Impact of expanded access to combination antiretroviral therapy in pregnancy: results from a cohort study in Ukraine

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Objective To investigate the scale-up of antenatal combination antiretroviral therapy (cART) in Ukraine since this became part of the national policy for the prevention of mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV).

Methods Data on 3535 HIV-positive pregnant women who were enrolled into the Ukraine European Collaborative Study in 2008–2010 were analysed. Factors associated with receipt of zidovudine monotherapy (AZTm) – rather than cART – and rates of mother-to-child transmission (MTCT) of HIV were investigated.

Findings cART coverage increased significantly, from 22% of deliveries in 2008 to 61% of those in 2010. After adjusting for possible confounders, initiation of antenatal AZTm – rather than cART – was associated with cohabiting (versus being married; adjusted prevalence ratio, aPR: 1.09; 95% confidence interval, CI: 1.02–1.16), at least two previous live births (versus none; aPR: 1.22; 95% CI: 1.11–1.35) and a diagnosis of HIV infection during the first or second trimester (versus before pregnancy; aPR: 1.11; 95% CI: 1.03–1.20). The overall MTCT rate was 4.1% (95% CI: 3.4–4.9); 42% (49/116) of the transmissions were from the 8% ($n = 238$) of women without antenatal ART. Compared with AZTm, cART was associated with a 70% greater reduction in the risk of MTCT (adjusted odds ratio: 0.30; 95% CI: 0.16–0.56).

Conclusion Between 2008 and 2010, access to antenatal cART improved substantially in Ukraine, but implementation of the World Health Organization's Option-B policy was slow. For MTCT to be eliminated in Ukraine, improvements in the retention of women in HIV care and further roll-out of Option B are urgently needed.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Among the countries of Europe, Ukraine has the highest prevalence of adult infection with human immunodeficiency virus (HIV) (1.6%) and the highest rate of mortality attributable to acquired immunodeficiency syndrome (AIDS) (8.2 deaths per 100 000 population in 2011).[1–3] The country's epidemic of HIV infection has been driven by the practice of injecting illicit drugs.[1] The quality of HIV care provided in Ukraine has been badly affected by the severe economic crisis that followed the country's independence in 1991 and by the limitations of its verticalized health-care system.[4] Although the national scale-up of antiretroviral therapy (ART) began in 2004, need has outstripped supply and the devolution of budgets has led to regional disparities in access to such therapy.[4,5] In 2011, 30% of individuals who were eligible for ART and in HIV care in Ukraine were not receiving ART, and 13% of those on ART were having their therapy financed by the *Global Fund to Fight AIDS, Tuberculosis and Malaria*.[1] In the same year, the ART regimens in common use in Ukraine cost at least 100 United States dollars per patient.[6]

The elimination of new HIV infections in infants by 2015 is a current global target,[7] and the prevention of mother-to-child transmission (PMTCT) of HIV has become a public-health priority in many countries, including Ukraine.[1] In 2010, the World Health Organization (WHO) published guidelines for the use of ART in pregnant women.[8] These guidelines recommended initiation of lifelong combination ART (cART) for all pregnant women with CD4+ T-lymphocyte (CD4+ cell) counts of ≤ 350 per μl and/or HIV disease in WHO stage 3 or 4. They also recommended two options for those pregnant women who require ART for PMTCT only: Option A, consisting of zidovudine monotherapy (AZTm) plus single-dose nevirapine (sdNVP), and Option B, consisting of antenatal cART.[8] In 2012, WHO published a programmatic update on "Option B+" – the initiation of lifelong cART for all HIV-positive pregnant women.[9] The potential benefits of this approach include improved maternal health and the harmonization of treatment programmes.[10]

Following the scale-up of PMTCT services in Ukraine, the rate of MTCT fell from 15% in 2001 to 6–7% in 2007, although the annual numbers of new infections in women of childbearing age – many of which had been acquired heterosexually –increased over the same period.[1,3,11–13] By 2011, the prevalence of HIV infection among pregnant women was higher in Ukraine (0.47%) than in any other country in Europe[1] and exceeded 3% in some regions of the country (personal communication, Natalya Nizova, 2012). In 2007, 92% of the HIV-positive pregnant women in Ukraine received ART, and PMTCT prophylaxis was based on AZTm and sdNVP.[13,14] In November 2007, the country's Ministry of Health recommended the national implementation of WHO's Option-B strategy. The present study was based on data collected in Ukraine between 2008 and 2010 as part of a larger, prospective, observational study of HIV-positive pregnant women and their infants. The aims of the present study were to investigate coverage with antenatal cART, the factors associated with receipt of AZTm – rather than cART – and MTCT rates.

