

Pregnancy and pregnancy outcome among women in the DART trial

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UPDATED ABSTRACT

Background: DART is a randomised trial of ART monitoring strategies among adults with symptomatic HIV infection and CD4-200 cells/mm³ initiating ART in Kampala and Entebbe (Uganda) and Harare (Zimbabwe). 1866/3316 enrolled participants are women of child-bearing age (>45 years).

Methods: Reported pregnancies are confirmed by testing and information is collected two weeks postpartum on outcome, mother and infant ART, breast-feeding and congenital abnormalities.

Results: After a median 2.8 years follow-up, 221 pregnancies have been reported in 198(10.6%) women <45 years at enrolment (4.6/100 person-years (95% CI 4.0-5.2)); 19 women had 2 and 2 women had 3 pregnancies. Median (IQR) baseline CD4 was 115 (49-158) cells/mm³ in women who became pregnant vs 87 (31-140) in those who did not (p=0.001); 18% vs 25% were WHO stage 4 at baseline (p=0.07). Pregnancy rate increased with time on ART (3.7, 4.3, 5.9/100 pyr 0-6, 7-12, >12 months from ART initiation respectively). Proportions of women becoming pregnant in Entebbe, Kampala and Harare were 14%, 8% and 10% respectively (2%, 15%, 20% women aged 18-30). All women took ART in pregnancy and all except one continued through delivery. 17 (21%) pregnancies are ongoing and 9 (4%) with gestation >40 weeks have outcome currently unknown. Among 164 with known outcome and pregnancy started >40 weeks ago, ART regimens at start of pregnancy were combivir with TDF (70%), NVP (15%) or ABC (4%), d4T containing regimens (3%) and other (2%). Overall, 78% took TDF at same time during pregnancy, 91 (55%) were live births, 11 (7%) stillbirths and 62 (38%) terminations (15 reported before 15 weeks; 31 reported as induced, varying by clinical site). 18 (18%) of the 102 births were delivered by caesarean (9 emergency, 9 elective), 18 (18%) had gestation <37 weeks (10 live births (6 <33 weeks), 8 stillbirths (8 <33 weeks)) and 3 (3%) had congenital abnormalities (2 club foot, 1 hydrocephalus (died)). Four women died (1 following post-partum haemorrhage, 1 puerperal psychosis, 1 septic abortion, 1 malaria), 70 of 91 (77%) infants received ART (sdNVP 42%, 7-15 days ZDV 13%, sdNVP+ZDV 20%, other 4%). There have been 5 neonatal deaths, 4 within 24 hours (<37 weeks gestation), 22 (26%) of 86 infants known to be alive at two weeks were breast-fed. No infants have been diagnosed as HIV infected.

Conclusions: Pregnancy rates increased over time and foetal loss varies by site. This is the largest dataset on in utero exposure to NRTI; so far, congenital abnormality rates appear similar to other studies. Despite taking HAART, a minority of women choose to breastfeed. Follow-up of infants to ascertain infection status and monitor effects of intramammary ART is ongoing.

DART: RATIONALE and DESIGN

The DART (Development of Antiretroviral Therapy) trial is the first to investigate strategies for monitoring ART in Africa. The trial is for six years and participants are randomised to:

- Clinical Monitoring Only (CMO): biochemistry and FBC performed if clinically indicated, no CD4
 - Laboratory and Clinical Monitoring (LCM): 12 weekly biochemistry and FBC, CD4
- There are no real-time viral load measurements in either arm
- A second randomisation addressing whether antiretroviral therapy (ART) could be given intermittently (12 weeks on, 12 weeks off) was terminated early on recommendation of DSMC in March 2006¹; all patients are now on continuous ART, or off ART for other reasons

WOMEN IN DART - COUNSELLING AND CARE

- 2156 women are enrolled in DART, 1866 (87%) of whom are of child-bearing age, i.e. aged less than 45 at enrolment
- Women were not enrolled if pregnant
- Women becoming pregnant in DART:
 - continue taking ART with regimen modifications if indicated
 - continue follow-up in their randomised group (CMO or LCM) with extra visits if necessary
 - may have extra blood tests requested by doctor at any time for management during pregnancy, whether in CMO or LCM arm
- Women are encouraged to:
 - avoid unwanted pregnancy: contraceptive advice is available (including free condoms)
 - seek counselling if they wish to become pregnant
 - disclose any pregnancy after enrolment, continue ART and attend usual ante-natal care outside of DART

