

# Single Antiretroviral Substitutions among Pregnant Women Compared to Non-Pregnant Women and Men Who Initiated ART in the MTCT-Plus Initiative

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## BACKGROUND

The **MTCT-Plus Initiative** supports family-focused HIV care and treatment in 14 sites in 9 resource limited countries in sub-Saharan Africa and Thailand. (Figure 1) HIV-infected women are enrolled during pregnancy or immediately postpartum and invited to enroll their HIV-exposed infants along with all other HIV-infected adults and children living in the household.

The care and treatment of infected adults includes:

- Provision of cotrimoxazole and ART
- Initiation of ART according to WHO and/or national guidelines
- Psychosocial counseling and adherence support

Starting ART regimens varied across countries and were determined based on national guidelines, local site preference and the WHO pre-qualification list.



Figure 1: MTCT-Plus Initiative Program Sites

## METHODS

**Cohort:** ART-naïve adults, 15 years or older, who initiated ART between Feb 2003 –Jan 2007 at MTCT-Plus Initiative sites. All adults had a potential for 6+ months of follow-up.

**Clinical follow-up:** All participants received a clinical evaluation, including WHO staging, and CD4 cell count and CBC at enrollment. Patients were followed up at least every 2 weeks after initiating ART during the first 6 months and at least every 3 months thereafter. At ART initiation, adults received CD4 testing, hemoglobin and liver function tests, followed by CD4 biannually. Women who were pregnant at ART initiation however, had more frequent laboratory monitoring with LFTs repeated every 2 weeks until delivery. Sites could do other laboratory investigation on a clinical basis, but it was not recommended for routine care on any regimen. Sites followed WHO and national guidelines for regimen changes based on clinical or laboratory findings.

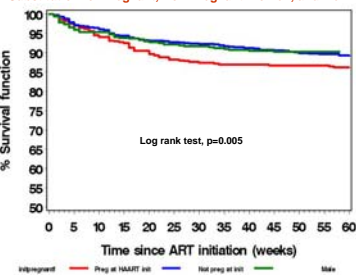
**Data:** Routine service delivery data including: age, sex, country of enrollment, ART start date and initial regimen, WHO staging, CD4 cell count, and pregnancy status at time of ART initiation (baseline), regimen changes, reason for change, and dates and vital status at follow-up visits. Data from Mozambique and Cameroon were excluded either because they were not operational for at least one year (Cameroon) or were no longer reporting routine clinical data (Mozambique). A **single drug substitution (SDS)** was defined as a change of one anti-retroviral for  $\geq 7$  days. At each follow-up visit if the regimen was changed the clinician could indicate the reason for stopping using six response options: 1. Toxicity/side effects, 2. Drug interaction, 3. Non-adherence, 4. Treatment failure, 5. Patient refusal, 6. Stockouts, 7. PMCT/breast feeding prophylaxis, 8. Other

**Statistical analysis:** Chi-square tests and Wilcoxon rank-sum tests were used to compare baseline characteristics among men, pregnant and non-pregnant women. Kaplan-Meier graphs were used to compare time to first SDS among the 3 groups (pregnant, non-pregnant female, and male) and by initial regimen. Cox proportional hazard models were used to adjust for the effect of demographic (age, country) and baseline clinical characteristics (WHO stage and CD4 count). Data was right censored at the date of last visit, or date of death, voluntary withdrawal or loss to follow-up.

Table 1. Baseline Characteristics of Cohort

	Total				Pregnant women				Non-pregnant women				Men	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Median age (IQR)	30	27.34	34	25.32	29	28.33	34	31.33	34	31.33	34	31.33	34	31.33
Median follow up time, weeks (IQR)	99.3	(58.1 - 135)	100.0	(80.0 - 137.1)	95.0	(53.3 - 131.6)	108.1	(62.7 - 140.0)						
Median CD4 count at ART initiation, cells/mm <sup>3</sup> (IQR)	156	(95 - 196)	148.5	(95 - 196)	163	(108.5 - 197.5)	146.5	(77 - 193)						
Gender														
0-50	222	10.6%	85	11.3%	73	7.2%	84	16.5%						
51-200	1227	58.9%	396	51.3%	678	67.1%	203	41.5%						
201-350	379	18.1%	113	14.7%	175	17.3%	91	17.8%						
> 351	32	1.5%	12	1.6%	19	1.9%	2	0.4%						
Unknown	238	11.3%	29	3.8%	169	16.7%	40	7.8%						
Median weight (IQR), kg	61	(53 - 70)	N/A		61	(53 - 71)	63	(57 - 71)						
WHO stage at ART initiation														
Stage I	560	26.7%	204	26.5%	229	22.6%	127	24.9%						
Stage II	588	28.0%	161	20.9%	288	28.2%	141	27.3%						
Stage III	684	31.1%	152	19.6%	379	37.4%	177	33.7%						
Stage IV	256	12.2%	54	7.0%	128	12.6%	70	13.1%						
Country														
Cote d'Ivoire	217	10.3%	116	15.0%	57	5.6%	44	8.6%						
Kenya	338	16.1%	108	14.1%	138	13.3%	95	18.6%						
Rwanda	140	6.7%	35	4.5%	63	6.2%	42	8.2%						
South Africa	439	20.9%	89	11.6%	261	25.7%	49	9.6%						
Thailand	229	10.9%	85	11.0%	56	5.5%	88	17.3%						
Uganda	471	22.4%	84	11.0%	255	25.2%	132	25.9%						
Zambia	284	13.6%	78	10.1%	126	12.4%	60	11.6%						
Initial ART regimen														
ZDV/3TC/NVP	1500	71.5%	430	56.4%	717	70.8%	353	69.2%						
d4T/3TC/NVP	409	19.8%	129	16.6%	178	17.6%	102	20.0%						
ZDV/3TC/EFV	86	4.1%	0	0.0%	46	4.5%	40	7.8%						
d4T/3TC/EFV	79	3.8%	1	0.1%	66	6.5%	12	2.4%						
Other	24	1.1%	15	2.0%	6	0.6%	3	0.6%						
Experienced single drug substitution	288	13.7%	93	12.0%	130	12.8%	59	11.6%						
Reasons														
Side effects/toxicity	106	44.8%	63	80.0%	68	67.7%	38	74.4%						
Drug interaction	36	14.5%	9	11.4%	19	18.6%	8	15.6%						
pMTCT/Emollient Prophylaxis	2	0.8%	2	2.6%	0	0.0%	0	0.0%						
Disruption in drug supply	1	0.4%	1	1.3%	0	0.0%	0	0.0%						
Other	63	24.9%	26	33.3%	23	22.7%	13	25.0%						

