Research Letter

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Immunologic status and virologic outcomes in repeat pregnancies to HIV-positive women not on antiretroviral therapy at conception: a case for lifelong antiretroviral therapy?

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During their second pregnancy with diagnosed HIV ($n = 1177$), two-fifths of women in the UK/Ireland not on antiretroviral therapy (ART) at conception had an immunological indication for treatment ($CD4^+$ <350 cells/μl), of whom nearly half had $CD4^+$ at least 350 cells/μl in their previous pregnancy. Those initiating ART during pregnancy had a 4.3-fold increased odds of detectable viral load at delivery compared with those conceiving on treatment, suggesting that continuation of ART after pregnancy may be beneficial for many women.

HIV-positive pregnant women not requiring treatment for their own health may take short-course antiretroviral therapy (ART) to prevent vertical transmission [1,2]. Although this is an effective prevention measure [3–5], increased morbidity and mortality among people randomized to scheduled HIV treatment interruptions have been reported in non-pregnant populations [6,7], which may have implications for optimal management of HIV in childbearing women. WHO guidelines provide the option of lifelong ART for pregnant women, irrespective of health status ('option B+') [8,9]. Pregnancy incidence among HIV-positive women in the UK is increasing [10], partly driven by the growing number of women having repeat pregnancies [11]. National surveillance data on diagnosed HIV-positive women reported with more than one pregnancy provide the opportunity to investigate immunological status at the start of second pregnancy, and viral suppression by delivery, in women not on ART at conception. This helps address the question of whether lifelong ART might be beneficial for all pregnant women.

In the UK/Ireland, pregnancies in diagnosed HIV-positive women are reported to the National Study of HIV in Pregnancy and Childhood (NSHPC) as described elsewhere [12]. We analysed data on repeat pregnancies (second reported since HIV diagnosis) during 2000–2010 in women not on ART at conception (53% of second pregnancies). First antenatal $CD4^+$ cell counts, prior to ART initiation, were used. UK national guidelines have recommended a treatment threshold of less than 350 cells/μl since 2008 [13,14]. For analyses exploring detectable maternal viral load at delivery (≥50 copies/ml), the comparison group comprised second pregnancies (resulting in live/stillbirth) to women conceiving on ART. Multivariable analyses were conducted using forward-fitted logistic regression models in STATA 12.0 (StataCorp, College Station, Texas, USA).

The main study group consisted of 1177 pregnancies to women not on treatment at conception; 1063 resulted in a live or stillbirth. Most (76.0%) were in women from sub-Saharan Africa, median age was 30.3 years [interquartile range (IQR) 26.9–33.8], and 43.4% occurred during 2008–2010. Median interval between conception of first and second pregnancies was 2.3 years (IQR 2.2–2.5).

Median pre-ART antenatal $CD4^+$ cell count at second pregnancy (available for 838/1177) was 390 cells/μl (IQR 271–534), measured at median 15.0 gestational weeks (IQR 9.6–20.6). Pregnancies in earlier years were more likely to have missing baseline $CD4^+$ cell counts (test for trend: $P < 0.001$), but there was no significant difference for other demographics (maternal age, world region of origin, probable source of HIV infection, or inter-pregnancy interval). Overall, 40.6% (340/838) of women not on ART at conception had reached the immunological threshold for treatment (39.8% during 2008–2010); 10% ($n = 85$) were severely immunosuppressed (<200 cells/μl). Half of those not yet requiring treatment for their own health (245/498) had $CD4^+$ 350–499 cells/μl. Among women requiring treatment for their own health at their second pregnancy, 44.3% (93/210) had $CD4^+$ at least 350 cells/μl at their first pregnancy; note also that 25.9% (93/359) with $CD4^+$ at least 350 cells/μl at first pregnancy had $CD4^+$ below 350 cells/μl by their second pregnancy.

Among 1063 women having a live/stillbirth, most ($n = 1028$) received antenatal ART, starting at median 23.7 gestational weeks (IQR 20.4–27.0), with earlier initiation over calendar time; from 25.6 weeks (IQR 23.4–29.5, 2000–2002) to 21.5 (IQR 18.6–24.5, 2009–2010) (test for trend: $P < 0.001$). Analyses of detectable viral load at delivery were conducted on these 1028 women, and 914 women conceiving on ART. The former were younger, more likely to have delivered during an earlier time period, and to have received protease inhibitor-based highly active antiretroviral therapy during pregnancy (all $P < 0.05$). Delivery viral loads were reported for similar proportions in both groups: 59.6% and 54.2%, respectively. Imputation of

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missing viral load at delivery as undetectable if there was an undetectable viral load earlier in pregnancy increased data to 86.8% (1686/1942) for all pregnancies: 81.7% among those not on ART at conception and 92.6% among those who were. Overall, 16.2% (273/1686) had detectable viral load (median 188 copies/ml, IQR 90–590, range 51–412 000) – 26.2% in women starting ART in pregnancy and 6.3% among those conceiving on ART (Table 1). Vertical transmission rates were 0.91% (8/878) and 0.27% (2/740), respectively ($P = 0.121$). Among those starting ART during pregnancy, the proportion not suppressing by delivery increased the later ART was started, from 15.8% (6/38) in the first to 35.7% (71/199) in the third trimester.

