Results contribute to interpretation of research and surveillance data of different countries.
- These results highlight the areas of management of HIV-positive women where the evidence base remains incomplete.
- PMTCT policy differences between countries relate to their specific context, in terms of epidemiology of HIV and their health care systems.

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Is tuberculosis crossing borders at the Eastern boundary of the European Union?

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Background: The Eastern border of the European Union (EU) consists of 10 countries after the expansion of the EU in 2004 and 2007. These 10 countries border to the East to countries with high tuberculosis (TB) notification rates. We analyzed the notification data of Europe to quantify the impact of cross-border TB at the Eastern border of the EU. **Methods:** We used TB surveillance data of 2010 submitted by 53 European Region countries to the European Centre for Disease Prevention and Control and the World Health Organization Regional Office for Europe. Notified TB cases were stratified by origin of the case (national/foreign). We calculated the contribution of foreign to overall TB notification. **Results:** In the 10 EU countries located at the EU Eastern border, 618 notified TB cases (1.7% of all notified TB cases) were of foreign origin. Of those 618 TB cases, 173 (28.0%) were from countries bordering the EU to the East. More specifically, 90 (52.0%) were from Russia, 33 (19.1%) from Belarus, 33 (19.1%) from Ukraine, 13 (7.5%) from Moldova and 4 (2.3%) from Turkey. **Conclusions:** Currently, migrants contribute little to TB notifications in the 10 EU countries at the Eastern border of the EU, but changes in migration patterns may result in an increasing contribution. Therefore, EU countries at the Eastern border of the EU should strive to provide prompt diagnostic services and adequate treatment to migrants.

Introduction

In 11 European Union and European Economic Area (EU/EEA) countries, >50% of the notified tuberculosis (TB) cases are diagnosed in individuals of foreign origin.[1] In 2010, 21% of the notified multidrug-resistant tuberculosis (MDR-TB) cases in the EU countries were diagnosed in individuals of foreign origin.[1] The number of notified TB cases in Norway and Sweden was 339 and