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Methods

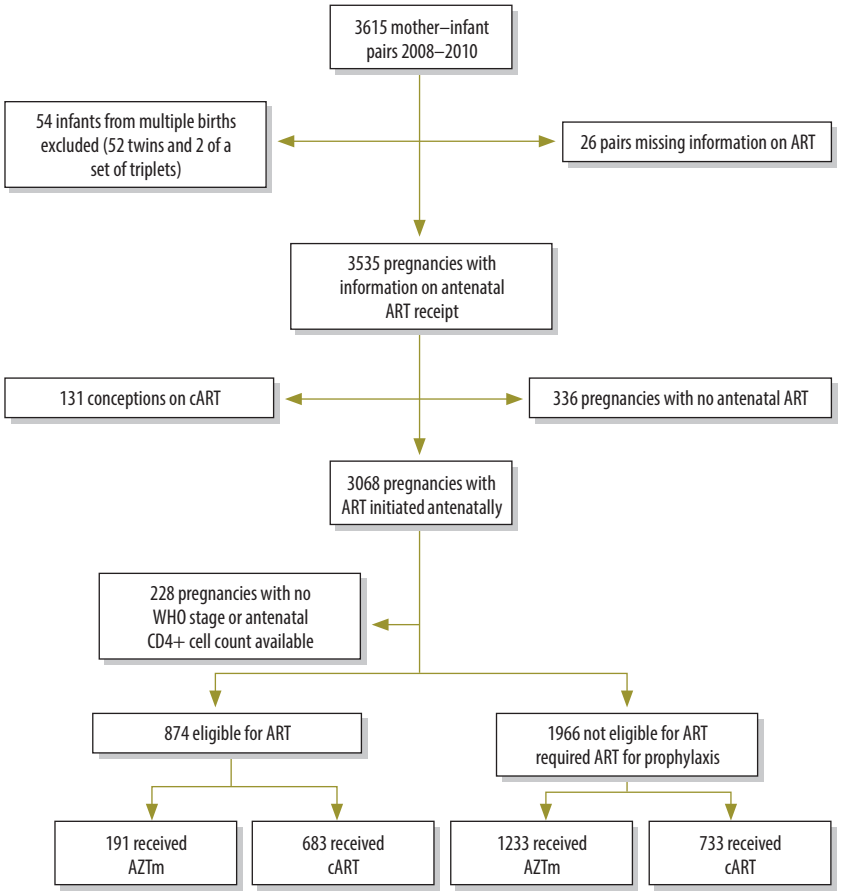
The European Collaborative Study is an ongoing, observational, birth cohort study in which HIV-positive pregnant women – diagnosed before or during pregnancy or around the time of delivery – are enrolled and their infants are prospectively followed, either for 18–24 months if HIV-negative or on an ongoing basis if HIV-positive.[13] Data collection takes place at delivery and then as often as infant follow-up allows. The study began enrolment in Ukraine in 2000 and seven Ukrainian centres for HIV care currently participate. Informed consent is obtained for collection of linked anonymous data on maternal, infant and delivery characteristics and clinical parameters.[13] The study protocol was approved by the Great Ormond Street Hospital for Children NHS Trust/Institute of Child Health Research Ethics Committee and by local institutional review boards.

For the present data analyses, 54 infants who were products of multiple pregnancies but were not the firstborn infant of the multiple birth were excluded from the study (Fig. 1) except in two cases of discordant infection status, in which the infected infant was retained instead of the uninfected firstborn infant.

Definitions

All 3535 infants included in the present study were 7 months of age or older at the time of data analysis. Most (69%) of these infants had been tested for HIV deoxyribonucleic acid (DNA) by polymerase chain reaction at least once by the time of the data analysis. Infants found positive using this assay were considered HIV-positive, regardless of age, as were infants with persistence of anti-HIV antibodies beyond 18 months of age. Infants who were negative for HIV DNA (except at birth) and/or negative for anti-HIV antibodies were classified as HIV-negative, regardless of age. Infants with conflicting results were classified as "indeterminate". A viral load of ≤ 75 copies of ribonucleic acid (RNA) per ml – the detection limit of the RealTime assays (Abbott Laboratories, Abbott Park, United States of America) used – was defined as "undetectable". cART was defined as three or more antiretroviral drugs taken simultaneously. Twenty of the pregnant women included in the data analysis received two antiretroviral drugs – rather than a full cART regimen – because of drug shortages (personal communication, Igor Semenenko, 2012); these women were assigned to the AZTm group. ART given to pregnant women before labour was categorized as "antenatal ART", whereas ART given during labour and/or delivery was categorized as "intrapartum ART". History of injecting drug use was determined by self-report, clinical assessment and/or the development of abstinence syndrome in the neonate. Pregnant women with CD4+ cell counts of ≤ 350 per µl and/or HIV disease in WHO stage 3 or 4 were considered eligible for ART.[15]

Fig. 1. **Study enrolment, showing the antenatal and intrapartum antiretroviral therapy (ART) received, Ukraine, 2008–2010**



cART, combination antiretroviral therapy; CD4+ cell, CD4+ T-lymphocyte; WHO, World Health Organization; AZTm, zidovudine monotherapy.
Note: The pregnant women who received no antenatal ART were diagnosed as HIV-positive before conception ($n = 120$), during pregnancy ($n = 69$), intrapartum ($n = 48$) or at an unrecorded time ($n = 99$). The denominator used for pregnancies with no antenatal ART or timing of diagnosis available was therefore 237. The women who were eligible for ART were considered eligible because they had HIV disease in WHO stage 3 or 4 ($n = 311$), ≤ 350 CD4+ cells per µl ($n = 707$) or both ($n = 144$). The women who were not eligible for ART had HIV disease in WHO stage 1 or 2 and no data on their CD4+ cells ($n = 665$) or > 350 CD4+ cells per µl and either no information on their WHO stage ($n = 110$) or HIV disease in stage 1 or 2 ($n = 1191$). In 24% (317/1301) of pregnancies, a CD4+ cell count of > 350 per µl was taken after ART initiation. These 317 pregnancies were included among the 1966 that were categorized as "not eligible for ART; required ART for prophylaxis".

Data analysis

The χ^2 test for categorical variables, the Wilcoxon Mann–Whitney test or the Kruskal–Wallis test were used in univariable comparisons. In analyses exploring factors associated with the initiation of AZTm rather than cART during pregnancy, Poisson regression models – with robust variance estimators to control for underdispersion[16] – were used to obtain prevalence ratios (PRs), adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs). Odds ratios (ORs) were avoided because they are more difficult to interpret than PRs when outcomes are common.[16]

These analyses were limited to the 2840 pregnancies for which data on WHO stage and/or antenatal CD4+ cell counts were available, which represented 93% of the 3068 pregnancies in which ART was initiated antenatally (Fig. 1). The contribution that each factor made to a model's goodness-of-fit was investigated using the Wald test; a covariate was included if it gave a *P*-value of < 0.1.

Logistic regression models were fitted to calculate ORs, adjusted ORs (aORs) and 95% CIs for factors associated with MTCT. All except one of the factors previously associated with MTCT risk in this cohort (i.e. type of antenatal/intrapartum ART, mode of delivery, preterm delivery and history of injecting drug use)[13] were included a priori. The exception was breastfeeding, which was excluded because very few of the women included in the data analysis breastfed their infants. Inclusion of maternal WHO stage and CD4+ cell count depended on these variables showing a level of significance of *P*-value < 0.1 in likelihood ratio tests. The effects on MTCT of antenatal ART duration and antenatal viral load – available for 54% of the 2854 infants with known infection status reported – were explored in subanalyses.

