Infection (2019) 47:847–852
https://doi.org/10.1007/s15010-019-01332-3

ORIGINAL PAPER

Impact of refugee influx on the epidemiology of late-presenting HIV-infected pregnant women and mother-to-child transmission: comparing a southern and northern medical centre in Germany

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Received: 29 December 2018 / Accepted: 1 June 2019 / Published online: 12 June 2019

Abstract

Purpose Due to early antenatal screening and treatment, HIV mother-to-child transmission (MTCT) rarely occurs in Germany. The study aimed to investigate the impact on prevalence of HIV infection in the antenatal population and the incidence of late-presenting HIV-infected mothers attributable to increased numbers of refugees.

Methods Retrospective analysis and comparison were performed for all deliveries in HIV-infected pregnant women presenting to medical care in Munich (southern Germany) and Hamburg (northern Germany) covering two time periods, A (2010–2012) and B (2013–2015).

Results In Munich, deliveries in HIV-infected pregnant women increased 1.6-fold from period A ($n=50$) to B ($n=79$) with late-presenting cases rising significantly from 2% (1/50) in period A to 13% (10/79) in B. In contrast, late-presenting cases in Hamburg decreased from 14% (14/100) in period A to 7% (7/107) in B, while the total number of HIV-infected women giving birth remained stable. From 2010 to 2015, one late-presenting pregnant woman transmitted HIV in Munich by presumed in utero mode of infection (case reviewed here), while no MTCT occurred in Hamburg.

Conclusions HIV infections diagnosed late in pregnancy and leading to delayed ART initiation are rising in Munich compared to Hamburg. Antenatal care of HIV-infected pregnant women in Munich appears to have been more affected by the recent refugee influx than Hamburg. Our study highlights the importance of screening all pregnant women for HIV early in pregnancy and providing timely health care access for pregnant refugees and asylum seekers to effectively prevent MTCT in Germany.

Keywords HIV · Mother-to-child transmission · MTCT · Late presenting · Refugees

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Introduction

Mother-to-child transmission (MTCT) is the most common mode of HIV infection in children. Relative proportions are estimated to range between 20 and 25% for in utero transmission, 35 and 50% for *intrapartum* transmission and 25 and 45% for postnatal transmission in breast-fed infants without antiretroviral therapy (ART) for mother or child [1]. Due to decreasing integrity of the placental barrier during pregnancy, 75–80% of in utero transmissions occur from 28 weeks of gestation onwards in untreated women [1]. Thus, there is an increased risk of MTCT in HIV-infected pregnant women not receiving ART after 28 + 0 weeks of gestation, defined as late-presenting pregnant women [2].

HIV testing is offered to every pregnant woman in Germany in the first trimester with optional repeated testing when there is a significant risk of HIV infection [3]. If there is no maternal treatment indication, current German guidelines recommend starting ART at the beginning of the second trimester with a protease inhibitor (PI)- or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen. For pregnant women presenting late in pregnancy, a raltegravir-containing regimen is recommended. Postnatal prophylaxis for neonates usually consists of oral zidovudine administered for 2–4 weeks. An extension to a double or triple prophylaxis (zidovudine, lamivudine, nevirapine) for 4–6 weeks is recommended for neonates at high risk for *intrapartum* transmission [3].

Due to early antenatal screening and treatment, MTCT of HIV is now a rare event in Germany. In 2015, 26 newly diagnosed MTCT cases were reported, with 22 of these children born abroad [4]. With regard to the four MTCT events occurring in Germany, three mothers had not been offered an HIV test during pregnancy. In the remaining case, the HIV infection was known, but ART was started late in pregnancy and the child got infected with HIV in utero. Two mothers originated from Russia and the remaining two were of Sub-Saharan origin [4]. With Germany receiving many refugees from high-prevalence countries, antenatal care becomes more challenging in some geographic areas due to an increase in late-presenting HIV-infected pregnant women.

Germany had seen a steadily increasing number of refugees, with a peak in 2015 of 890,000 migrants registered by the EASY system [5]. In 2015, the main asylum-seeking refugees registering in Germany originated from countries with a low HIV incidence rate (such as Syrian Arab Republic, Albania or Kosovo). Besides the considerable increase in refugees from the Middle East and Balkan regions, the influx of asylum seekers from Sub-Saharan Africa sustained in high numbers. Eritrea continued to be within the top ten countries of origin of asylum seekers in 2015 [5]. Being located near the southern German border, Munich was the primary arrival point for many refugees with the number rising tremendously from 14,255 in 2013 to 120,718 in 2015. A total of 49,093 of the 120,718 refugees arriving in 2015 were admitted for the long term to the region of upper Bavaria (government of upper Bavaria, personal communication). In light of these developments, the aim of this study was to assess the number of deliveries among HIV-infected women, including late presenters, at the university hospital, Ludwig-Maximilians-University Munich (LMU Munich), in the South of Germany between 2010 and 2015 and to compare the situation to a medical centre in the North of Germany, the University Medical Center Hamburg-Eppendorf.