ANALYSIS

- A description of incidence and outcome of pregnancy in DART
 - Follow-up to December 2006
 - Pregnancy incidence: by maternal age, time since starting ART and clinical site
 - Disease severity: CD4 and WHO stage at enrolment by ever pregnant or not in DART
 - Use of ART: Maternal ART during pregnancy, infant and maternal ART at delivery
 - Outcome of pregnancy: restricted to pregnancies with estimated date of onset more than 40 weeks ago to avoid over-counting miscarriages whose outcome will be known sooner
 - Follow-up at two weeks post partum: infant survival, HIV testing and breastfeeding

ALL PREGNANCIES

198 women - 221 pregnancies

Table 1: Baseline characteristics of those ever pregnant versus never pregnant in DART (women aged <45)

	Ever pregnant	Never pregnant	ALL
Women aged <45 at enrolment	198 (11%)	1668 (89%)	1866 (100%)
Age at enrolment (mean, (s.d.), (range))	30.7 (4.6) (18-43)	34.9 (5.5) (19-44)	34.5 (5.6) (18-44)
CD4 at enrolment (median, IQR)	115 (49-158)	87 (31-140)	90(32-142)
WHO stage at enrolment			
2	48 (24%)	345 (21%)	393 (21%)
3	114 (58%)	898 (54%)	1012(54%)
4	36 (18%)	425 (25%)	461 (25%)

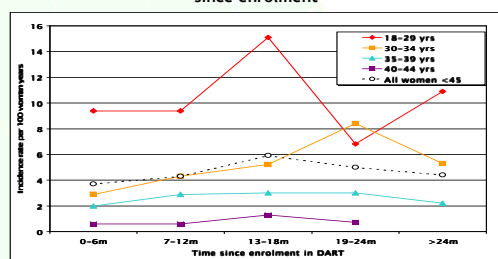
- Women who get pregnant have higher CD4 (Wilcoxon p<0.001) and less severe WHO staging (chi-square p=0.07) at baseline than those who do not

Table 2: Women ever pregnant in DART and multiple pregnancies by centre

	Centre			
	Entebbe	Kampala	Harare	ALL
Women in DART	685	893	578	2156
Aged < 45 at enrolment	589	775	502	1866
Ever pregnant in DART	85	65	48	198
ever preg aged <45 (n,%)	85 14.4%	65 8.4%	48 9.6%	198 10.6%
ever preg aged >30 (n,%)	47 29.2%	24 14.6%	21 20.4%	92 21.5%
Two pregnancies in DART	12	4	3	19
Three pregnancies in DART	1	0	1	2
Total pregnancies	99	69	53	221

- Median follow-up time is 2.8 years
- Pregnancy rates vary by centre with younger women in rural Entebbe having almost double the rates seen in urban Kampala, 30 miles away.
- Almost half the pregnancies (104/221 (47%)) were in women aged under 30; all were aged under 45 at enrolment to DART

Figure 1: All pregnancies: incidence by age group and time since enrolment



- Overall, pregnancy rates rose during the first 18 months of follow-up and are now stabilising
- Rates in younger women show a marked increase after a year, followed by a decline
 - A possible explanation is unexpected return of fertility as health improves on ART, followed by improved contraception with counselling

PREGNANCY OUTCOMES

164 pregnancies started > 40 weeks ago

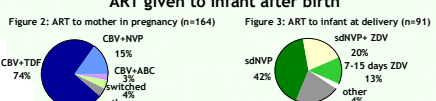
TERMINATIONS AND MISCARRIAGES

Defining the type of termination

- The distinction between induced abortion and spontaneous abortion/miscarriage is not well defined in this setting
 - medical abortion is not generally legal in either Uganda or Zimbabwe although, in Zimbabwe, an HIV positive woman may have an elective medical abortion on medical advice. These are recorded as induced abortion
 - women sometimes terminate unwanted pregnancies themselves and are usually reluctant to disclose this at counselling. These may be recorded as spontaneous abortion/miscarriage
- Pregnancy intentions are not recorded in DART, prospectively or retrospectively