All models were adjusted a priori for year and HIV centre of enrolment; the latter variable was included as a random effect in the logistic regression models[17] and as a covariate in the Poisson regression models. Maternal educational status, which was only available for 44% ($n = 1545$) of the women included in the data analysis, was excluded from the main multivariable models to avoid bias.

All of the statistical analyses were performed using Stata version 11.0 (StataCorp. LP, College Station, USA).

Results

Antenatal cART was received by 45% (1606) of the 3535 pregnant women overall. Coverage of cART increased significantly over the study period, from 22% (270) of the 1217 pregnant women who delivered in 2008 to 61% (627) of the 1027 who delivered in 2010 (*P* for trend: 0.03). Overall 45% (1593/3535) of women received AZTm, with or without sdNVP; 5% (163/3535) received sdNVP alone and another 5% (173/3535) received no antenatal or intrapartum ART. Of the 3429 women with the date of HIV diagnosis available, 38% (1315) were diagnosed as HIV-positive before their current pregnancy and 131 (10%) of these women had conceived while on cART. Of 841 women who were diagnosed as HIV-positive before their current pregnancy and had their CD4+ cell count determined during pregnancy, 335 (40%) had a count of ≤ 350 cells per µl. Of the 336 HIV-positive pregnant women who received no antenatal ART, 237 had the dates of their HIV diagnosis recorded. Of these, 189 (80%) were diagnosed as HIV-positive before delivery and 120 (51%) had been diagnosed as HIV-positive before they had conceived.

Maternal and delivery characteristics are shown, according to the ART received, in Table 1. Most of the women were either married or cohabiting and 15% (514/3505) had been or were injecting drug users. Of the 1606 women who received cART, 91% (1458) received a regimen that was protease-inhibitor-based – predominantly a combination of zidovudine, lamivudine and lopinavir/ritonavir. Overall, 96% (3236/3388) of infants received neonatal prophylaxis. Of the 2872 infants who received neonatal prophylaxis of known type, 85% (2443) received zidovudine for 7 days, with or without sdNVP.

The results of at least one antenatal CD4+ cell count were available for 64% (2264/3535) of the women. This proportion increased from 50% (606/1217) of the women who delivered in 2008 to 73% (749/1027) of the women who delivered in 2010. For 2213 women with both the date of their first CD4+ cell count in pregnancy and date of ART initiation available, 67% (1493) had had their CD4+ cell count measured before they initiated ART. Of the 2264 first antenatal cell counts recorded, 34% (774) and 11% (249) were ≤ 350 and ≤ 200 CD4+ cells per µl, respectively. Overall, of the 2990 women who had the WHO stage of their HIV disease recorded, 14% (411) had stage 3 or stage 4 disease. Of the 3182 pregnancies for which CD4+ cell counts and/or WHO stage were recorded, 32% (1009) were in ART-eligible women. For 59% (598) of these women, ART eligibility was identified only by CD4+ cell count. Of the women who were ART-eligible and initiated ART during pregnancy, cART was received by 56% (137/244), 83% (276/332) and 91% (270/298) of those delivering in 2008, 2009 and 2010, respectively (*P* for trend: < 0.01).

Among the women with data available on WHO stage and/or CD4+ cell counts who initiated ART for PMTCT only, cART was received by 12% (84/709), 49% (360/731) and 55% (289/526) of those delivering in 2008, 2009 and 2010, respectively (*P* for trend: < 0.01). In general, women initiating AZTm had higher CD4+ cell counts than those initiating cART (Table 1; $P < 0.01$). Only 68% (239) of the 353 women without a recorded WHO stage or CD4+ cell count received antenatal ART, compared with 93% (2960) of the other 3182 women ($\chi^2 = 236.79$; $P < 0.01$). Women without a recorded WHO stage or CD4+ cell count were also more likely to have had their HIV infection diagnosed in the third trimester or intrapartum [16% (51/318) versus 11% (331/3111) of the women with one or both measures; $\chi^2 = 8.49$; $P < 0.01$]. Women with histories of injecting drug use were less likely to receive antenatal ART than the other women [82% (419/514) versus 93% (2769/2991); $\chi^2 = 65.23$; $P < 0.01$].

Factors associated with receipt of antenatal AZTm

The proportion of women initiating AZTm (rather than cART) during pregnancy varied significantly by HIV centre (data not shown; $\chi^2 = 232.70$; $P < 0.01$). Overall, almost two thirds of the women who did not require treatment for their own health – but only 22% of the ART-eligible women – initiated AZTm rather than cART (Table 2). In addition to year of delivery, HIV centre and ART eligibility, other factors that were found to be associated with initiation of AZTm in univariable analyses included a history of injecting drug use in the woman or her partner, marital status, previous live births, timing of HIV diagnosis and educational status (Table 2). For the women who delivered in 2010 and who initiated ART during pregnancy, the probability of receiving antenatal AZTm was less than half the probability among women who delivered in 2008, after adjusting for other factors (Table 2). In the adjusted models, having had at least two previous live births (versus none) and cohabiting (versus married) were both associated with an increased likelihood of receiving AZTm. Women diagnosed as HIV-positive during pregnancy were also more likely to receive AZTm than those diagnosed before conception, partly because they were less likely to be ART-eligible [27% (500/1847) eligible versus