Methods

Using the PIA fetal database software (GE Healthcare GmbH, Solingen, Germany), a retrospective analysis of all deliveries in HIV-infected women at the Department of Obstetrics and Gynaecology at LMU Munich between 2010 and 2015 was performed. These are referred to as deliveries from Munich. To analyse dynamic and geographic differences, the number of cases in two different time periods, A (2010–2012) and B (2013–2015), and two tertiary care centres were compared. In Munich, HIV-infected pregnant women are primarily managed at LMU Munich; only few are transferred to another hospital when there is no capacity. In Hamburg, HIV-infected pregnant women deliver in various hospitals, but all HIV-exposed children are followed up at University Medical Center Hamburg-Eppendorf. Therefore, in addition to the PIA fetal database, the medical reports of all HIV-exposed children followed up at University Medical Center Hamburg-Eppendorf were analysed and compared with the LMU Munich data. In our study, these are referred to as deliveries from Hamburg.

Results

From 2010 to 2015, a total of 129 deliveries among HIV-infected women took place in Munich and 207 deliveries in Hamburg. In Munich, the number increased 1.6-fold from period A ($n = 50$) to B ($n = 79$), while in Hamburg the situation remained stable comparing periods A ($n = 100$) and B ($n = 107$) (see Fig. 1). Further, late-presenting cases increased significantly in Munich from 2% (1/50) in period A to 13% (10/79) in B (p value 0.0497, Fisher's exact test). All of these women arrived as refugees to Germany during the study period and originated from Sub-Saharan Africa, except for one woman coming from Albania. In contrast,

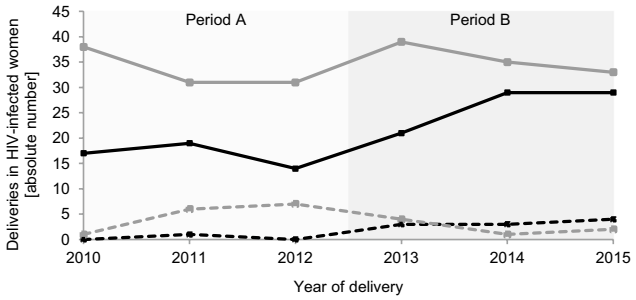

Fig. 1 Absolute number of deliveries in HIV-infected women presenting at two medical centres in Germany from 2010 to 2015 (period A: 2010–2012, period B: 2013–2015). Numbers are given in total (solid line) and separately for late-presenting pregnant women (dotted line) in Munich (black) and Hamburg (grey)

the late-presenting cases in Hamburg decreased from 14% (14/100) in period A to 7% (7/107) in B, but not causing a significant change in prevalence due to the overall number (p value 0.1682). They were mainly migrants from Sub-Saharan Africa except for three women from Germany, Russia and Poland. Interestingly, only 8/21 women had refugee status when presenting to the Hamburg hospitals. Of the late-presenting pregnant women, 3/11 (Munich) and 13/21 (Hamburg) had previously been diagnosed and started on ART, but discontinued treatment due to inconsistent medical care or non-compliance. Whereas in Hamburg late initiation of ART was often due to non-compliance or inconsistent follow-up, late HIV diagnosis was the main reason for late presentation of pregnant women to medical care in Munich (Table 1).

Of the 11 late-presenting pregnant women in Munich, MTCT occurred only once (9%) (case is reviewed here). No MTCT occurred in Hamburg from 2010 to 2015 in neonates born to late-presenting pregnant women. One child of a late-presenting pregnant woman was lost to follow-up in Munich.

Case vignette

To illustrate the particular challenges in preventing MTCT in individual cases of late-presenting pregnant women and to complement the data presented above, we are highlighting an exemplary case that occurred in period B of the study.

