Fundació irsiCaixa

A Multicenter, Randomized Controlled Clinical Trial of Continuous vs. Intermittent HAART Guided by CD4+ T Cell Counts and Plasma HIV-1 RNA Levels: Two-year Follow-up

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on behalf of Tibet Study Group

Background

PI/NNRTI-based HAARTs

- Control of virus replication
- Increase in CD4+ T cell counts

↓ Mortality

↓ Morbidity

- Toxicity (LPD)
- Poor quality of life
- Cost

Unkown long-term clinical consequences (osteopenia/osteoporosis cardiovascular risk, etc.)

Multicenter, open label, randomized clinical trial

Screening Phase

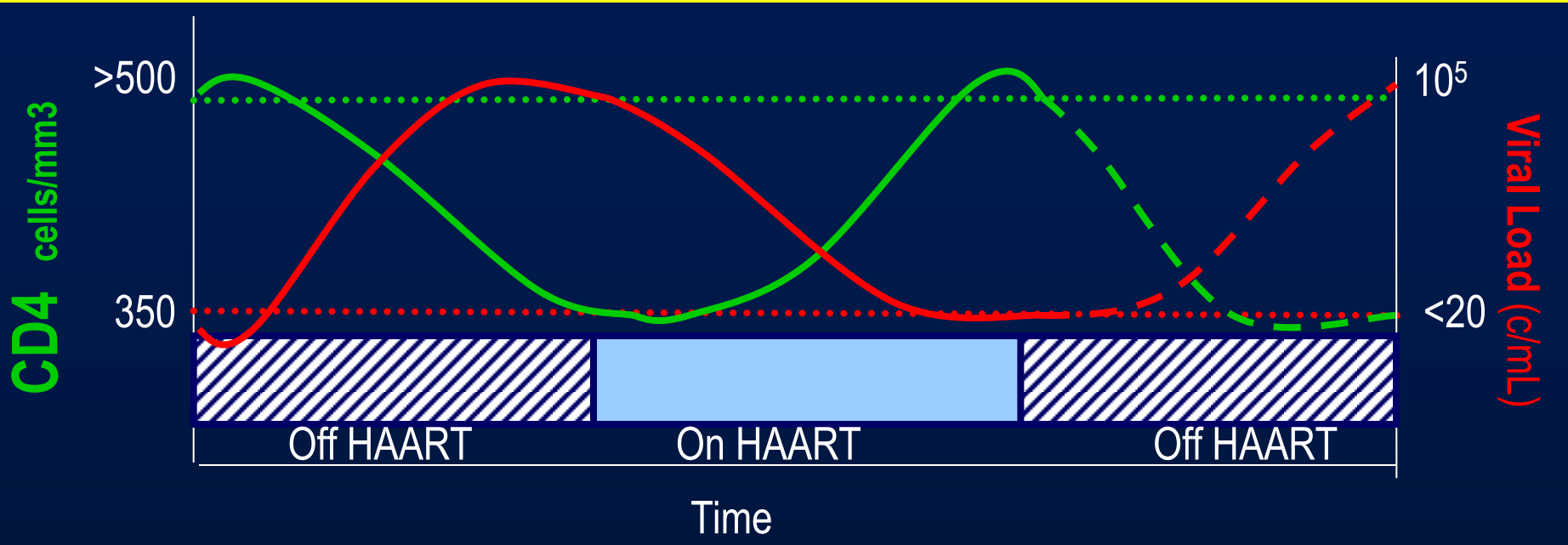
- Patients on HAART > 1 year
- CD4 counts > 500 cells/mm^3
- pVL< 50 copies/ml and prior pVL<400 copies/mL for >1 year

↓

Enrolled in Trial and randomization

Follow-up: median: **123** weeks (74-183) (**n = 201**)

Study Design – Treatment Interruption Group



HAART restarted if:

- ↓ $CD4^+$ to ≤ 350 cells/mm^3 (× 2)
- ↑ Viral load ≥100,000 c/mL (× 2)
- Development of any AIDS-defining event or severe Acute HIV Syndrome

HAART stopped again if:

