



Decrease in HIV-1 Mother-to-Child Transmission in Women Receiving Postnatal Highly Active Antiretroviral Therapy (HAART): 12 month Follow-up Data

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ABSTRACT

Background: We currently provide antiretrovirals (ARVS) to 7,000 HIV-1 infected patients in Sub-Saharan Africa as part of a comprehensive effort. Pregnant women in our program receive HAART antenatally and continue the regimen throughout the first 6 months of breastfeeding or indefinitely when HAART is initiated because of maternal health.

Methods: A prospective cohort study of HIV-1 infected women treated with HAART from the prenatal to the postnatal period is ongoing in Mozambique. We presently report 12-month data on maternal and infant outcomes. Infants were tested for HIV-1 at 1, 6 and 12 months of age using bDNA. Mothers were counseled to exclusively breastfeed up to 6 months of age. Additional sources of nutrition were introduced thereafter.

Results: Three hundred forty one women enrolled and initiated ARVS during pregnancy. Two women (0.6%) died during the 12-month postnatal period. Follow-up data is available for 276/341 children at 12 months of age (81%). Fifty one children (15%) were lost to follow-up and 14 (4.2%) died in the first 12 months of life (7 in the first semester). Thirteen children who died had negative HIV bDNA results until the time of death and one was HIV-infected. The observed IMR was 48.3/1000 (IMR Mozambique 2005 101/1000). A small portion of women (2.5%) had a history of prior ARV exposure. Fifty-five women continued HAART beyond 6 months because of baseline CD4 counts < 200 or symptomatology (1 transmission at 6 months in this group). The median maternal plasma virus load among infants who acquired HIV-infection was 4.38 log at the time of infant diagnosis, as opposed to 3.79 log (Levene test : NS, t-Test: NS) in the mothers who did not transmit. No correlation was noted between infant HIV infection and maternal baseline CD4 cell count, virus load or duration of pre-natal ARV treatment, likely due to the small number of infections noted. New cases of HIV-1 MTCT at different infant ages are reported.

	1 Month N= 341	6 Months N= 313	12 Months N= 276	Cumulative Total
HIV+ & TR	4 (1.2%)	2 (0.6%)	2 (0.7%)	8 (2.9%)

Conclusions: Among breastfed children born to women on HAART in the prenatal and postnatal period, HIV-1 MTCT rates were low overall although higher in the first month. Rates stabilized after one month with no increase in transmissions after 6 months following introduction of mixed feedings. Late postnatal transmission of HIV-1 is decreased by maternal use of HAART. The effect appears to be protective up to 12 months of age.

BACKGROUND

• **The DREAM Program :** DREAM stands for Drug Resource Enhancement against AIDS and Malnutrition. This is a public health program developed in 2001 by the Community of Sant'Egidio, a faith based Catholic organization centered in Rome, Italy.

• **Donors:** The program is sponsored by multiple donors including the World Bank Treatment Acceleration Program (TAP), several Italian private banks, several governmental cooperations including the German Agency for Technical Cooperation, the Agence Française de Développement, the Catalan Agency for Development Cooperation, the Belgium Development Cooperation and PEPFAR.

• **Staff:** The DREAM program staff includes a multi-professional team of volunteer physicians, psychologists, pharmacists, public health professionals, nurses, virologists, immunologists, nutritionists, and community activists.

• **Objectives:** The goal of our program is the provision and dissemination of the best available practices in HIV medicine to resource limited settings.

• **History:** The program was first initiated in Mozambique, where the Community of Sant'Egidio had been active for over a decade as a peace organization involved in the resolution of the civil war.

• **DREAM Centers:** The program currently has 27 clinical centers and 13 laboratory centers including P3 facilities in 10 African countries:

- Mozambique (10 clinical centers and 4 laboratories)
- Malawi (7 clinical centers and 2 laboratories)
- Tanzania and Kenya (2 clinical centers and 1 laboratory each)
- Nigeria, Angola, Guinea Bissau, Guinea Conakry, Cameroon and Congo DRD (1 clinical center and 1 laboratory each)

• There are currently 45,000 patients followed at DREAM centers throughout Africa. Many of these receive HAART, primarily sponsored through PEPFAR.