A 24-year-old woman of Sub-Saharan Africa origin presented to the Munich gynaecology department at 35 (+3) weeks of gestation having been in Germany for only 2 weeks. Upon her first pregnancy screen in Munich, she was diagnosed with HIV (viral load of 58,607 copies/ml and CD4+ cell count of 200/µl) and latent syphilis of unknown duration. ART (raltegravir, tenofovir and emtricitabine PO)

Table 1 Characteristics of late-presenting pregnant women in Munich ($n=11$) and Hamburg ($n=21$)

	Munich ($n=11$)	Hamburg ($n=21$)
GA at ART initiation [weeks + days]	36 + 4 (30 + 4–39 + 4)[a]	34 + 3 (28 + 5–39 + 4)[b]
VL at ART initiation [copies/ml]	17,476 (570–58,607)[a]	33,552 (64–200,000)[b]
Duration of ART [days]	27 (1–57)[a]	25 (1–68)[b]
ART regimens		
NRTI	11/11	19/21[b]
NNRTI	3/11	2/21
PI	3/11	14/21
INSTI	7/11	5/21
Entry inhibitors	0/11	1/21
VL at delivery [copies/ml]		
< 50	5/11	6/21[b]
50–1000	5/11	10/21
> 1000	1/11	4/21
Country of origin		
Sub-Saharan Africa	10/11	18/21
Others	1/11 (Albania)	3/21 (Germany, Poland, Russia)
Reason for late presenting		
Late initial diagnosis	8/11	8/21
Others[c]	3/11	13/21

GA gestational age, *VL* viral load, *PI* protease inhibitor, *NRTI* nucleos(t)ide reverse transcriptase inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *INSTI* integrase strand transfer inhibitor

[a]For one patient exact GA/VL at ART initiation and duration of ART are not known due to non-compliance

[b]For two patients exact GA at ART initiation unknown. For two patients VL at ART initiation and for one patient VL at delivery is unknown. Two patients received no treatment

[c]Other reasons for late presenting were non-compliance or inconsistent follow-up on ART

was initiated immediately and the patient received three doses of benzathine penicillin G IM. Viral load was fully suppressed at the time of delivery following 45 days of treatment. Her child was born at 41 weeks of gestation by normal vaginal delivery. Rupture of membranes occurred 20 h before birth. The neonate received zidovudine mono-prophylaxis and formula feeds according the German–Austrian guidelines [3]. In addition, IV penicillin was administered for exposure to maternal syphilis infection and IV ampicillin/cefotaxime was started for suspected early-onset neonatal sepsis. PCR of cord blood showed HIV-1-DNA pol near the limits of detection, while HIV-1-DNA env and gag were negative. A control PCR from the same cord blood sample for HIV-1-DNA V3-Loop was also negative, as was a repeat HIV-PCR testing on day six. Surprisingly, on day 28, the next routine PCR for HIV-1-DNA pol and V3-Loop was positive and HIV-1 infection with a viral load of 150,000 copies/ml was confirmed. Subtype A1 was identified with no resistance to antiretrovirals. The infant tested negative for HLA-B*57:01. Immediately following HIV diagnosis (month two of life), ART was initiated with nevirapine, abacavir, lamivudine and zidovudine PO. The child is regularly followed up in the HIV outpatient clinics and currently doing well on triple ART (nevirapine, lamivudine and abacavir) with an undetectable viral load and CD4 + cell count of 2769/µl (42%). Congenital syphilis infection was excluded.

Discussion

Our study analysed the epidemiology of late-presenting HIV-infected pregnant women comparing two distinct time periods and geographic areas in Germany. Since Germany is an HIV-low endemic country and paediatric HIV care is only provided in a limited number of specialist centres (< 10), two large medical institutions representing Germany's north and south were selected as study sites. In general, Hamburg accounted for more children born to HIV-infected pregnant women than Munich, most probably due to the fact that Hamburg generally accommodates for more inhabitants from high-prevalence countries [6]. In Munich, however, a considerable rise in cases was noted (from 50 in period A to 79 cases in period B) compared to a rather stable situation in Hamburg.

It is important to highlight that at the peak of migration in 2015, Syria was the most important country of origin of refugees and asylum seekers to Germany. As a result of the increased migration from the Middle East and Kosovo region, the relative proportion of asylum applications from the African continent decreased (2015: 9.4%; 2014: 22.7%) [5]. Though the relative numbers (i.e., percentages) of asylum seekers originating from HIV-high-prevalence countries appear to be low in view of the high numbers of refugees from other, HIV-low-prevalence countries, it is critical to be aware that there was a sustained influx of migrants from HIV-high-prevalence countries during the study period. From 2011 to 2014, asylum applications from the African continent steadily increased and remained on a high in 2015 (2015: 41,712; 2014: 39,322) [5]. A recent study looking at integration processes of women seeking asylum in Germany demonstrated that only three Sub-Saharan African countries range amongst the top ten countries of origin (Eritrea, Nigeria and Somalia). However, and of particular note, absolute numbers of asylum-seeking women from these three countries increased significantly by a fivefold margin between 2012 and 2015 (2012: 1104; 2015: 5981), a trend that was continuing even more profoundly in the year following our study period (2016: 13.584) [7].

