Poster
THPEB 063

Efficacy of a Maintenance Four-Days-A-Week Regimen, the ANRS162-4D trial

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Abstract

Background: Previous studies (FOTO, BREATHER) have given encouraging results with a 5/7days efavirenz-based maintenance regimen. Based on pilot experience (Leibowitch, FASEBJ 2015), we conducted a 48-week multicenter, open-label, single-arm prospective study evaluating efficacy and safety of a 4/7days maintenance therapy in HIV infected patients with controlled VL.

Methods: The main inclusion criteria were age>18 years; current regimen with 2 nucleoside analogs and either a boosted protease inhibitor PI/r or a NNRTI; no treatment modification in the last 6 months; VL<50 c/ml for at least one year; no resistance mutation to the drugs in the current regimen. Maintenance therapy used the same regimen, taken 4 consecutive days of each week. Virological failure (VF) was defined as VL>50 c/ml confirmed within 4 weeks between D0-W48. Patients were evaluated at D0, W4, W8, W12, W16, W24, W32, W40, and W48. The study was designed to show that the efficacy of the strategy is superior to 80%, assuming a success rate equal to or above 90%, with a power of 87% and a 5% type-one error. Values are presented as median [range]. Adherence to therapy was assessed by questionnaires, pill count, and MEMS caps for a subgroup of patients.

Results: One hundred patients were included in the study, 82 men and 18 women, median age 47[25-75], CD4 nadir 282[7-1044] cells/µl, and receiving ARV therapy since 5.1[1.3-25.2] years with VL<50 since 4.1[0.5-15.5] years. Current regimen included tenofovir-DF+FTC (89 patients) or abacavir+3TC (11 patients), combined with a PI/r for 29 individuals (lopinavir/r:1, atazanavir/r:13, darunavir/r:15) or a NNRTI for 71 (EFV:41, RPV:25, ETV:5). After 48 weeks, 96% [95% CI 90-98, Kaplan-Meier estimate] were still under maintenance 4/7days regimen without failure; 1 patient returned to 7/7 regimen and left the study at W4, VF was confirmed in 3/100 patients at W4, W8, W40, with VL 785, 124, and 969 c/ml respectively. These 3 patients returned to 7/7 regimen and VL was subsequently suppressed in all 3.

Conclusion: Over 48 weeks, maintenance ARV therapy with a 4 days a week regimen was effective in these patients with suppressed VL under 2 nucleosides and either a PI/r or a NNRTI, resulting in a success rate of 96%.

Background

Given the earlier recommended initiation of ART and the need for long life therapy, strategies reducing ART intake will have to be investigated for minimizing long-term cumulative toxicity of ARV drugs. A short-cycle therapy strategy with planned short breaks from ART could be an alternative for reducing long-term toxic effects and costs.

Previous studies (FOTO, BREATHER) have given encouraging results with a 5/7days efavirenz-based maintenance regimen.

Based on pilot experience (Leibowitch, FASEBJ-2015), we conducted a 48-week multicenter, open-label, single-arm prospective study evaluating efficacy and safety of a 4/7days maintenance therapy in HIV infected patients with controlled VL

Objective

The ANRS-162 4D study, a short-cycle therapy strategy with 4-day on consecutively and 3-day off, aimed to evaluate the capacity of this strategy to maintain therapeutic success over 48 weeks in HIV-1-infected patients with controlled viral load for at least 12 months under antiretroviral treatment.

Therapeutic success is defined by the absence of virologic failure (occurrence of two successive values of viral load> 50 copies / mL within 2 to 4 weeks apart), and the absence of study strategy discontinuation for more than 30 days .

Study Design

2 weekly modalities of antiretroviral taken

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
on	on	on	on	off	off	off
off	on	on	on	on	off	off

Samples collected within the visit off have been done at the end of the 3-days off

	D0	W4	W8	W12	W16	W24	W32	W40	W48	W51
Samples: time point	on	off	off	off	on	off	off	on	off	off

Main inclusion criteria

- age>18 years
- current regimen with 2 nucleoside analogs and either a boosted protease inhibitor PI/r or a NNRTI
- no treatment modification in the last 4 months
- plasma VL< 50 c/ml for at least one year
- no resistance mutation to the drugs in current regimen

Patients were evaluated at D0, W4, W8, W12, W16, W24, W32, W40, W48 and W51.

