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Does initiation of highly active antiretroviral therapy (HAART) before pregnancy increase risk of adverse outcomes: miscarriage, prematurity, stillbirth?

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Background: prevention of mother-to-child transmission

- Strategies to prevent MTCT overwhelming success
  - RCT (ACTG 076) shows AZT to significantly reduce MTCT
- Overall perinatal transmission rate 2012 ~2% UK [1]
  - <1% in women diagnosed pre-delivery

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Background: Adverse pregnancy outcomes

- Miscarriage ~ 17% [3]
  - Decreasing with gestational age [4]
- Preterm Delivery ~ 8.6% (developed regions) [6]
- Role of HIV infection [7]
- Role of HAART: inconclusive evidence

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Objectives

- To investigate the rate of adverse pregnancy events

- Are adverse events associated with timing of initiation of HAART?

Methods

Study population

- All women registered at UHB HIV pregnancy services
- October 1997 to June 2012
- Managed according to hospital policy:
  - Monthly follow-up until delivery

Methods: Adverse Outcomes

Miscarriage

- Any delivery occurring < 24 weeks gestation not resulting in a live birth

Preterm delivery

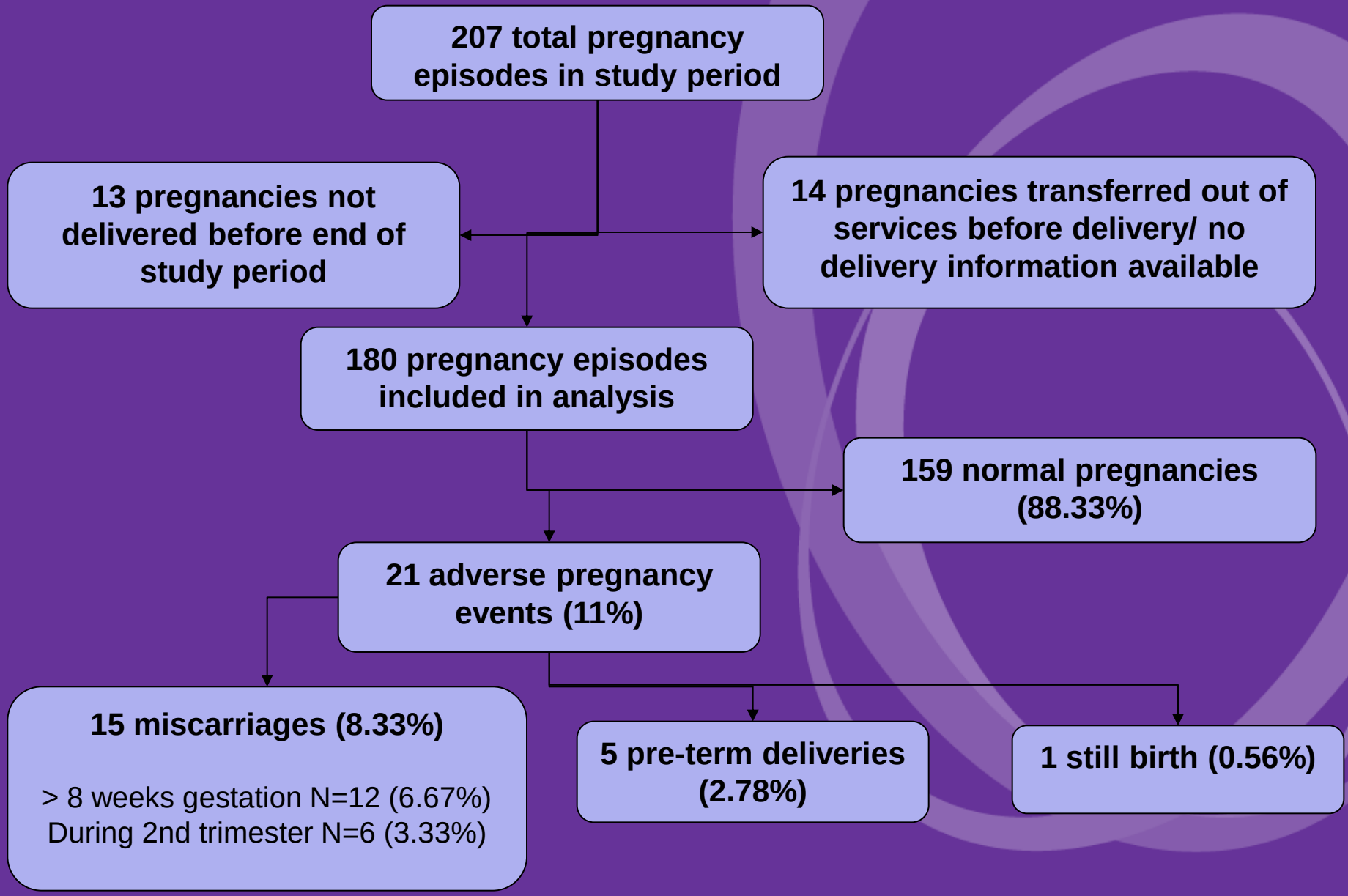
- Any delivery occurring ≥ 24 weeks and < 37 weeks gestation resulting in a live birth