ART TO MOTHER AND INFANT

ART taken by mother during pregnancy and at delivery, ART given to infant after birth



- Mothers during pregnancy
 - 87% of women stayed on the same ART regimen throughout pregnancy, or had breaks of < 4 weeks
 - 4% switched one or more drugs
 - 8% had more than 4 weeks off ART during pregnancy
- Mothers during delivery
 - Virtually all women took their DART ART during delivery, one was off DART drugs for three weeks, three missed ART on the day of caesarean section.
- Infants at birth
 - Rationale for giving NVP to babies whose mothers received CBV-TDF was to provide post-exposure prophylaxis with a new drug (viral load is not measured)
 - 75% of infants whose mothers were taking TDF or ABC were given NVP, ZDV or both at birth

MATERNAL AND OBSTETRIC OUTCOME

- Maternal deaths: four pregnant women had died
 - Two during pregnancy: one severe malaria, one septic abortion
 - Two at delivery: one post-partum haemorrhage, one puerperal psychosis
- Mode of delivery (live and still births, n=102)
 - 74 (73%) vaginal delivery
 - 18 (18%) by caesarean section: 9 elective, 9 emergency
 - 10 (10%) were of unknown delivery type

PREGNANCY OUTCOME BY CENTRE

Table 3: Outcome of pregnancy by centre (n,%) (164 pregnancies starting more than 40 weeks ago)

	Centre			
	Entebbe	Kampala	Harare	Total
Termination (any type)	34 (44%)	20 (40%)	8 (22%)	62 (38%)
induced	22 (28%)	5 (10%)	4 (11%)	31 (19%)
spontaneous	12 (15%)	15 (30%)	4 (11%)	31 (19%)
Termination <15 wks*	28 (82%)	14 (70%)	5 (63%)	47 (76%)
Still birth (>=24 wks)	7 (9%)	3 (6%)	1 (3%)	11 (7%)
Live birth (>=24 wks)	37 (47%)	27 (54%)	27 (75%)	91 (55%)
All pregnancies started more than 40 weeks ago	78 (100%)	50 (100%)	36 (100%)	164 (100%)

* Gestational age is not precisely known, particularly for pregnancies first reported when already aborted or miscarried. For two, gestation is unknown

INFANT OUTCOME AND EARLY FOLLOW-UP

Table 4: Live births: Characteristics by centre (n,%) for pregnancies starting more than 40 weeks ago

	Centre			
	Entebbe	Kampala	Harare	Total
Live births	37	27	27	91
Premature (24-36 wks)	5(14%)	2 (7%)	3 (11%)	10 (11%)
Birthweight known*	31	25	26	82
Birthweight kg; mean (sd)	2.8 (0.5)	3.0 (0.5)	2.7 (0.7)	2.8 (0.6)
low: <2.5kg; n (%)	7 (23%)	3 (12%)	7 (27%)	17(21%)

* For some babies details of birth were not available; some of these were born at home

- Foetal abnormalities: three infants affected
 - One with hydrocephalus (died), two congenital talipes (club foot)
- Infant deaths:
 - Five infants did not survive to two weeks; four died on the day of delivery (one with hydrocephalus, one mother died) and one the next day. Cause of infant deaths will be included in a now approved infant follow-up study
- Breastfeeding:
 - Only 22 (26%) were breastfeeding at two weeks, 7 (19%) in Entebbe, 3 (13%) in Kampala and 12 (48%) in Harare.
- HIV status of infant:
 - No infant has yet been reported as HIV positive, the numbers known to have been tested at two weeks is small and status later on will be better ascertained in the specific infant follow-up study.