Methods

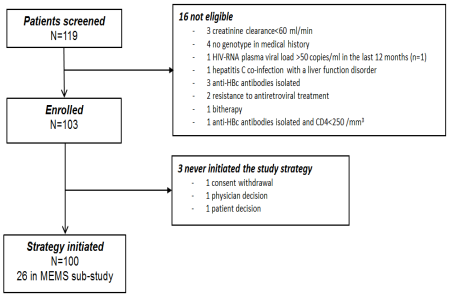
- **Primary end point :** occurrence of therapeutic failure, as defined by 2 consecutive plasma viral load measurements > 50 copies/mL within two to four weeks, during the 48 weeks of follow-up (**Virological failure)** or discontinuation of the study/study strategy for more than 30 days (**Strategic failure**).
- **Secondary endpoints :** tolerability, drug concentration, changes in CD4, CD4/CD8 ratio, metabolic parameters, and HIV DNA at week 48. For these secondary endpoints missing data were replaced by the last observation.
- **Genotypic resistance test :** performed in patients in case of virological failure.
- **Adherence to the study strategy:** assessed by self-reported questionnaires, pill count, drug concentrations, and MEMS caps for a subgroup of patients.
- **Quality of life and felt symptoms :** assessed by self-reported questionnaires at week 0, 24 and 48

The study was designed to show that the efficacy of the strategy is superior to 80%, assuming a success rate equal to or above 90%, with a power of 87% and a 5% one-type error.

A maximum of 10 treatment failures including a maximum of 5 virological failures was expected over the study for success. The viral load monitoring was online and the DSMB decision was required every two virological failures.

Results

Study flowchart



Patients baseline characteristics

Characteristics		Main study N=100	MEMS Sub-study N=26
Age , Year, median (IQR)		47 (40 – 53)	44 (36 – 50)
Male sex – n (%)		82 (82.0)	23 (88.5)
Origin – n (%)			
	- Caucasian	81 (81.0)	25 (96.2)
	- Sub-saharan Africa	10 (10.0)	0 (0.0)
	- Others	9 (9.0)	1 (3.8)
Transmission group – n (%)			
	- MSM	65 (65.0)	18 (69.2)
	- Heterosexual	31 (31.0)	7 (26.9)
	- Others/Unknown	4 (4.0)	1 (3.8)
HBV co-infection – n (%)		0 (0.0)	0 (0.0)
HCV co-infection – n (%)		2 (2.0)	1 (3.8)
Prior AIDS Event – n (%)		9 (9.0)	4 (15.4)
Date of HIV diagnosis, Years, median (IQR)		2006 (1999 – 2011)	2007 (2005 – 2011)
Duration of suppressed HIV viremia (<50 copies/ml), Year, median IQR		4.0 (2.3 – 6.4)	3.9 (1.8 – 5.1)
Duration of ARV therapy, Years, median (IQR)		5.1 (2.9 – 9.3)	4.8 (2.8 – 7.2)
Duration of last cART, Months, median (IQR)		32.3 (18.8 – 57.5)	21.4 (13.3 – 48.6)
Baseline ART regimen – n (%)			
○ 2NRTIs + NNRTI		71 (71.0)	21 (80.8)
	- efavirenz	40 (40.0)	7 (26.9)
	- etravirine	5 (5.0)	2 (7.7)
	- rilpivirine	26 (26.0)	12 (46.2)
○ 2NRTIs + PI/r		29 (29.0)	5 (19.2)
	- darunavir/r	15 (15.0)	2 (7.7)
	- atazanavir/r	13 (13.0)	3 (11.5)
	- lopinavir/r	1 (1.0)	0 (0.0)

MSM=Men who have sex with men MEMS=Medication Event Monitoring System

Conclusion

Over 48 weeks, maintenance ARV therapy with a 4 days a week regimen was effective in these patients with suppressed VL under 2 nucleosides and either a PI/r or a NNRTI, resulting in a success rate of 96%.

High adherence to therapy was assessed by questionnaires and MEMS caps.

A comparative randomized trial and longer-term follow-up will further inform the real efficacy and sustainability of this strategy.

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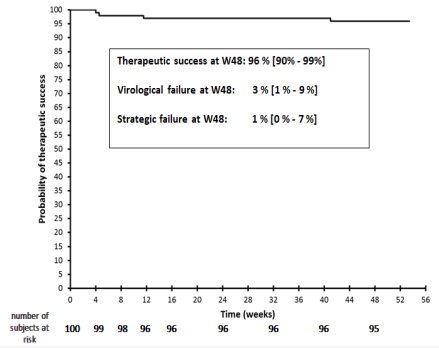
Probability of therapeutic success



Kaplan-Meier Curve of probability of therapeutic success.
1 virological failure and 1 strategic failure (discontinuation at W4 due to anxious and asthenia) occurred during the study.
One patient discontinued the study at W12 for Pregnancy and was censored at the date of study discontinuation

Patients with therapeutic failure

N°	cART	Age	Sex	CDC	Duration of VL suppressi on (Years)	pVL pre-cART (cp/ml)	CD4 Nadir (/mm³)	CD4 (/mm³) D0	CD4 (/mm³) W48	pVL (cp/ml) D0	pVL (cp/ml) failure	ART concentration (ng/ml) W48	ART concentration (ng/ml) 1st VL recovered	ART concentration (ng/ml) VL Control	Resistance	Self-reported Adherence
1	ABC 3TC LPV/r	48	M	C	6.7	206 681	125	1119	814	<40	271 (S04) CTR (13 days after): 785	<40	OFF LPV: <2	OFF LPV: <75 RTV : <10	No	100%
2	TDF FTC EFV	52	M	A	5.9	311 000	209	574	547	40	124 (S12) CTR (9 days after): 55	47	OFF EFV: 1543	ON TDF: 71 FTC: 207 EFV: 3669	No	100%
3	ABC 3TC ATV/r	31	F	A	4.2	61 500	422	1136	1229	<20	969 (S40) CTR (22 days after): 227	<20	ON ATV: <20	ON ATV: 4190 RTV: 1080	No	100%
4	TDF FTC EFV	35	M	A	3.0	18 498	330	500		<20	<20 (S04)		OFF EFV: 709	Discontinuation by pt at W04, related to the study strategy		100%

