Highly Active Antiretroviral Therapy (HAART) as a Strategy for Reduction of HIV-1 Transmission in Sub-Saharan Africa: Survival and Virus Load Parameters from the Drug Resource Enhancement Against AIDS and Malnutrition (DREAM) Program

Leonardo Palombi[1], Giuseppe Liotta[1], Sandro Mancinelli[1], Anna Maria Doro Altan[1], Pasquale Narciso[2], Susanna Ceffa[3], Karin Nielsen-Saines[4], Ines Zimba[5], M Cristina Marazzi[6]
[1]University Tor Vergata, Rome, Italy; [2]Istituto Nazionale per le Malattie Infettive (INMI), Rome, Italy; [3]DREAM Program, Community of Sant`Egidio, Rome, Italy;
[4]David Geffen UCLA School of Medicine, Department of Pediatrics, Los Angeles, CA; [5]DREAM Program Coordination, Maputo, Mozambique; [6]LUMSA, Rome, Italy

Karin Nielsen,MD,MPH
10833 LeConte Ave
Los Angeles, CA 90095
Tel 310 206-6640
Fax 310 825-9175
knielsen@mednet.ucla.edu

ABSTRACT

Background: The concept of universal antiretroviral use as a strategy for reduction of new cases of HIV infection has been evaluated in mathematical models as a potential approach to curtailing the Sub-Saharan African epidemic. In order to further substantiate such models, additional strategic parameters based on robust patient data should be considered, including survival of HIV-infected populations under HAART and subject infectivity as determined by HIV RNA levels.
Methods: A retrospective cohort study was conducted in a population of patients enrolled in DREAM centers throughout sub-Saharan Africa in order to determine survival under HAART. Cox regression analysis was performed evaluating parameters associated with survival such as CD4 cell count, viral load, body mass index (BMI) and hemoglobin (HB) levels. DREAM criteria for HAART initiation included (1) WHO stage 3-4 regardless of CD4 cell value (2) <350 CD4 cells if asymptomatic (3) virus load >100,000 copies in any subject. Virus load response to HAART was assessed in a subset of patients.
Results: Adult non-pregnant patients who accessed DREAM centers from 1/2002 to 7/2009 were evaluated. A total of 34,295 patients (22,249 females/12,041 males) were included. Median age was 34 years (IQR:29-42) and median observation time 476 days (IQR:206 – 950). Baseline median viral load, CD4 cell counts, HB and BMI values were 4.4 (IQR:3.6-5.0), 243 (IQR:109-416), 10.8 (IQR:9.2-12.4), and 20.3 (IQR:18.3-22.7). Over time 23,795 patients initiated HAART. Cox survival analysis (adjusted for Viral Load and HB) according to CD4 cell strata was performed. The relative risk of death in the lowest CD4 stratum (<100) versus the highest stratum (>500) was 3.3 [2.7 – 4.1]. Survival estimates at ≥ 7 years of HAART ranged from 50% to 95% according to baseline CD4 cell count and HB levels. In a subset of 13,405 subjects who received HAART for ≥ 6 months with at least 2 virus load measures available, 55.9% achieved < 50 copies/ml and an additional 19.7% achieved levels < 400 copies/ml (75.6% total). Final median virus load value was 58 (IQ: 0 – 2000).
Conclusions: Contrary to more conservative estimates used in mathematical modeling studies, patients in our cohort demonstrated a significant survival benefit even within the lowest CD4 cell stratum. Patients on HAART had low potential infectivity as measured by plasma virus load. Cohort data from African patients can contribute to the further refinement of predictive models.

INTRODUCTION

- Approximately 2 to 3 million individuals become HIV- infected each year worldwide.
- It is estimated that only about 1/3 of HIV- infected individuals in immediate need of HAART actually receive it in resource-limited settings.
- However, viral suppression due to adequate treatment with HAART is likely capable of reducing the number of new infections.
- Successful treatment of HIV-infected individuals and prophylaxis of individuals at risk of HIV-acquisition with antiretrovirals has been, so far, the most effective approach for prevention of HIV transmission, as seen in multiple PMTCT antiretroviral studies, studies of HIV serodiscordant couples, and studies of occupational post-exposure prophylaxis.
- Strategies for the potential reduction of HIV incidence with widespread use of antiretroviral therapy have been evaluated via mathematical modelling with encouraging results.[1]
- In such studies, the use of ample HIV testing followed by rapid implementation of HAART could potentially transform an endemic HIV scenario to an HIV elimination phase, with significant reduction of HIV mortality to 1 case per 1000 within 10 years of implementation and reduction of HIV prevalence to 1% within 50 years.[1]

STUDY OBJECTIVES

In order to validate this model for elimination of HIV transmission, robust clinical data from a large sample size of patients enrolled in our program, was used to determine the following parameters:

1. Survival of HIV-infected patients under HAART stratified by baseline CD4 cell count.
2. Determination of subject infectivity as determined by plasma HIV RNA levels over time.