Table 1. **Maternal and infant characteristics, Ukraine, 2008–2010**

Characteristic[a]	Conceived while on cART (*n* = 131)	ART initiated during pregnancy or received at delivery		
		cART (*n* = 1475)	AZTm, with or without sdNVP (*n* = 1593)	sdNVP only or no ART (*n* = 336)
Maternal age (years) (*n* = 3523), median (IQR)	30.0 (27.2–32.6)	27.3 (23.7–31.1)	26.1 (22.9–30.0)	27.5 (24.0–32.0)
Marital status (*n* = 3523), No. (%)				
Married	81 (62)	698 (47)	694 (44)	90 (27)
Cohabiting	43 (33)	561 (38)	653 (41)	147 (45)
Single	7 (5)	211 (14)	246 (15)	92 (28)
Previous live births at enrolment (*n* = 3463), No. (%)				
No	34 (27)	781 (54)	907 (57)	118 (37)
Yes	95 (74)	654 (46)	676 (43)	198 (63)
Timing of HIV diagnosis (*n* = 3428), No. (%)				
Before pregnancy	131 (100)	588 (40)	476 (30)	120 (51)
First or second trimester	0	749 (51)	950 (60)	33 (14)
Third trimester	0	135 (9)	163 (10)	36 (15)
Delivery	0	0	0	48 (20)
Age at leaving full-time education (years) (*n* = 1990), No. (%)				
≤ 16	14 (19)	104 (13)	180 (20)	41 (23)
17–18	24 (32)	253 (31)	255 (28)	82 (46)
≥ 19	37 (49)	463 (56)	481 (53)	56 (31)
History of IDU (*n* = 3505), No. (%)				
No	86 (66)	1251 (85)	1431 (90)	222 (70)
Yes	44 (34)	217 (15)	158 (10)	95 (30)
Partner with history of IDU (*n* = 3440), No. (%)				
No	89 (68)	1016 (71)	1208 (77)	245 (81)
Yes	42 (32)	415 (29)	366 (23)	59 (19)
Maternal WHO stage (HIV disease severity), No. (%) (*n* = 2 990)				
1 or 2 (asymptomatic/mild)	45 (39)	1096 (82)	1251 (95)	187 (86)
3 or 4 (advanced/severe)	70 (61)	240 (18)	71 (5)	30 (14)
CD4+ cell count (*n* = 2263)[b]				
Cells per µl, median (IQR)	370 (260–490)	360 (250–510)	530 (410–660)	410 (295–530)
≤ 350 cells per µl, no. (%)	49 (48)	577 (48)	130 (14)	18 (45)
Mode of delivery (*n* = 3533), No. (%)				
Vaginal/emergency CS	77 (59)	1021 (69)	1130 (71)	311 (93)
Elective CS	54 (41)	454 (31)	461 (29)	25 (7)
Gestation at delivery (weeks) (*n* = 3520), No. (%)				
≥ 37	113 (86)	1336 (91)	1482 (94)	267 (81)
< 37	18 (14)	137 (9)	103 (6)	64 (19)
MTCT rate (*n* = 2854),[c] % (95% CI)	0 (0–3.5)	1.4 (0.8–2.2)	3.8 (2.8–5.0)	20.6 (15.6–26.3)

ART, antiretroviral therapy; AZTm, zidovudine monotherapy; cART, combination antiretroviral therapy; CD4+ cell, CD4+ T-lymphocyte; CI, confidence interval; CS, caesarean section; HIV, human immunodeficiency virus; IDU, injecting drug use; IQR, interquartile range; MTCT, mother-to-child-transmission; sdNVP, single-dose nevirapine; WHO, World Health Organization.

[a] The *n*-values indicate the number of women for whom the relevant information was available.

[b] Results of the first count in pregnancy, obtained at a median of 23 weeks' gestation.

[c] The values shown are for mother–infant pairs showing transmission.

38% (374/987); $\chi^2 = 35.32$; $P < 0.01$]. This association remained significant after adjusting for treatment eligibility and other factors (Table 2). Among the ART-naive women, those who had been or were injecting drug users were more likely to be ART-eligible than the other women [41% (148/358) versus 29% (720/2471); $\chi^2 = 21.89$; $P < 0.01$]. In the adjusted models, a history of injecting drug use was not significantly associated with receipt of AZTm.

In a multivariable model that included adjustment for educational status when known – in addition to the other factors in Table 2 ($n = 1555$) – women who had left full-time education when they were younger than 16 years or 17–18 years of age were found to have been more likely to receive AZTm than the women who had stayed in full-time education until they were 19 or older, with an aPR (and 95% CI) of 1.43 (1.25–1.64) and 1.18 (1.05–1.33), respectively.

Table 2. **Factors associated with receipt of zidovudine monotherapy (AZTm) among women who initiated antiretroviral therapy during pregnancy, Ukraine, 2008–2010**

Characteristic	No. of women	No. (%) of women receiving AZTm	PR (95% CI)	
			Crude	Adjusted[a]
Year of delivery				
2008	1082	842 (78)	2.36 (2.14–2.62)	2.32 (2.11–2.55)
2009	1129	469 (42)	1.26 (1.12–1.42)	1.25 (1.12–1.39)
2010	857	282 (33)	1.00	1.00
History of IDU				
Yes	375	158 (42)	1.00	1.00
No	2682	1431 (53)	1.27 (1.12–1.43)	1.10 (0.99–1.23)
Partner with history of IDU				
Yes	781	366 (47)	1.00	
No	2224	1208 (54)	1.16 (1.07–1.26)	
Marital status				
Married	1392	694 (50)	1.00	1.00
Cohabiting	1214	653 (54)	1.08 (1.00–1.16)	1.09 (1.02–1.16)
Single	457	246 (54)	1.08 (0.98–1.19)	1.01 (0.91–1.11)
ART-eligible[b]				
Yes	874	191 (22)	1.00	1.00
No	1966	1233 (63)	2.87 (2.52–3.27)	2.53 (2.22–2.87)
Previous live births at enrolment				
0	1688	907 (54)	1.00	1.00
1	976	475 (49)	0.91 (0.84–0.98)	1.01 (0.93–1.08)
≥ 2	354	201 (57)	1.06 (0.96–1.17)	1.22 (1.11–1.35)
Timing of HIV diagnosis				
Before conception	1064	476 (45)	1.00	1.00
First or second trimester	1699	950 (56)	1.25 (1.15–1.35)	1.11 (1.03–1.20)
Third trimester	298	163 (55)	1.22 (1.08–1.38)	1.02 (0.91–1.15)
Age at leaving full-time education (years)				
≥ 19	944	481 (51)	1.00	ND
17–18	508	255 (50)	0.99 (0.89–1.10)	ND
≤ 16	284	180 (63)	1.24 (1.12–1.39)	ND

ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; IDU, injecting drug use; ND, not determined because of missing data; PR, prevalence ratio.