- $CD4^+$ > 500 cells/mm^3 (× 2)
- Viral load < 50 c/mL (× 2)

Objectives

Main Goals

- To investigate the safety in terms of:
  - Lack of appearance of AIDS-related events and acute retroviral syndrome
  - Maintenance of CD4 $\geq$ 200 cells/mm^3
- Percentage of patients off therapy during 48 weeks
- To assess the time elapsed until the reinstitution of HAART in patients assigned to therapy interruption

Methods

Monitoring

- Baseline and monthly in Interruption Group
- Baseline and every three months in Control Group

Measurements

- Hematologic and biochemistry parameters
- Plasma HIV RNA levels
- Peripheral CD4 T cell counts
- Genotype
- Proviral DNA
- Quality of Life
- Adherence
- DEXA

Methods

Statistic Analyses

- Non-Continuous variables - Chi Squared analysis
- Continuous variables - Mann-Whitney and Wilcoxon rank-sum tests
- Univariate Survival analysis - Kaplan Meier
- Multivariate analysis - Cox proportional hazard model was fitted to determine predictors of time OFF HAART until treatment resumption and comparisons were based on log rank test.

Patients's Characteristics (I)

	Int. Group	Control Group
Patients (n=200)	100	101
Gender, no; (%)		
Female	31	23
Age, median (range)	38 (25-56)	37 (25-76)
HIV Exposure (%)		
MSM	45	50
HET	24	24
IDU	28	26
Others	3	-
CD4 BL, median (range)	841 (496-1946)	786 (418-1620)
CD4 nadir, median (range)	339 (50-1230)	364 (53-1012)
Pre-ART CD4, median (range)	401 (51-1560)	426 (50-1211)
Pre-ART pVL, median (range)	4.6 (2.3-6.2)	4.5 (2.6-6.1)

P > 0.05

Patients's Characteristics (II)

	Int. Group (100)	Control Group (100)
Prior AIDS (%)	5	13
Pre-HAART ART (%)	46	52
Time on ART (y) median, (range)	4.6 (1.7-14.2)	3.9 (1.6-19.2)
Time with undetectable VL (mo) median, (range)	38 (13-94)	37 (14-66)
Exposure to ART No. of drugs; median, (range)	8 (3-16)	7 (3-14)