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 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.

•DREAM Centers: The program currently has 31 clinical centers and 18 laboratory centers including P3 facilities in 10 African countries. There are currently 80,000 patients followed at DREAM centers in Africa.

• Treatment and prevention of HIV-associated morbidity and mortality with nutritional supplementation (as well as HIV PMTCT) are the major goals of our program.

METHODS

STUDY DESIGN: Retrospective cohort study of patients enrolled in all DREAM centers from 01/ 2002 to 07/ 2009 in order to determine survival under HAART.
STUDY POPULATION: Adult non-pregnant HIV-infected patients receiving medical care at DREAM centers in Mozambique, Malawi, Tanzania, Kenya, Angola, Nigeria, Guinea Bissau, Guinea Conakry, Cameroon and the DR of Congo.
ANTIRETROVIRAL TREATMENT GUIDELINES: DREAM criteria for HAART initiation included (1) WHO stage 3-4 regardless of CD4 cell value (2) <350 CD4 cells if asymptomatic (3) virus load >100,000 copies in any subject. First line HAART consisted of zidovudine (or stavudine), lamivudine and nevirapine. The DREAM Programme also included active tracing of patients by peer-to-peer educators (patients on treatment themselves) in order to increase and facilitate adherence and nutritional supplementation. Food packages were delivered periodically to patients with a body mass index (BMI) value of less than 18.
INCLUSION AND EXCLUSION CRITERIA: (1) Age ≥ 15 years. (2) No pregnancy throughout the duration of the observational period. (3) Availability of pre-HAART CD4 cell count and HIV-1 virus load results. (4) At least 180 days of follow-up since HAART initiation for patients on ongoing treatment. (5) Inclusion of all patients with less than 180 days of followup since HAART initiation who ceased medical care because of death or loss to follow-up. (6) Indication for starting HAART as described above and according to WHO guidelines[2].
PATIENT FOLLOW-UP: According to the following protocol: 1. In the first month of treatment once a week 2. In the second and third months of treatment twice a month 3. From the third to the sixth month of treatment monthly 4. After 6 months of treatment: visits every 3 months unless there was a clinical problem. Patients came monthly to the centers for retrieval of medications, and in case there was a clinical problem, they were referred by the nursing staff to the clinicians. The clinical stage was assessed according to the WHO staging system.
INFORMED CONSENT: All patients provided consent. The DREAM protocol was approved by regulatory institutions in Italy and in all participating African countries.

LABORATORY EVALUATIONS: Included liver function tests and hemoglobin levels at baseline, start of HAART, 4, 8, and 12 weeks postinitiation of treatment, and every 3 months thereafter. CD4 cell subsets were performed every 3 months and virus loads were performed twice a year. The same techniques were used at all participating laboratories. CD4 cell counts were performed by a Beckman-Coulter, EPICS-XL MCL flow cytometer. The lymphocyte subset count was performed in dual platform mode using a hematology analyzer SISMEX KN 21. Viral load assessments were performed with System 340 Bayer using the branched- DNA technology (vs. 3.0, detection limit 50–500,000 copies RNA/ml).
DATA ANALYSIS: Performed with SPSS v. Win 14.0. Cox regression analysis evaluated parameters associated with survival such as CD4 cell count, viral load, body mass index (BMI) and hemoglobin (HB) levels[2]. Virus load response to HAART was assessed in a subset of patients. Paired t-test was used to assess difference between mean baseline and final VL, CD4 cell counts and HB values. The risk for every single variable was estimated stratified for the dichotomized level of a CD4 cell count. The resulting values were pooled using the Mantel–Haentzel procedure.The hazard ratio for time-to-event outcome such as death was estimated using the Cox proportional hazard regression mode. Patients with missing data were excluded from the analysis, i.e., patients lost to follow-up were excluded from any time-dependent analysis, as were patients who missed one of the parameters included in the time dependent analysis. Data was censored on 8/31/09. All covariates were included in the model as categorical ones except for age, which was considered a numerical variable.