• PMTCT is a major focus of the DREAM program. We previously reported HIV-1 transmission rates at 6 months for a prospective cohort of HIV-exposed infants whose mothers received HAART postnatally while breastfeeding [1, 2].

• Here we report 12 month follow-up data for the same cohort of infants.

STUDY OBJECTIVES

1. To determine HIV-1 free survival at 12 months in old HIV-exposed infants whose mothers received prenatal and postnatal HAART for at least 6 months following delivery.
2. To compare postnatal HIV-1 transmission rates at 12 months in infants of women who continued HAART until 6 months postpartum and infants of mothers who continued HAART indefinitely following delivery.
3. To evaluate maternal parameters potentially associated with postnatal HIV-1 transmission including maternal virus load and duration of antiretroviral treatment.

METHODS

STUDY DESIGN: Prospective observational cohort study initiated in Mozambique in August 2005.

STUDY POPULATION: HIV-1 pregnant women receiving prenatal and postnatal care at DREAM centers in Mozambique and their HIV-exposed infants.

DREAM ARV TREATMENT GUIDELINES: HAART is provided at DREAM centers to HIV-infected patients in need of treatment according to WHO guidelines as part of a comprehensive care package which also provides nutritional supplementation to patients with low BMI. For PMTCT purposes the program established its own treatment guidelines.

DREAM PMTCT RATIONALE: PMTCT is one of the main focus areas of the program. DREAM opted to provide the best prophylactic regimen available to pregnant women at its centers in Africa. HAART to all pregnant women (regardless of CD4 cell count and virus load) is the standard medical practice at our centers for a number of reasons:

- Given resources available to the program, DREAM investigators felt it was unethical to provide medical treatment that was considered substandard in westernized countries such as Europe or the USA to African patients.
- There was a need to circumvent the development of resistance mutations arising from the use of simplified regimens for PMTCT. These regimens could jeopardize the efficacy of subsequent first line treatments in a setting where back-up options are not readily available.
- The uptake of simplified regimens for PMTCT by patients in our setting was extremely poor, while adherence to HAART regimens was excellent.

DREAM PMTCT GUIDELINES: Our centers are primarily located within established medical facilities. HIV+ women are referred to our centers for prenatal care. Antiretroviral treatment is initiated at 15 weeks of gestation and is maintained until 6 months postnatally if women choose to breastfeed. HAART is continued to all women postnatally in order to reduce the risk of HIV transmission via breastfeeding. HAART is continued beyond 6 months for all women with < 200 cells/mm3 or HIV-related symptoms at baseline. Our PMTCT HAART approach has proven to be more cost effective and efficient for reduction of HIV PMTCT than provision of formula and water filters.

- **HAART regimens:** Zidovudine (or stavudine), lamivudine, nevirapine. Nefinavir was previously used in a subset of patients who did not tolerate nevirapine. Lopinavir/ritonavir is a back-up HAART regimen in many centers, but there is variation according to country specific guidelines.
- **Breastfeeding:** All women are counseled to exclusively breastfeed during the first 6 months.
- **Weaning:** Approaching 6 months, women discontinuing HAART are counseled to wean their infants. Regular follow-up for viral load and CD4 cell count is continued as well as treatment when needed. HAART is stopped once weaning is finalized. Supplemental foods are provided to mothers and infants.

Assessment of HIV-1 infant infection: Infants are evaluated for HIV-1 infection by branched DNA assay at 1, 6 and 12 months of age.

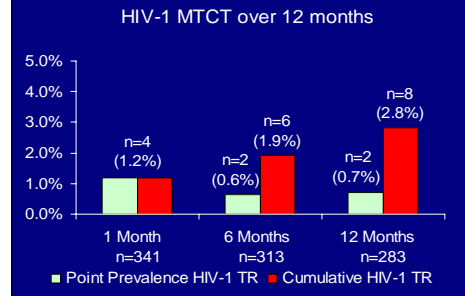
Data analysis: Performed with SPSS v. Win 14.0. Incidence rates, relative risk and confidence intervals were calculated for mortality, HIV transmission events and risk factors potentially associated with transmission.