ART concentration during « ON » and « OFF » periods

ARV	N	« ON »	« OFF »	Δ(OFF – ON)	% of change Δ(OFF – ON)/ON	P*
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
EFV	38	2218 (1046)	692 (391)	-1526 (781)	-69% (10)	<0.0001
ETV	5	447 (360)	269 (266)	- 179 (101)	-47% (11)	0.0625
RPV	26	106 (51)	39 (20)	-66 (40)	-63% (13)	<0.0001
ATV	12	1087 (644)	52 (146)	-1035 (637)	-96% (11)	0.0005
DRV	15	2587 (1393)	17 (18)	-2570 (1382)	-99%(0)	<0.0001
LPV	1	3922	0	-3922	-100%	

* Wilcoxon paired test
Limit of quantification: < 20 ng/ml

Efficacy cut-offs: DRV > 2000 ng/ml ; ATV > 200 ng/ml; LPV > 4000 ng/ml ; EFV > 1000 ng/ml ; ETV > 50 ng/ml ; RPV > 40 ng/ml

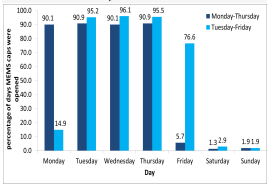
Changes from baseline in biological parameters at week 48

Biological parameters	Baseline (BL) N=100	W48 N=100	Δ (W48 – BL) N=100	P-value*
HIV DNA log10 (copies/10^6 PBMC) n=96	2.4 (0.7)	2.4 (0.7)	0.0 (0.6)	0.7650
CD4 /mm³	708 (243)	748 (259)	+ 39 (168)	0.0207
CD4/CD8 Ratio	1.15 (0.43)	1,19 (0,43)	+0,04 (0,21)	0.0335
AST, UI/L	26 (9)	24 (9)	-2 (8)	0.0004
ALT, UI/L	31 (16)	28 (11)	- 3 (12)	0.0071
GGT, UI/L	41 (55)	33 (29)	- 9 (39)	0.0003
DFG (CKD-EPI), ml/min	94.5 (15.4)	95.7 (15.4)	+ 1.2 (9.7)	0.1949
Glycaemia, mmol/L	5.0 (0.6)	5,2 (0,7)	+0,2 (0,6)	0.0282
Triglyceride, mmol/L	1.5 (0.8)	2.1 (6.6)	+ 0.7 (6.7)	0.5982
Cholesterol total, mmol/L	5.0 (0.9)	4.9 (0.9)	0.0 (0.8)	0.6847
HDL-C, mmol/L	1.3 (0.3)	1.3 (0.4)	0.0 (0.2)	0.6347
LDL-C, mmol/L, N=99**	3.0 (0.7)	3.0 (0.8)	0.0 (0.7)	0.3236

* Wilcoxon Paired Test

Adherence to the study strategy

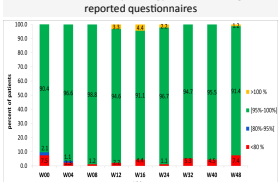
Proportion of days **MEMS caps** were opened according to the 2 weekly modalities of ARV taken



Number of weeks MEMS caps were open

	Median (range)
Exactly 4-days a week	44 (16 – 53)
Less than 4-days a week	5 (0 – 31)
More than 4-days a week	2 (0 – 5)
Total number of weeks per participants in the study	51 (46 – 53)

Adherence to the study strategy estimated using self-reported questionnaires



Percentages of participants with observance rate <80% or >100% in at least one visit

	Observance rate	
	<80%	>100%
1 visit	21 (21.0%)	6 (6.0%)
2 visits	4 (4.0%)	2 (2.0%)
3 visits	1 (1.0%)	0 (0.0%)

Adherence was estimated **with self-reported questionnaires** based on the last-week recall at each visit. Observance rate for each participant was estimated by the number of pills consumed divided by the number of pills that should be theorically consumed and classified as low (<80%), medium (80-95%), high (95-100%) or not respect strategy (>100%)

Overall, the percentage of participants with a cumulated observance rate between 95% - 100% at all evaluated visits was **67%**

Grade 3 or 4 adverse events

Epilepsy	1
Muscle pain	1
Nasal septum deviation	1
Plastic surgery	1
Left scapula abscess	1
AST increased	1
Neutropenia	1

Seven severe adverse events occurred in 7 participants during the course of the study. All events were not related to the study strategy.
Globally, participants felt that their symptoms did not change over time.

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