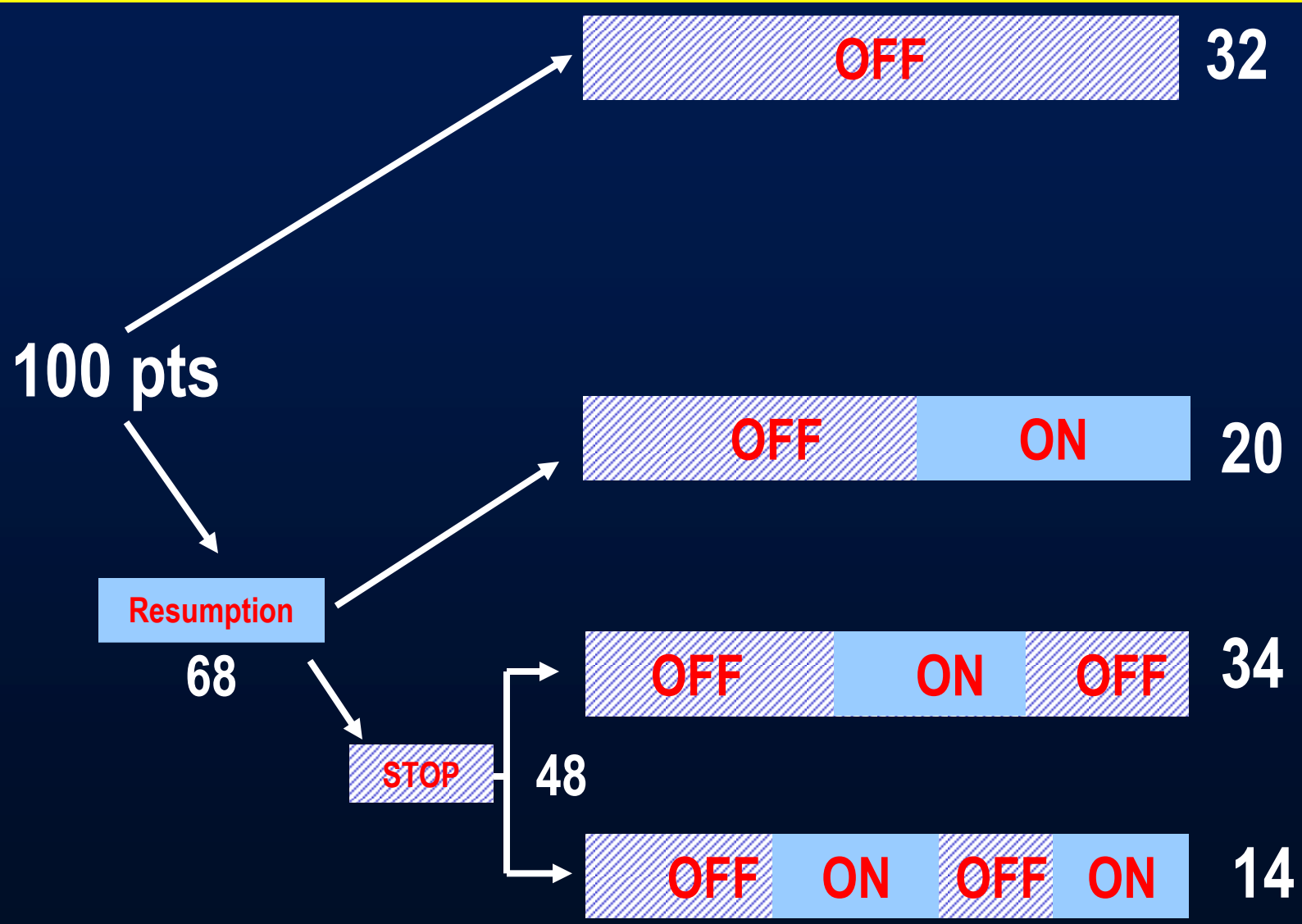
P **>0.05**

Adverse Events* (Interruption Group)

- No patient has developed OI or tumors
- Acute Retroviral Syndrome was observed in 6 patients (6%) and appeared during the first 6 wks "off therapy"

Results- Interruption Group

Follow-up: median: **123** weeks (74-183) (**n = 201**)



Results- Interruption Group

Reasons to restart HAART (n = 68)