Informed consent: Subjects provided consent for participation in the program. Data was analyzed in a blinded fashion with removal of all patient identifiers. The DREAM protocol was approved by regulatory institutions in Italy and Mozambique.



RESULTS

- Of the original cohort of 341 infants followed from birth, 313 mother infant-pairs (92%) completed 6 months and 283 (83%) completed 12 months of follow-up.
- There were 8 cases of HIV-1 transmission over 12 months:



Mortality Parameters 12 Months	N (%)	Maternal Mortality/100,000	Infant Mortality/1000 P-Yr
Maternal Deaths Cohort	2 (0.6%)	587	-
Infant Deaths Cohort	11 (3.2%)	-	33.2
Infant Mortality Mozambique	-	-	101
Maternal Mortality Mozambique	-	1000	-

Risk Reduction in MMR: (1000 - 587) / 1000 = 41%

Risk Reduction in IMR: (101 - 33) / 101 = 67%

- 4 infants died in the first 6 months and 7 in the second semester of life.
- Only 1/11 infants who died had a documented HIV-infection (at 1 month).
- 3 infants who died after 6 months had a negative PCR at the time of death.
- HIV diagnosis was ascertained for 287 infants (84%) by 12 months.

Loss to Follow-up Rates at 12 months:

- At 12 months, 47 infants (14%) were lost to follow-up. Eleven infants (3.2%) died.
- HIV-1 diagnosis was not ascertained in 54 infants (16%) from the original cohort.

Risk Reduction in MTCT at 12 months: (113 - 8) / 113 = 93%

- Expected cumulative risk of HIV-1 MTCT in the absence of treatment combining in utero, intrapartum and postnatal transmission at 12 months: 40%
- 40% of 283 infants (# in cohort at 12 months) = Expected # of infections: 113
- 40% of 341 infants (# in cohort at 1 month) = Expected # of infections: 136
- If one assumed that all 54 infants who did not have an HIV diagnosis at 12 months were infected, in addition to the 8 with proven HIV infection, the HIV MTCT Risk Reduction would still be significant: (136-62)/136 = 54%

HIV-1 Free Survival at 12 months: 92%

Maternal Parameters	N= 341	%
Prior history of ARV exposure before pregnancy	8	2.5
Postnatal HAART beyond 6 months post partum	55	16%

- All 8 women who transmitted HIV had CD4 values > 200 at baseline. Only one woman continued HAART beyond 6 months for her own health. Her transmission event was diagnosed at 6 months.

Maternal VL, Duration of Antepartum HAART and MTCT:

HAART Antepartum	VL log	HIV +	Total (n=283)	Risk Estimate of HAART Duration on MTCT
< 86 days	> 4	5	61	RR: 6.2 95%CI: (0.7-51.9)
	≤ 4	1	76	
TOTAL		6	137	
≥ 86 days	> 4	1	83	RR: 0.8 95%CI: (0.05-11.9)
	≤ 4	1	63	
TOTAL		2	146	

- 6/8 transmissions (75%) were in women with a VL > 4 log at baseline.
- 6/8 transmissions (75%) were in women with < 86 days of antepartum HAART.
- MTCT was more frequently observed in women with < 86 days of antepartum HAART and VL > 4 log: 5/61 (8.2%) versus 1/76 (1.7%). Due to low transmission events, p = NS.

CONCLUSIONS

- We observed 4 late post-natal HIV-1 infections (> 1 month of age) in our cohort of infants whose mothers received HAART during pregnancy and postpartum.
- Infant and maternal mortality rates were low in comparison to country standards with an appreciable risk reduction in IMR, MTCT and a high HIV-free survival rate.
- There were no differences in rates of MTCT between women who stopped HAART at 6 months and those who continued HAART for their own health.
- Duration of antepartum HAART in combination with baseline virus load appeared to be associated with HIV-1 MTCT, however because of the small number of transmission events, a statistically significant difference was not observed.
- Our current MTCT approach is safe and effective in the reduction of HIV-1 MTCT.

REFERENCES & ACKNOWLEDGMENTS

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