In multivariable analyses, women starting ART during pregnancy had 4.3-fold increased odds of detectable viral load adjusting for time period, region, ART type, and earliest $CD4^+$ cell count, compared with women conceiving on ART (Table 1). Earliest viral load was not included in the model as most women conceiving on ART had undetectable viral load. As a sensitivity analysis, the model was re-run using the original non-imputed viral load variable; the adjusted odds ratio (aOR) was similar [3.85, 95% confidence interval (CI) 2.65–5.59]. The association was also similar when the main model was re-run excluding seven 'high-risk' women who received less than 14 days ART (aOR 4.31, 95% CI 3.01–6.18).

Our results should be interpreted in the light of some international guidelines now recommending ART initiation regardless of $CD4^+$ cell count [15,16], and the debate around potential benefits and risks of option B+ [17]. Here, two-fifths of women not on ART at conception of their second pregnancy had an immunological indication for treatment according to current UK guidelines [13,14]. For some, this may reflect disengagement from HIV care postnatally, which needs addressing,

Table 1. Univariable and multivariable analyses of the association between timing of ART and detectable maternal viral load at delivery among second pregnancies to diagnosed HIV-positive women.

		Univariable analyses			Multivariable analysis ($n = 1590$)		
	Detectable/total (%)	OR	95% CI	*P*-value	aOR	95% CI	*P*-value
Timing of ART							
After conception	220/840 (26.2)	5.31	(3.86–7.30)		4.34	(3.03–6.20)	
Prior to conception	53/846 (6.3)	1		<0.001	1		<0.001
Maternal age group (years)							
<25	33/184 (17.9)	1		0.046			
25–34	183/1049 (17.4)	0.97	(0.64–1.46)				
≥35	57/452 (12.6)	0.66	(0.41–1.05)				
Maternal region of origin							
UK/Ireland	30/234 (12.8)	1		0.288			
Sub-Saharan Africa	218/1317 (16.6)	1.35	(0.90–2.03)				
Elsewhere	24/134 (17.9)	1.48	(0.83–2.66)				
Maternal HIV risk factor							
Other[a]	260/1612 (16.1)	1		0.499			
Injecting drug use	7/34 (20.6)	1.35	(0.58–3.13)				
Time period							
2000–2002	12/47 (25.5)	2.34	(1.16–4.70)	<0.001	3.32	(1.38–8.00)	
2003–2005	76/338 (22.5)	1.98	(1.39–2.81)		1.90	(1.24–2.90)	
2006–2008	110/715 (15.4)	1.24	(0.90–1.70)		1.05	(0.74–1.49)	
2009–2010	75/586 (12.8)	1			1		0.002
Reporting region							
London	141/830 (17.0)	1		0.001	1		<0.001
Elsewhere in England	116/647 (17.9)	1.07	(0.81–1.40)		1.34	(0.98–1.83)	
Wales/Scotland/N Ireland	3/63 (4.8)	0.24	(0.08–0.79)		0.31	(0.09–1.06)	
Ireland	13/145 (9.0)	0.48	(0.26–0.88)		0.42	(0.22–0.80)	
Type of antenatal ART							
Mono/dual	33/71 (46.5)	3.96	(2.42–6.50)	<0.001	2.89	(1.65–5.06)	
HAART – PI-based	177/985 (18.0)	1			1		<0.001
HAART – NNRTI-based	45/536 (8.4)	0.41	(0.29–0.58)		0.48	(0.32–0.74)	
HAART – other[b]	18/94 (19.1)	1.13	(0.66–1.91)		1.16	(0.62–2.18)	
Earliest $CD4^+$ cell count[c] (cells/μl)							
≥500	60/534 (11.2)	1		<0.001	1		<0.001
350–499	82/486 (16.9)	1.60	(1.12–2.29)		1.94	(1.31–2.87)	
200–349	77/442 (17.4)	1.67	(1.16–2.40)		2.00	(1.34–2.97)	
<200	38/128 (29.7)	3.34	(2.10–5.31)		4.50	(2.69–7.51)	

aOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor.
[a]Includes heterosexual transmission, originating from a high HIV prevalence area, and vertical transmission.
[b]Includes those receiving NNRTIs and PIs, and those receiving NRTIs only – groups combined due to small numbers.
[c]Earliest measurement in women's second reported pregnancy, not restricted to measurements taken prior to ART initiation.

particularly for women initiating ART late in their subsequent pregnancy. Possible barriers to access include stigma, fear of disclosure, and childcare responsibilities [18–20]. It is also salient that a quarter of women with $CD4^+$ at least 350 cells/μl at their first pregnancy had fallen below the treatment threshold by their second pregnancy. Significant levels of disease progression after discontinuation of antenatal ART have been reported elsewhere [21–24]. Longer duration of antenatal ART decreases risk of detectable viral load at delivery, and hence the risk of vertical transmission [4,5,25–27], but the four-fold increased odds of detectable virus among those initiating ART during, rather than before, pregnancy is striking.

In conclusion, these findings suggest that in terms of maternal health and vertical transmission, continuation of ART post-natally could have benefits for many HIV-positive women and their future pregnancy outcomes. However, this needs consideration in the broader context of issues such as potential toxicity (particularly first-trimester ART exposure), adherence, drug resistance, obstetric outcomes, and women's views and preferences.

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Conflicts of interest

We declare that there are no conflicts of interest.

Ethical approval: The National Study of HIV in Pregnancy and Childhood has London Multi-Centre Research Ethics Committee approval (MREC/04/2/009).

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