	(%)
Viral Load	70
CD4 cell count	6
Both	24

* Patients who restart HAART

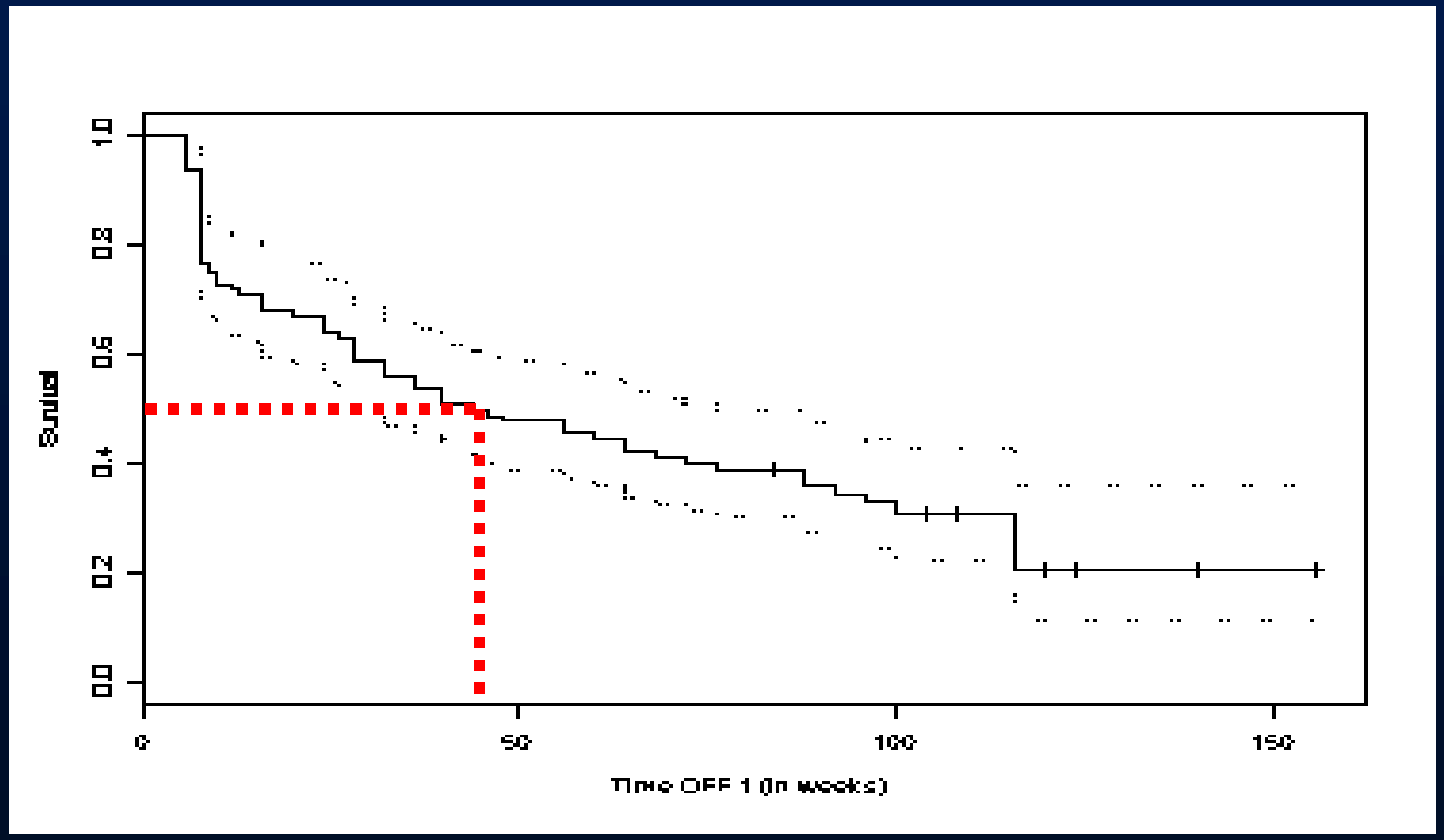
Results – Interruption Group

	Interruption Group (n=100)		
	OFF HAART (n=32)	**Restarted HAART** (n=68)	
	Median		*P*- Value
CD4 nadir	554	272	<.001
Prior time on ART (w)	194	263	<.001
CD4 pre-ART	612	312	<.001
CD4 pre-HAART	629	391	<.001
Pre-ART logVL	4.45	4.76	.047

Mann-Whitney test

Results- Time Off HAART

- Global median time off therapy: 44 weeks (6 to ≥116)
- Median time to treatment resumption: 8 weeks (6-116)



Int. Group - Hazard Risk to restart Therapy

Logistic regression

Univariate analysis. (Categorical)

	OR	*P*- Value
Age(>35)	3.2	.01
Non-Naive	4.5	.002
CD4 nadir (<350)	10.4	<0.001
CD4 BL (<841)	3.1	.012
CD4 pre-HAART(<464)	7.9	<0.001
Nº. Drugs (>7)	3.9	.002

Int. Group - Hazard Risk to restart Therapy

Logistic regression

Multivariate analysis (Categorical)

	OR	*P*- Value
Age(≥35)	4.7	.013
CD4 nadir (≤350)	5.3	.018
CD4 pre-HAART(>464)	4.4	.034
No. Drugs (>7)	3.9	.023