[a] Based on observations on the 2770 women for whom data were available on all variables included in the multivariable model, and including a priori adjustments for year of delivery and HIV centre of enrolment.

[b] Women with antenatal CD4+ T-lymphocyte counts of ≤ 350 cells per µl and/or HIV disease in World Health Organization stage 3 or 4 were considered ART-eligible.

Among the women who were ineligible for ART, lower educational status was also associated with lower CD4+ cell counts: the median CD4+ cell counts for such women who left full-time education when aged 16 or less, 17–18 and 19 years or older were 510, 530 and 560 cells per µl, respectively ($P = 0.05$). After adjusting for educational status, the associations between AZTm initiation and having had at least two previous live births or cohabiting were no longer statistically significant, with an aPR (and 95% CI) of 1.14 (1.00–1.30) and 1.06 (0.97–1.17), respectively.

Mother-to-child transmission

Among the 2854 infants with recorded HIV infection status, the overall rate of MTCT was 4.1% (95% CI: 3.4–4.9). The rate of MTCT was 1.3% (95% CI: 0.7–2.0) among the women who received antenatal cART, 3.8% (95% CI: 2.8–5.0) among those who received AZTm, 18.6% (95% CI: 12.3–26.4) following sdNVP only and 22.9% (95% CI: 15.4–32.0) among the untreated women. Overall, 42% (49) of the 116 transmissions from mothers to infants occurred in the 8% of cases ($n = 238$) in which antenatal ART had not been received. MTCT occurred among 3.0% (95% CI: 1.0–6.8) of the 167 ART-eligible women who received AZTm compared with 3.7% (95% CI: 2.7–5.1) of the 1045 ART-ineligible women who received AZTm.

In the adjusted analysis, the reduction in MTCT was 70% greater in women who received antenatal cART than in those who received AZTm (Table 3). Delivery before 37 completed weeks of gestation was associated with a twofold increased risk of MTCT, although in analyses stratified by ART type this association was only statistically significant in the AZTm group (aPR: 3.45; 95% CI: 1.54–7.73) and not among the women who received cART (aPR: 2.32; 95% CI: 0.50–10.65). Maternal CD4+ cell count and WHO stage were not included in the final model because they gave *P*-values above 0.1 (0.20 and 0.42, respectively) in likelihood ratio tests.

The median duration of antenatal AZTm (12.6 weeks; interquartile range, IQR: 9.9–14.9) was shorter than that of cART (13.9 weeks; IQR: 10.1–16.6).

Table 3. **Factors associated with mother-to-child transmission of human immunodeficiency virus (HIV) within 2854 mother–infant pairs, Ukraine, 2008–2010**

Characteristic	No. of mother–infant pairs	No. (%) of pairs with MTCT	OR (95% CI)	
			Crude	Adjusted[a]
Antenatal or intrapartum ART				
cART	1274	16 (1.3)	0.32 (0.18–0.57)	0.30 (0.16–0.56)
AZTm	1342	51 (3.8)	1.00	1.00
sdNVP only	129	24 (18.6)	5.79 (3.42–9.77)	4.59 (2.51–8.39)
None	109	25 (22.9)	7.53 (4.45–12.76)	4.62 (2.49–8.59)
Mode of delivery				
Vaginal	1916	94 (4.9)	1.00	1.00
Elective CS	800	20 (2.5)	0.50 (0.30–0.81)	0.74 (0.43–1.27)
Emergency CS	137	2 (1.5)	0.29 (0.07–1.18)	0.25 (0.06–1.09)
Gestation at delivery (weeks)				
≥ 37	2597	92 (3.5)	1.00	1.00
< 37	247	23 (9.3)	2.80 (1.74–4.50)	2.25 (1.29–3.91)
History of IDU				
No	2416	92 (3.8)	1.00	1.00
Yes	414	22 (5.3)	1.42 (0.88–2.28)	1.06 (0.60–1.85)
Year of delivery				
2008	1102	52 (4.7)	1.00	1.00
2009	1086	23 (2.1)	0.44 (0.27–0.72)	0.50 (0.28–0.89)
2010	666	41 (6.2)	1.32 (0.87–2.02)	1.56 (0.95–2.56)

AZTm, zidovudine monotherapy; ART, antiretroviral therapy; cART, combination antiretroviral therapy; CI, confidence interval; CS, caesarean section; IDU, injecting drug use; MTCT, mother-to-child transmission; OR, odds ratio; sdNVP, single-dose nevirapine.

[a] Based on observations on the 2819 women for whom data were available on all variables included in the multivariable model. Adjusted odds ratios were estimated including a random effect to account for any unobserved variables that were specific to each HIV centre involved.

Among the 2527 women who had received ART for at least 14 days by the time that they delivered – and after adjusting for ART duration (categorized as 2–7, 8–11 or ≥ 12 weeks) and the other factors given in Table 3 – compared with AZTm, cART was associated with a 61% greater reduction in the risk of MTCT (aOR: 0.39; 95% CI: 0.20–0.74).

Among 1421 women who received antenatal ART, each $\log_{10}$ increase in antenatal viral load (measured a median of 41 days before delivery) was associated with a 78% increase in transmission risk (aOR: 1.78; 95% CI: 1.26–2.53). Adjusting for viral load and the other factors given in Table 3 had little effect on the association seen between MTCT risk and cART (aOR: 0.35; 95% CI: 0.15–0.79).

Infection status was unknown for 29% (98/336) of the infants born to women with no antenatal ART and 18% (583/3199) of the infants whose mothers had received antenatal ART ($\chi^2 = 23.41$; $P < 0.01$). When the number of HIV infections in these infants was estimated – on the assumption that the risk of infection for each of these infants was the same as for the other infants whose mothers had received the same treatment, if any – the estimated overall rate of MTCT increased from 4.1% to 4.2% (95% CI: 3.6–4.9).