Between 2011 and 2015, new HIV diagnoses in Germany rose steadily (2899 in 2011; 3674 in 2015) and decreased afterwards. The rise in numbers of new HIV diagnoses in the heterosexual population in Germany was mainly due to the rapidly increasing number of patients with Sub-Saharan background with respective numbers more than doubling from 2012 to 2015. In its 2015 epidemiological report, the Robert-Koch-Institute (RKI), the German federal government agency and research institute responsible for disease control and prevention, suggested that the higher influx of refugees from HIV-high-prevalence countries contributed to this increase in new HIV diagnoses in this time period [4]. This interpretation is in line with and supports the findings of our study further highlighting the importance of being aware of these epidemiological trends. Amongst German federal states, Bavaria recorded the highest number of "new HIV diagnoses (median) acquired in a foreign country" from 2013 to 2015 [4].

In addition to the marked increase of the total number of HIV-infected pregnant women in Munich, the late-presenting cases increased significantly (1.6-fold) from period A to B compared to Hamburg. Tantalisingly, all 11 late-presenting cases in Munich arrived as refugees compared to only 8/21 of respective cases in Hamburg. We postulate that in our study the increase in delayed diagnosis of HIV-infected pregnant women in Munich is directly linked to a change in the migration route with Munich having been significantly more affected by this development than Hamburg for geographical reasons. Until 2014, most refugees entered the European Union via Italy using the central Mediterranean route with pregnant women receiving first antenatal care in Italy, including HIV testing. In 2015, the eastern Mediterranean route spanning from Turkey to the Aegean islands via western Balkan states became the main migration route [8] (see Fig. 2). Many pregnant women using this route received their first antenatal care and HIV screening in Germany.

Schaefer et al. had recently reviewed cases of patients with delayed HIV diagnosis in Hamburg aiming to identify

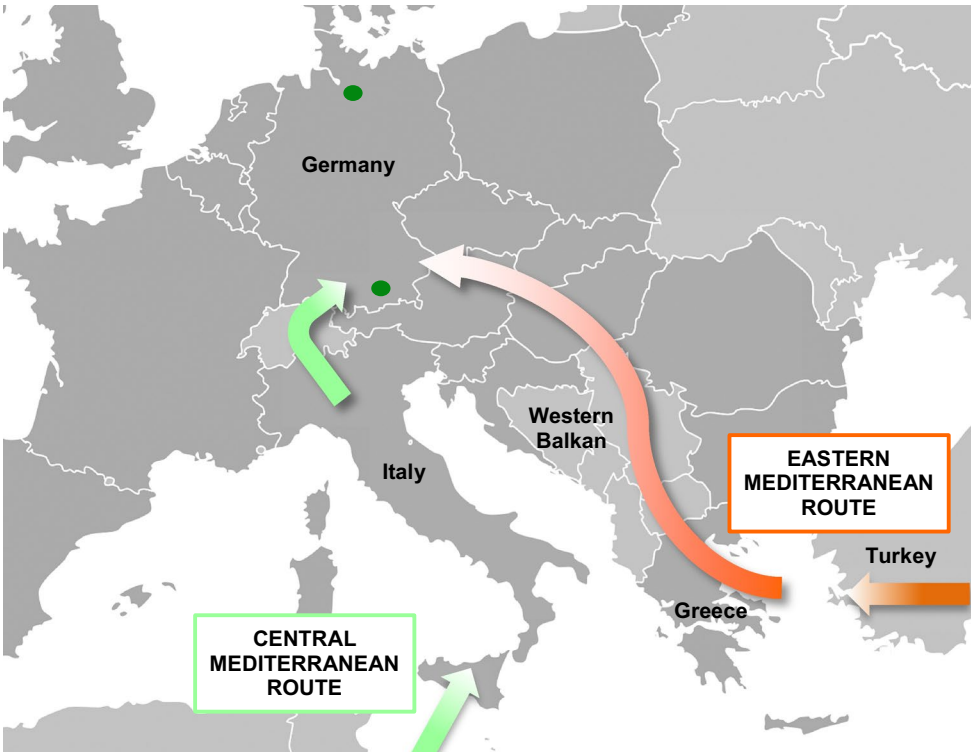

Fig. 2 Change in migration routes. Until 2014, most migrants entered the European Union via Italy using the central Mediterranean route (green). From 2015, the eastern Mediterranean route became the main route with most migrants travelling from Turkey to the Aegean islands into Greece and further north through the western Balkan countries (orange). As a consequence, many pregnant women received their first antenatal care not until arriving in Germany. Green dots are representing Munich (South) and Hamburg (North) (Routes adapted from Frontex [8]. Map from Pixabay [9])

risk factors for delayed presentation [10]. Amongst other factors, such as old age or heterosexual transmission risk, migrant background had been found to be an associated risk factor for late presentation. Though Schaefer et al. looked at delayed HIV diagnosis in general rather than at HIV-positive women presenting late in pregnancy, the findings from this Hamburg cohort underline the increased vulnerability of the migrant population with regard to delayed HIV care.