RESULTS

• 34,295 patients were included: 22,249 women/ 12,041 men

• Median patient age: 34 years (IQR: 29.0-42.0): 29% (n=9942) were < 29 years of age, 21% (n=7207) between 29 - < 34 years, 26% (n=9024) between 34-<42 years and 24% (n=8122) ≥ 42 years.

• Median observation time was 476 days (IQR: 206 – 950).

Baseline characteristics of Patient Population:

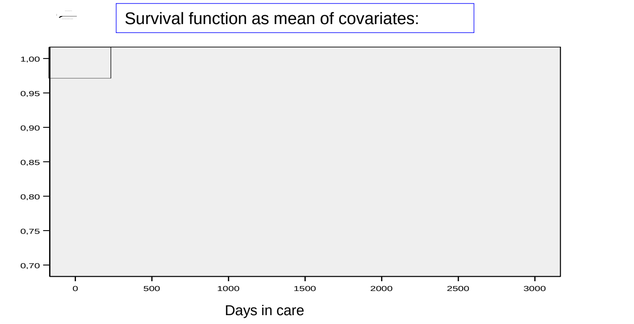
n = pts with results available	Age n=34295	Log_{10}VL n=26686	CD4 n=31239	BMI n=32965	HB n=31124	Days of Care n=34295
Median Value	34	4.46	243	20.3	10.8	476
25th %ile	29	3.58	109	18.3	9.2	206
75th %ile	42	5.04	416	22.7	12.4	950

• Over the years, 23,795 patients initiated HAART:

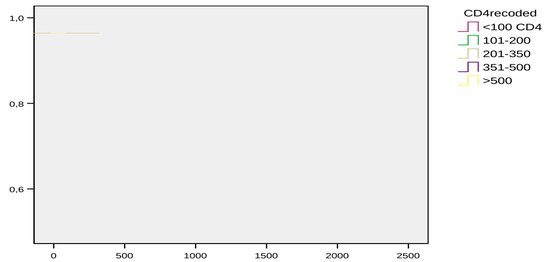
Mean baseline values of HB, VL, CD4s, BMI in patients initiating HAART vs. patients who did not start HAART

HB (g/dl)	HAART	N=23,379	10.6 g/dl	SD=2.3
	No HAART	N=7,745	11.3 g/dl	SD=2.4
HIV-1 logVL	HAART	N=20,686	4.07 log	SD=1.6
	No HAART	N=6,000	3.75 log	SD= 1.4
CD4 cells	HAART	N= 23,512	230 cells	SD=227
	No HAART	N= 7,727	529 cells	SD=282
BMI	HAART	N=23,795	20.6	SD=4.03
	No HAART	N=9,170	21.3	SD=4.13

Cox Survival Regression Analysis of patients who initiated HAART:



Cox Survival Regression Analysis (adjusted for baseline CD4 cell count and HB values) of patients who initiated HAART (Forward stepwise):



• The estimated patient survival after 7 years of HAART ranged from 50% to 95% according to baseline CD4 cell counts and HB values.

• The risk of death in the lowest CD4 stratum (< 100) vs. the highest strata (> 500) was 3.3 (95%CL: 2.7 - 4.1)

• Virologic response to treatment was evaluated in a subset of patients who received HAART for at least 6 months and who had at least 2 measures of VL available within this period. A total of 13,405 patients fulfilled this criteria with a median time of HAART exposure of 485 days.

• 7494 subjects (55.9%) had an HIV-1 VL value of < 50 cps/ml at the end of the observation period and an additional 2641 patients had a final VL of < 400 cps/ml (76% of patients with successful virologic response). Median final VL of the cohort was 58 copies/ ml (IQ: <50 – 2000).

CONCLUSIONS

• A significant survival benefit was observed in patients receiving HAART even in the lowest CD4 count threshold (100 cells). Over 3/4 of patients on HAART had minimal HIV infectivity as measured by plasma RNA levels.

• Our clinical data supports mathematical modeling studies of HAART as a tool in the elimination of the HIV epidemic and demonstrates that its widespread use can significantly reduce HIV-associated mortality and likely contribute to significant decreases in HIV transmission.

References

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