Discussion

The present study covered three years during which cART coverage for HIV-positive pregnant women was scaled up in Ukraine. Over this period, the overall rate of MTCT recorded in the study cohort was 4.1%. The rate of MTCT among women who received cART antenatally was 1.3%. This represented a 70% reduction in MTCT risk relative to the reduction observed among the women who received AZTm. This marked reduction in risk was detected even though those women who had the more severe HIV disease – who were at relatively high risk of transmitting their infection – were more likely to receive cART than AZTm.[18] Although our observations demonstrate the effectiveness of antenatal cART for PMTCT, they also indicate that the scale-up in cART coverage for pregnant women has been a slow process in Ukraine. About 32% of the women who delivered in 2010 – two years after WHO's Option B became part of Ukraine's national health policy – received AZTm rather than cART during their pregnancies.

In Ukraine over the study period, ART-eligible women were prioritized for receipt of the limited cART supplies, as recommended by WHO guidelines.[8] In the present study, 91% of the ART-eligible women who delivered in 2010 and initiated ART during pregnancy received cART – up from a corresponding value of 56% among the women who delivered in 2008. In over half of the cases, ART eligibility was identified only by low CD4+ cell counts, a fact that underscores the importance of such counts in assessing ART eligibility.[19,20] Although the probability of a woman having her CD4+ cell count measured at least once during pregnancy increased markedly over the study period, more than a quarter of the women who delivered in 2010 had no records of CD4+ cell counts during pregnancy.

In the adjusted analyses, women diagnosed as HIV-positive in the first or second trimester were slightly more likely to have initiated AZTm than those diagnosed as HIV-positive before conception. The latter women may have had more opportunity to undergo counselling in preparation for initiation of

cART. Women who had had two or more previous live births (versus none) and those who were unmarried but in cohabiting partnerships (versus married) were also more likely to have initiated AZTm. However, both of these groups of women had relatively low educational status, which was also associated with an increased probability of AZTm receipt – even though CD4+ cell counts indicated that, in general, the women with low educational status were in relatively poorer health. In both Switzerland and the United States of America, people with lower educational attainment or socioeconomic status have been found to be relatively less likely to initiate cART.[21,22] However, among treated individuals, data on the association between educational attainment and the progression of HIV disease are conflicting,[21,23] probably because context-specific factors (e.g. adherence support) may mitigate the health-related sequelae of social deprivation. Ukraine's verticalized system of HIV care, in which most care is provided at regional centres, probably presents practical and financial barriers to women with childcare responsibilities. Clinicians may be less likely to prescribe cART to women attending infrequently for care,[24,25] particularly when supplies of the necessary drugs are limited. If access to cART is to be made equitable in Ukraine, more work is needed to determine the structural and individual barriers to HIV care for mothers, people with low educational status and other groups. Peer support and practical assistance with transport and childcare costs may help to remove some of the barriers.

In the present study, 5% of the women received no antenatal or intrapartum ART. This represents a slight improvement on the corresponding value (7%) recorded in the same cohort study in 2007.[13] By using the MTCT rates observed among women receiving cART and AZTm in the present study, it is possible to estimate the overall rates of MTCT achievable under different scenarios. If all of the women on AZTm had received cART instead, the predicted overall MTCT rate would have been 2.9% (95% CI: 2.3–3.6), compared with 2.2% (95% CI: 1.8–2.8) if cART coverage had remained unchanged but the 336 untreated women had received AZTm. In the present study, four in every five of the women who received no antenatal ART had been diagnosed as HIV-positive before delivery and 50% of them had been diagnosed before conception. Improvements in the retention of women in HIV care after HIV diagnosis will therefore be key for achieving MTCT rates of < 2%.[26–28] Two observations made in the present study – that over a third of the women who had been diagnosed as HIV-positive before conception had antenatal CD4+ cell counts of ≤ 350 cells per μl and that only one in every 10 such women conceived while on cART – indicate possible disengagement from HIV care and a substantial unmet need for HIV treatment in Ukraine.[1] The expansion and maintenance of access to cART for people requiring treatment remains a priority.[1] Postnatally, continuation of ART in eligible women is crucial for preventing morbidity and mortality in the women[29] and poor outcomes in their HIV-exposed infants,[30,31] including those associated with maternal illness and death.

In the present study, women with histories of injecting drug use were at increased risk of not receiving any antenatal ART, as reported previously in Ukraine[32] and also in the Russian Federation.[33] However, such women who had initiated ART were no less likely to have received cART than the women who had no histories of injecting drug use.

A move to Option B+ is not currently planned in Ukraine, although research to explore the feasibility of such a move was recently recommended following an external evaluation of the country's PMTCT programme (personal communication, Ruslan Malyuta, 2012). The present observations, which indicate inequitable access to, and slow implementation of, Option B in Ukraine, should contribute to discussions regarding the future adoption of Option B+ in the country, as should the general shortfall of ART for eligible individuals.[1] Some of the advantages offered by Option B+ (e.g. the reduction of future MTCT risk and the avoidance of repeated exposure to short-course ART for PMTCT[9]) may be more apparent in areas with higher rates of fertility than in Ukraine, where the overall fertility rate is just 1.5 children per woman.[4] However, nearly one third of HIV-positive childbearing women in Ukraine have HIV-negative partners,[34] a fact that highlights the potential benefit of Option B+ in preventing onward sexual transmissions.[35] Questions regarding Option B+ – including the risk–benefit ratio for the long-term treatment of ART-ineligible individuals and how to achieve equitable and sustainable ART access and improve retention in HIV care – are currently being addressed in other settings.

The Ukraine European Collaborative Study enrols around 30% of the HIV-positive women delivering nationwide, making its findings broadly generalizable despite some regional differences. For the present analyses, we used data for the first three complete years since the Option B policy was adopted in Ukraine. The corresponding data for 2011–2012 are not yet complete due to time lags in reporting, particularly in the reporting of infant infection status.

In conclusion, cART access for pregnant women in Ukraine improved substantially between 2008 and 2010, particularly for women eligible for ART, although national implementation of the Option B policy has been slow. If MTCT is to be eliminated by 2015, improvements in access to PMTCT services and in the retention of women in HIV care are urgently needed in Ukraine, alongside further roll-out of Option B. ■

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ملخص

توسيع نطاق الوصول إلى العلاج التوليفي بمضادات الفيروسات القهقرية في الحمل: نتائج مستخلصة من دراسة أترابية في أوكرانيا

الغرض تحري زيادة العلاج التوليفي بمضادات الفيروسات القهقرية (cART) قبل الولادة في أوكرانيا حيث أصبح جزءاً من السياسة الوطنية لتوقي انتقال فيروس العوز المناعي البشري من الأم إلى الطفل (PMTCT).