Interruption Group

Factors associated with time OFF-therapy

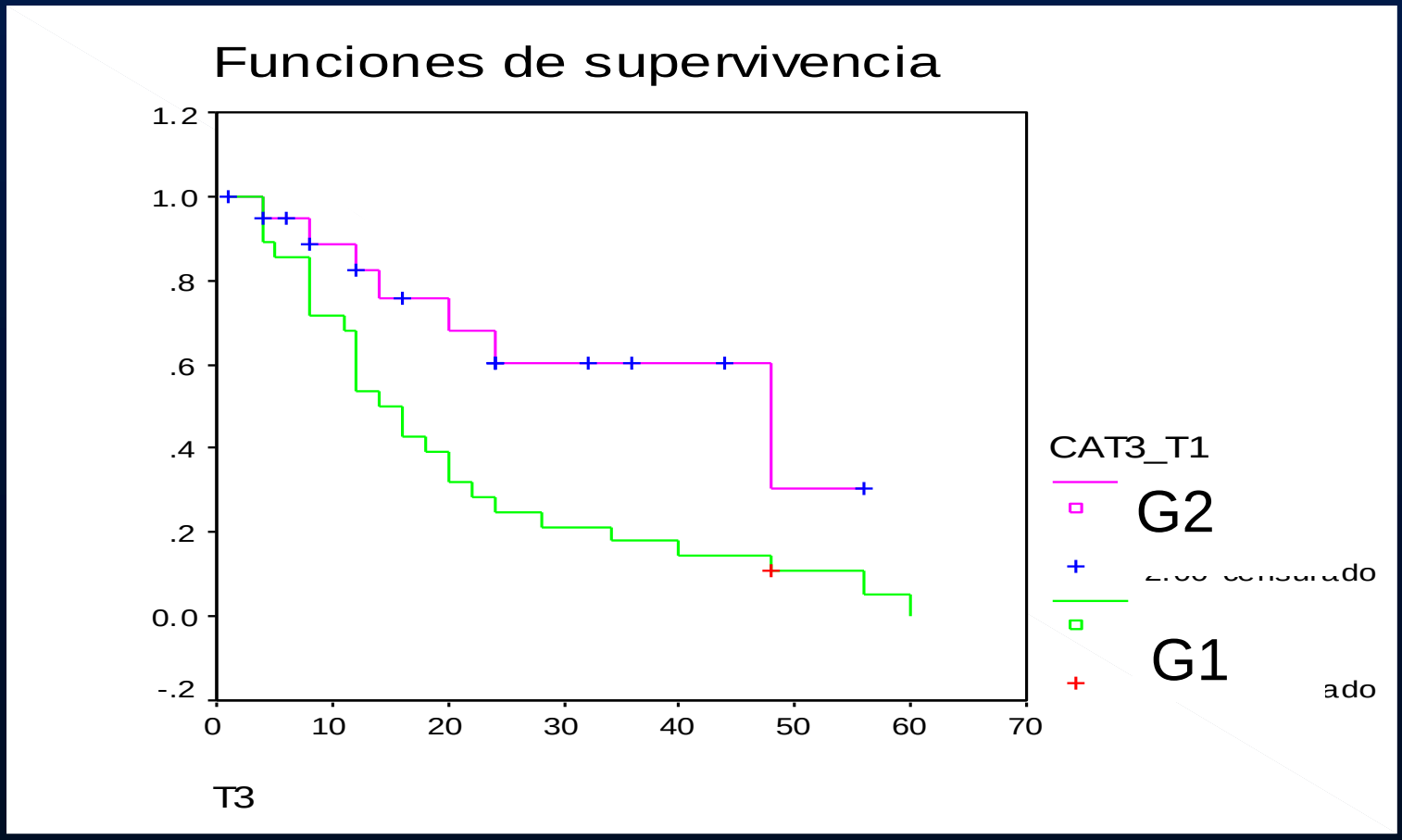
Multivariate Cox model. Categorical

	RR	*P*- Value
Nº. Drugs (<8)	2.61	.001
Pre-HAART log_{10}<5	2.26	.022
Age(≤ 35)	1.88	.033
CD4 nadir (>200)	1.87	.048

Results – Time OFF1 (T1)/OFF2 (T3) Therapy

T1< 24 (< 6 mo. OFF) → 28 pts (G1)
T1>=24 (> 6 mo. OFF) → 20 pts (G2)

P= .0125 Tarone-Ware test




NO WAR!


PAS DE GUERRE EN IRAK