SUMMARY

- 198 (10.6%) of 1866 women aged <45 in DART have so far had at least one pregnancy and 21 (1.1%) have had two or more. The pregnancy rate is low compared with uninfected African women (for example, as observed in the microbicides programmes).
- Women who have become pregnant had less severe HIV disease at enrolment than those who have not, as observed in other studies*
- There was an increase in incidence across all ages to about 18 months, after which rates declined or stabilised
- Amongst the 164 pregnancies estimated to have started more than 40 weeks ago, 91 (55%) have resulted in live births, with 86 surviving at two weeks after birth
- The rate of spontaneous miscarriage is relatively high, but similar rates have been reported elsewhere*
- Almost all women continued to take their DART drugs during pregnancy and delivery
- No infant has so far been found to be HIV positive
- This is the largest reported study of triple NRTIs given throughout pregnancy, and the only current one including tenofovir.
- Follow-up of infants born to DART mothers has received ethical approval and is about to start

* Ross A. AIDS. 2004 Mar 26 * Gray HG. Lancet 1998 Jan 10

ACKNOWLEDGEMENTS

We thank all the patients and staff from all the centres participating in the DART trial. **MRC Programme on AIDS/Uganda Virus Research Institute, Entebbe:** G Grosskurth, P Munderi, K Wangati, D Kajungu, B Amuron, D Nsubambi, R Kasirye, E Zalwango, M Nakazibwe, B Kikaire, G Nassura, R Massa, K Fadhiri, M Namalya, A Zalwango, L Generous, P Phauka, H Rutikarayo, W Nakahira, A Mugisha, J Nakinyi, P Hughes, Joint Clinical Research Centre, Kampala, Uganda: P Mugenyi, C Kityo, D Tamukunde, F Ssali, D Atwine, G Mulindwa, G Kabuye, R Byaruhanga, T Bakiemyaga-Grace, H Katzirira, E Ninwestiga, G Barungi, S Atwine, F Ahimbisibwe, S Tugume, T Otini, J Takubwira, M Mulindwa, S Muringi, J Tukumushaba, D Muebeza, H Kyomugisha, J Kagira, L Namale, University of Zimbabwe, Harare, Zimbabwe: J Hakim, A Latif, A Reid, V Robertson, R Bilaya-Tembo, C Chimberete, A Jamu, S Matoka, I Mupuzi, G Musoro, H Ngorima, M Pascoe, F Taziwa, C Warambwa, E Chidziva, E Chigwevede, M Phiri, C Chakona, G Tinago, H Chirairo, G Musoro, F Mapepe, A Mawora, R Shoniva, E Zengeza, J Chimani, J Machingura, C Maweni, S Mutsai, R Warara, M Matongo, P Baranani, N Mweje, S Mudzingira, M Jangano, I Machingura, K Moyo, L Vere, C Tsipa, N Mavandani, Academic Alliance, Mulago Hospital, Uganda: E Katzirira, J Oyugi, A Ronald, A Kambugu, J Martin, R Nalumenya, R Nairubi, E Bulume, M Teoptisa, C Twijukye, F Sematala, H Byakwaga, The AIDS Support Organisation (TASO), Uganda: A Coutinho, B Etkoiti, Imperial College London, UK: C Gilks, K Boocock, C Pudgehatti, D Winogron, MRC Clinical Trials Unit, London, UK: J Darbyshire, DM Gibb, A Burke, D Bray, A Babiker, AS Walker, H Wilkes, M Rauchenberger, S Sheehan, L Peto, K Taylor, Trial Steering Committee: I Weller (Chair), A Babiker (Trial Statistician), S Bahendeka, M Bassett, A Chogo Wapakhabulo, J Darbyshire, B Gazzard, C Gilks, H Grosskurth, J Hakim, A Latif, C Mupfuchere, O Mugurungi, P Mugenyi, Observers: S Jones, E Louieger, P Haidoo, M Palmer, J Rooney, J Strens, Data and Safety Monitoring Committee: A McLaren (Chair), P Matenga, A Pozniak, D Serwadda, Endpoints Review Committee: T Peto (Chair), A Palireema, M Borok, E Katzirira. Funding: DART is funded by the UK Medical Research Council, the UK Department for International Development (DFID), and the Rockefeller Foundation. GlaxoSmithKline, Gilead and Boehringer-Ingelheim donated first-line drugs for DART. Thanks also to Dr Hermione Lyall, St Mary's Hospital, London, UK, and Dr Graham Taylor, Imperial College, London, UK, for advice on management of pregnancy in DART.