الطريقة تم تحليل البيانات التي تخص 3535 سيدة حاملاً إيجابية لفيروس العوز المناعي البشري تم تسجيلهن في الدراسة التعاونية الأوروبية الأوكرانية في الفترة من 2008 إلى 2010. وتم تحري العوامل المرتبطة بتسلم العلاج أحادي الدواء من نوع زيدوفودين (AZTm) – بدلاً من العلاج التوليفي بمضادات الفيروسات القهقرية – ومعدلات انتقال فيروس العوز المناعي البشري من الأم إلى الطفل.

النتائج ازدادت تغطية العلاج التوليفي بمضادات الفيروسات القهقرية بشكل كبير، من 22 ٪ من الولادات في عام 2008 إلى 61 ٪ من الولادات في عام 2010. وبعد تصحيحه من أجل العوامل المسببة للالتباس المحتمل، كان بدء العلاج أحادي الدواء بالزيدوفودين قبل الولادة – بدلاً من العلاج التوليفي بمضادات الفيروسات القهقرية – مرتبطاً بالمعاشرة (في مقابل الزواج؛ نسبة الانتشار المصححة: 1.09؛ فاصل الثقة 95 ٪: من 1.02 إلى 1.16) ومولودين حيين على الأقل في السابق (في مقابل عدم إنجاب مولود؛ نسبة الانتشار المصححة: 1.22؛ فاصل الثقة 95 ٪: من 1.11 إلى 1.35) وتشخيص الإصابة بعدوى فيروس العوز المناعي البشري أثناء الثلاثة شهور الأولى أو الثانية (في مقابل قبل الحمل؛ نسبة الانتشار المصححة: 1.11؛ فاصل الثقة 95 ٪: من 1.03 إلى 1.20). وكان المعدل الإجمالي لانتقال الفيروس من الأم إلى الطفل 4.1 ٪ (95 ٪ فاصل الثقة: من 3.4 إلى 4.9)؛ وكانت نسبة 42 ٪ (49/116) من حالات الانتقال ناجمة عن 8 ٪ (العدد = 238) من السيدات اللاتي لم تحصلن على العلاج بمضادات الفيروسات القهقرية قبل الولادة. وكان العلاج التوليفي بمضادات الفيروسات القهقرية، مقارنة بالعلاج أحادي الدواء بالزيدوفودين، مرتبطاً بزيادة الانخفاض بنسبة 70 ٪ في مخاطر انتقال الفيروس من الأم إلى الطفل (نسبة الاحتمال المصححة: 0.30؛ فاصل الثقة 95 ٪: من 0.16 إلى 0.56).

الاستنتاج في الفترة من 2008 إلى 2010، تحسن الوصول إلى العلاج التوليفي بمضادات الفيروسات القهقرية قبل الولادة بشكل كبير في أوكرانيا، غير أن تنفيذ سياسة الخيار "ب" لمنظمة الصحة العالمية كان بطيئاً. وثمة حاجة ماسة لإجراء تحسينات على استبقاء السيدات في رعاية فيروس العوز المناعي البشري وزيادة نشر الخيار "ب" من أجل التخلص من انتقال الفيروس من الأم إلى الطفل في أوكرانيا.

摘要

扩大使用孕期联合抗逆转录病毒疗法的影响：乌克兰队列研究结果

目的 调查在产前联合抗逆转录病毒疗法（cART）成为乌克兰预防艾滋病（HIV）母婴传播国家政策组成部分之后在该国的推广情况。

方法 对参与 2008-2010 年乌克兰欧洲合作研究的 3535 名 HIV 阳性孕妇的数据进行分析。调查了接受非 cART 的齐多夫定单药治疗（AZTm）与 HIV 母婴传播（MTCT）率的关联因素。

结果 cART 覆盖率显著增加，从 2008 年 22% 分娩增加到 2010 年 61%。在针对可能的混杂因素进行调整后，开始产前 AZTm（而非 cART）与同居生活（较之已婚；调整患病率比，aPR：1.09；95% 置信区间，CI：1.02 – 1.16）、之前至少两次活产（对比无活产；aPR：1.22；95% CI：1.11 – 1.35）以及孕前期或孕中期 HIV 感染诊断（对比孕前；aPR：1.11；95% CI：1.03 – 1.20）相关。整体 MTCT 率为 4.1%（95% CI：3.4 – 4.9）；42%（49/116）的传播来自 8%（n = 238）不进行产前 ART 治疗的女性。较之 AZTm，与 cART 关联而降低的 MTCT 风险要多 70%（调整优势比：0.30；95% CI：0.16 – 0.56）。

结论 在 2008 和 2010 年间，乌克兰产前 cART 的可及性得到显著改善，但是实施世界卫生组织方案 B 政策实施缓慢。要在乌克兰中消除 MTCT，迫切需要改善女性 HIV 医疗保持率和进一步推出方案 B。

Résumé

Impact de l'accès élargi au traitement par association d'antirétroviraux pendant la grossesse: résultats d'une étude de cohorte en Ukraine

Objective Étudier le renforcement du traitement prénatal par association d'antirétroviraux (TPAA) en Ukraine puisqu'il fait partie intégrante de la politique nationale pour la prévention de la transmission mère-enfant (PTME) du virus de l'immunodéficience humaine (VIH).

Méthodes Une analyse a été menée sur les données de 3535 femmes enceintes séropositives qui ont été inscrites dans l'étude collaborative européenne pour l'Ukraine en 2008-2010. Une étude a aussi été réalisée sur les facteurs associés à un traitement à la zidovudine en monothérapie (TZM), plutôt qu'à un TPAA, et sur le taux de transmission de la mère à l'enfant (TME) du VIH.