Figure 2. K-M Curve Comparing Time to Single Drug Substitution for Pregnant, Non-Pregnant Women, and Men

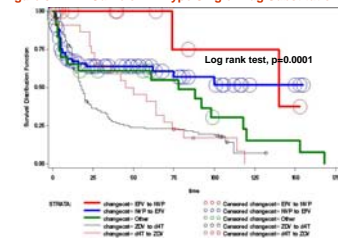


## RESULTS

Table 2. Proportion of Single Drug Substitutions (All Type) by ART Regimen and Gender/Pregnancy Status Among 288 Patients

Type of drug substitution	Overall		Pregnant women			Adult non-pregnant women			Adult men			Median time to substitution (weeks)
	N initial regimen	n switched	N initial regimen	n switched	% switched	N initial regimen	n switched	% switched	N initial regimen	n switched	% switched	
ZDV-inclusive regimen -> d4T	1586	140	430	64	14.9%	763	50	6.6%	393	26	6.6%	17.4
d4T-inclusive regimen -> ZDV	488	22	130	4	3.1%	244	14	5.7%	114	4	3.5%	47.5
NVP-inclusive regimen -> EFV	1909	89	559	19	3.4%	795	51	6.4%	455	19	4.2%	11.9
EFV-inclusive regimen -> NVP	165	12	1	0	0.0%	112	6	5.4%	52	6	11.5%	39.6

Figure 3. K-M Curve of All-Type Single Drug Substitutions



## KEY FINDINGS

- Overall rate of single drug substitutions (SDS) was 73.4 per 1,000 p-y (Table 1)
- 140/288 (48.6%) were changes from ZDV to d4T at a median of 17 weeks after ART initiation (Table 2)

- Pregnant women accounted for a larger proportion of AZT to d4T substitutions, and a smaller proportion of NVP to EFV changes compared to non-pregnant women and men (Table 2)

- In the first year of ART, the probability of remaining on initial regimen was 86.4% for pregnant women, compared to 89.8% for non-pregnant women and 89.7% for men (Figure 2: KM)

- In multivariate models, gender and pregnancy status remained strongly associated with substitutions: pregnant women were 1.56 times more likely (p=0.0084) to have a substitution compared to non-pregnant women and men, after controlling for baseline WHO stage and country of enrollment differences (Table 4)

## CONCLUSIONS

- Pregnant women had higher rates of any single drug substitutions (SDS), most involving a change from AZT to d4T, most post-partum. This may be due to unclear physiologic factors or that women were evaluated more often intra- or post-partum (as they came with their infant) with more opportunities to have a SDS (Figure 2, Table 3)

- The rate of single drug substitutions from NVP to EFV was low among pregnant women; Thus pregnant women appear to tolerate NVP-based regimens which are common in Resource-Limited Country (RLC) settings (Table 2)

- Country differences (Table 3) remained sizable after controlling for numbers of pregnant women. More study into site/country differences is needed

- This rate of SDS is similar or lower than SDS's reported in similar RLC settings, and this analysis presents additional information on pregnant women who start ART in RLCs. Given the potential positive impact of ART on a mother's and infant's health, ART should be started without reservation when indicated

**ACKNOWLEDGEMENTS:** Funding provided by the Bill & Melinda Gates Foundation, the Williams and Flora Hewlett Foundation, the Robert Wood Johnson Foundation the Henry J. Kaiser Family Foundation, the John D. and Catherine T. MacArthur Foundation, the David and Lucile Packard Foundation, the Rockefeller Foundation, the Starr Foundation, and the U.S. Agency for International Development