Clinical care of late-presenting pregnant women is challenging as illustrated by our case vignette. Though the exact mode of MTCT in the respective scenario remains unclear, in utero HIV transmission seems to be most likely. First, there were multiple risk factors for in utero transmission (high viral load before therapy, late treatment initiation with 35 weeks of gestation, syphilis coinfection), while viral load was fully suppressed at the time of delivery. Second, a cord blood HIV-1-DNA pol PCR near detection limits as well as a negative PCR at day six of life can easily be explained as a consequence of viral suppression in the neonate due to maternal raltegravir-based ART crossing the placenta [11]. In this particular case, it may have been reasonable to test neonatal viral load more frequently after discontinuation of zidovudine mono-prophylaxis to detect HIV infection earlier, thus, minimizing the viral reservoir by means of early ART. Guidance on how to best manage babies born to HIV-infected women presenting late in pregnancy, including the choice of postnatal antiretroviral prophylaxis, remains controversial when reviewing international recommendations [2, 3, 12]. In Germany, any child born to an HIV-infected mother with an undetectable viral load (< 50 copies/ml) at birth will receive 2(–4) weeks of zidovudine (PO); the UK BHIVA guidance opts for 4 weeks zidovudine (PO) [2, 3]. The U.S. guidelines, however, appear to be the most stringent ones, since they define women with a detectable viral load near delivery (on or after the 36th week of gestation) as "higher risk of perinatal transmission" prompting 2-/3-drug prophylaxis. Thus, neonates born to a late-presenting mother fulfilling these criteria may receive extended prophylaxis according to the U.S. guidance. However, the U.S. guideline also refers to a continuing debate amongst the panel members in favour or against extended prophylaxis [12]. In summary, the reviewed guidelines appear to be more in favour of administering zidovudine mono-prophylaxis rather than extended prophylaxis for any baby born to a woman with an undetectable viral load at birth, regardless of her presenting late or not. This seems to be reasonable since neither mono- nor triple prophylaxis can prevent or undo in utero transmission. Prophylaxis will only be able to prevent transmission events perinatally, where an undetectable viral load at birth is of key importance. Thus, it will remain a matter of debate whether our patient could have profited from a very early combined antiretroviral prophylaxis (zidovudine, lamivudine, nevirapine) to prevent MTCT or whether such an intervention would have made no difference at all.

The relevance of the trend we report for the respective time periods A and B is further highlighted by a recent

publication giving compelling evidence of continuously increasing numbers of new HIV diagnoses amongst refugees and asylum seekers presenting with a notifiable disease in Germany from 2015 onwards [13]. Due to the increasing number of refugees in Germany, particularly in Munich, more late-presenting HIV-infected pregnant women are attending medical care. Even with late treatment, highly effective ART, including integrase strand transfer inhibitors (INSTI), limits the risk of *intrapartum* infection. However, risk of in utero transmission increases with late ART initiation. Many late-presenting pregnant women have additional risk factors for in utero transmission, including high viral load and co-infections (i.e., syphilis).

In general, since late presentation in pregnancy puts the unborn child in a high-risk situation of both in utero and perinatal MTCT, it will be imperative to screen all pregnant women early in pregnancy, as recommended in our national guidelines. Our study further highlights the importance of timely health care access for pregnant refugees and asylum seekers to effectively prevent MTCT in Germany. In view of the latest BHIVA guidance to recommend ART for all persons diagnosed with HIV [14], the group of late-presenting pregnant women would ideally grow smaller. However, guidance from the German and Austrian AIDS societies currently does not recommend treatment for all HIV-positive individuals [15], but this is likely to change with a revision of these respective guidelines currently underway. Further studies will be necessary to evaluate the significance of late-presenting pregnant women for in utero MTCT in Germany, particularly with regard to ongoing migration dynamics and a potentially increasing number of refugees seeking medical care in Germany after fleeing HIV-high-prevalence areas of war and devastation.

Acknowledgements The authors like to thank Dr Andrew Prendergast for advice and critical review of the manuscript and Karen Olah and Sandra Hertling for their support in finalizing maternal data in Hamburg.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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