Stillbirth

- Any delivery occurring ≥ 24 weeks not resulting in a live birth

Methods: Statistical analysis

- Primary exposure variable: initiation of HAART pre-pregnancy
- Univariate analysis
  - logistic regression
- Multivariate analysis
  - step-wise multiple logistic regression model


207 total pregnancy episodes in study period
13 pregnancies not delivered before end of study period
14 pregnancies transferred out of services before delivery/ no delivery information available
180 pregnancy episodes included in analysis
159 normal pregnancies (88.33%)
21 adverse pregnancy events (11%)
15 miscarriages (8.33%)
> 8 weeks gestation N=12 (6.67%)
During 2nd trimester N=6 (3.33%)
5 pre-term deliveries (2.78%)
1 still birth (0.56%)

HAART Combinations

HAART combination	Started pre-pregnancy, N (%)	Started during pregnancy, N (%)	Difference (%, 95% CI, P-value)
Combivir/ Kaletra	12 (15.19)	67 (68.37)	-53.1 (-65.3, -41.0) P<0.001
Combivir/ Neveripine	7 (8.89)	15 (15.31)	-6.4 (-15.9, -3.1) P=0.198
Atripla	12 (15.19)	0 (0)	15.2 (7.3, 23.1) P<0.001
Kivexa/ Kaletra	4 (5.06)	1 (1.02)	4.0 (1.2, 9.3) P=0.1067
Truvada/ Kaletra	7 (8.89)	2 (2.04)	6.9 (0.1, 13.7) P<0.001
Other	35 (44.30)	13 (13.27)	31.0 (18.2, 43.9) P<0.001
Total	**79 (100.00)**	**98 (100.00)**	

Descriptive Analysis

	Normal Pregnancy (N=159)	Adverse Outcome (N=21)	Difference (%, 95% CI, P-value)
HAART pre-pregnancy (%)	61 (38.3)	18 (85.7)	- 47.4 (-64.2, - 30.6) P<0.001
Late presentation (>13 weeks) (%)	90 (56.6)	7 (33.33)	23.3 (1.7, 44.9) P=0.04
Baseline CD4 count < 350 cells/mm3 (%)	59 (38.8)	3 (15.8)	23.0 (5.7, 40.3) P=0.03
Viral load < 50 copies/ mL at pregnancy event (%)	55 (34.6)	15 (71.4)	- 36.8 (- 58.5, -16.1) P=0.001
New diagnosis HIV at ANC (%)	7 (4.4)	0 (0.0)	4.4 (3.6, 5.2) P<0.001
Median age at delivery (range)	30.74 (19.3 – 42.3)	32.3 (20.8 – 43.2)	-1.71 (-4.4, 1.1) P=0.21

Multivariate Analysis: Adverse Outcomes

Variables in model	Odds ratio (95% CI)	P-value
HAART initiated pre-pregnancy	**8.817 (1.326 – 58.610)**	**0.024**
Viral load <50 copies/mL	1.273 (0.281 – 5.759)	0.754
Late presentation	0.646 (0.201 – 2.078)	0.464
CD4 <350 cells/mm3	0.429 (0.111 – 1.662)	0.220