Résultats La part du TPAA a considérablement augmenté, passant de 22% des traitements en 2008 à 61% en 2010. Après ajustement pour les facteurs confondants possibles, le TZM prénatal, plutôt que le TPAA, a été associé au cas de cohabitation (par rapport au mariage; ratio de prévalence ajusté, RPa: 1,09; intervalle de confiance (IC) à 95%: 1,02 à 1,16), à au moins deux naissances antérieures (par rapport à aucune; RPa: 1,22; IC à 95%: 1,11 à 1,35) et à un diagnostic d'infection au VIH au cours du premier ou du deuxième trimestre (par rapport à avant la grossesse; RPa: 1,11; IC à 95%: 1,03 à 1,20). Le taux de TME global était de 4,1% (IC à 95%: 3,4 à 4,9), 42% (49/116) des transmissions provenaient des 8% (n = 238) de femmes n'ayant pas reçu de TPAA. Par rapport au TZM, le TPAA a été associé à une réduction supérieure à 70% du risque de transmission mère-enfant (rapport des cotes ajusté, RCa: 0,3; IC à 95%: 0,16 à 0,56).

Conclusion Entre 2008 et 2010, l'accès au TPAA s'est nettement amélioré en Ukraine, mais la mise en œuvre de l'option B de la politique de l'Organisation mondiale de la Santé a été lente. Pour que la TME soit éliminée en Ukraine, l'amélioration de la rétention des femmes dans les services de soins du VIH et la poursuite du déploiement de l'option B sont des points urgents à régler.

Резюме

Влияние расширения доступа к комбинированной антиретровирусной терапии во время беременности: результаты когортного исследования на Украине

Цель Проведение исследования в области увеличения масштабов применения дородовой комбинированной антиретровирусной терапии (кАРТ) на Украине с того момента, как она стала частью национальной политики в области профилактики передачи от матери к ребенку (ППМР) вируса иммунодефицита человека (ВИЧ).

Методы Были проанализированы данные по 3535 ВИЧ-инфицированным беременным женщинам, которые приняли участие в Украинско-Европейском совместном исследовании в 2008-2010 годах. Были исследованы факторы, связанные с использованием монотерапии зидовудином (АЗТм), вместо кАРТ, и количеством случаев передачи ВИЧ от матери к ребенку (ПМР).

Результаты Охват терапией кАРТ существенно вырос с 22% рождений в 2008 году до 61% в 2010 году. После поправки на возможные искажающие факторы, использование дородовой АЗТм, вместо кАРТ, было связано с сожительством (по сравнению с браком; скорректированный коэффициент распространенности (СКР): 1,09; 95% доверительный интервал (ДИ): 1,02-1,16), по крайней мере с двумя предыдущими живорождениями (по сравнению с их отсутствием; СКР: 1,22, 95% ДИ: 1,11-1,35) и постановкой диагноза ВИЧ-инфекции в течение первого или второго триместра (по сравнению с его постановкой до беременности, СКР: 1,11, 95% ДИ: 1,03-1,20). Общая частота ПМР составила 4,1% (95% ДИ: 3,4-4,9), 42% (49/116) случаев передачи были у 8% (N = 238) женщин без дородовой АРТ. По сравнению с АЗТм, кАРТ привела к 70%-му снижению риска ПМР (скорректированное соотношение шансов: 0,30, 95% ДИ: 0,16-0,56).

Вывод Между 2008 и 2010 годами доступ к дородовой кАРТ на Украине существенно улучшился, но реализация проводимой Всемирной организацией здравоохранения политики "Вариант Б" была слишком медленной. Для полного устранения ПМР на Украине требуется расширение участия женщин в программах лечения ВИЧ-инфекции и дальнейшее проведение в жизнь политики "Вариант Б".

Resumen

Repercusión del mayor acceso al tratamiento antirretroviral combinado durante el embarazo: resultados de un estudio de cohorte en Ucrania

Objetivo Investigar la generalización del tratamiento antirretroviral combinado prenatal en Ucrania desde que entró a formar parte de la política nacional de prevención de la transmisión de madre a hijo del virus de la inmunodeficiencia humana (VIH).

Métodos Se analizaron los datos de 3535 mujeres embarazadas seropositivas incluidas en el Estudio Colaborativo Europeo Ucraniano entre 2008 y 2010. Se investigaron los factores asociados a la recepción de una monoterapia con zidovudina —y no el tratamiento antirretroviral combinado prenatal— y las tasas de transmisión de madre a hijo del VIH.

Resultados La cobertura del tratamiento antirretroviral combinado prenatal aumentó significativamente, del 22% de partos en 2008 al 61% de los de 2010. Tras ajustarla por los posibles factores de confusión, el inicio de la monoterapia con zidovudina —y no el tratamiento antirretroviral combinado prenatal— estuvo asociado con la cohabitación (frente a los matrimonios; razón de prevalencia ajustada: 1,09; intervalo de confianza 95%: 1,02–1,16), al menos dos nacimientos vivos anteriores (frente a ninguno; razón de prevalencia ajustada: 1,22; intervalo de confianza 95%: 1,11–1,35) y un diagnóstico de infección por VIH durante el primer o segundo trimestre (frente a antes del embarazo, razón de prevalencia ajustada: 1,11; intervalo de confianza 95%: 1,03–1,20). La tasa total de transmisión de madre a hijo fue del 4,1% (intervalo de confianza 95% 3,4–4,9); el 42% (49/116) de las transmisiones fueron del 8% (n = 238) de las mujeres que no recibieron antirretrovirales prenatales. En comparación con la monoterapia con zidovudina, el tratamiento antirretroviral combinado prenatal estuvo asociado con una reducción un 70% mayor del riesgo de transmisión (razón de posibilidades ajustada: 0,30; intervalo de confianza 95%: 0,16–0,56).

Conclusión Entre 2008 y 2010, el acceso al tratamiento antirretroviral combinado prenatal mejoró sustancialmente en Ucrania, pero la implementación del enfoque en la opción B de la Organización Mundial de la Salud se reveló lenta. Para eliminar la transmisión de madre a hijo en Ucrania, se necesitan con urgencia mejoras en la retención de las mujeres en la atención al VIH y un mayor despliegue de la opción B.

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