Limitations

- Small numbers in the outcome variables
  - Sufficient power (96%) at the 5% level to detect an effect
- Lack of data on potential confounders:
  - Maternal medical and gynaecological history
  - Social factors
- Potential bias from late presentation:
  - Miscarriages in late presenters missed
  - Higher proportion of late presenters in during pregnancy HAART group

Conclusions

- High rate (11%) of adverse pregnancy events in HIV infected women
- Initiation of HAART before pregnancy appears to increase the rate of adverse pregnancy outcomes

Acknowledgments

- Joyful Chigiga – Data collection
- Kaveh Manavi – Supervision
- UHB HIV services

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Univariate Analysis:

Odds ratios for adverse outcomes in women initiated on HAART before pregnancy compared to during pregnancy

Variable	Odds ratio (95% CI)	P-value
Adverse outcome	9.639 (2.725 - 34.096)	0.000
Miscarriage	9.75 (2.13 – 44.62)	0.003
Preterm delivery	5.33 (0.58 – 48.70)	0.138
Stillbirth	-	-

Univariate Analysis: Miscarriage

Variable	Odds ratio (95% CI)	P-value
CD4 count <350 cells/mL	0.503 (0.133 – 1.903)	0.312
Viral load at pregnancy event <50 copies/mL	3.500 (1.142 – 10.720)	0.028
Age at delivery >35 years	1.041 (0.269 – 4.035)	0.953
Time diagnosed pre-pregnancy	1.016 (1.002 – 1.031)	0.028
Late presentation (>13 weeks)	0.282 (0.086 – 0.921)	0.036

Results

Prematurity

- 5.1% (4/79) initiating HAART pre-pregnancy
- 1% (1/101) starting HAART during pregnancy
- not statistically significant: OR 5.33 (95% CI 0.58 – 48.70)

Stillbirth

- 1.3% (1/79) initiating HAART pre-pregnancy
- 0% (0/101) starting HAART during pregnancy
- due to small numbers, this was not significant

Power and sample size

- 96.7% power to detect a difference at 5% significance level

HAART Combinations

HAART combination	Pre-pregnancy, N (%)		During Pregnancy, N (%)	
Combivir/ Zidovudine/ Lamivudine	32	(17.78)	130	(72.22)
Truvada/ Tenofovir	26	(14.44)	34	(18.89)
Kivexa/ Abacvir	14	(7.78)	14	(7.78)
Atripla/ Efavirenz	20	(11.11)	9	(5.00)
Kaletra/ protease inhibitor	42	(23.33)	132	(73.33)

Univariate Analysis:

Predicting factors for adverse outcome (preterm delivery, miscarriage, still birth) in HIV infected pregnancies

Variable	Odds ratio (95% CI)	P-value
HAART pre-pregnancy	**9.639 (2.725 – 34.096)**	**0.000**
Viral load at pregnancy event <50 copies/mL	**4.727 (1.736 – 12.869)**	**0.002**
Time diagnosed pre-pregnancy	**1.013 (1.000 – 1.026)**	**0.043**
Late presentation (>13 weeks)	0.383 (0.146 – 1.001)	0.050
CD4 count <350 cells/mm3	0.296 (0.083 – 1.058)	0.061
Age at delivery >35 years	1.649 (0.579 – 4.696)	0.349

Total on HAART	**79/ 180 (43.89)**	**98/ 180 (54.44)**	**-10.6 (-21.2, -0.6) P=0.037**
Not on HAART	**101/ 180 (56.11)**	**3/ 180 (1.67)**	**54.4 (47.0, 61.9) P<0.001**

Variables in model	Odds ratio (95% CI)	P-value
Combivir-regime pre-pregnancy	**6.91 (1.66 – 28.70)**	**0.008**
Atripla-regime pre-pregnancy	**6.07 (1.11 – 33.2)**	**0.037**
Truvada-regime pre-pregnancy	1.73 (0.34 – 8.97)	0.511
Kivexa-regime pre-pregnancy	0.45 (0.05 – 4.25)	0.488
Protease inhibitor pre-pregnancy	1.46 (0.27 – 7.80)	0.657
Late presentation	0.44 (0.13 – 1.49)	0.186
Viral Load <50 copies/ L at event	1.32 (0.28 – 6.29)	0.728
Baseline CD4 <350 cells/ mm3	0.56 (0.14 – 2.30)	0.424

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