

A 2-Months-off/4-Months-on Antiretroviral Therapy Is Clinically Non Inferior to Continuous Therapy but Leads to Unacceptable Resistance Rates in African Adults: Final results of the Trivacan ANRS 1269 Trial

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1. Background

- In 2002, we launched a randomized trial in Cote d'Ivoire, West Africa, to compare continuous ART with two Scheduled Treatment Interruption (STI) strategies, a fixed one and a CD4-guided one. The CD4-guided strategy was prematurely interrupted in 2005 because of a high rate of severe morbidity (Danel, *Lancet* 2006). The Fixed STI (F-STI) and continuous strategies were continued until trial termination. We report here the results of the final analysis comparing these two strategies.

2. Methods

- Design: randomized, multicenter, non inferiority trial
- Main randomization criteria: (1) ART started since 6 to 18 months; (2) CD4 count > 350/mm³, (3) plasma HIV-1 RNA < 300 copies/ml
- Trial strategies: (1) continuous treatment (C-ART), (2) 2-months-off/4-months treatment arm (F-STI)
- Primary endpoints: (1) mortality, (2) WHO clinical stage 3 or 4-classifying morbidity, (3) % of patients with a CD4 count < 350/mm³ at 24 months.
- Secondary endpoints: (1) viral and immunological efficacy, adherence, resistance, cost of care, severe adverse events.
- Sample size: number of patients in the F-STI arm threefold higher than in the C-ART arm
- Analysis (intent-to-treat and per-protocol approaches): F-STI considered non-inferior to the C-ART if the lower bound of the 95% CI for the difference of failure between C-ART and F-STI > noninferiority bound (NIB). The NIB was -5% for death and -15% for morbidity and CD4 count.

3. Results

- 325 patients were randomized in the F-STI arm and 110 in the C-ART arm (Trial profile, figure1).
- Main characteristics at randomization:
 - 77% female,
 - median current CD4 count : 460/mm³ (IQR, 396-554)
 - median nadir of CD4 count : 271/mm³ (IQR, 203-340)
 - mean duration of ART before randomization: 7.3 months (IQR, 7.1-10.2)
 - Ongoing ART regimen: 91% 2NNRTIs + Efavirenz.
- Primary outcomes: the F-STI strategy was non-inferior to the C-ART strategy for all primary endpoints (table1)
- Secondary outcomes (tables 2 and 3):
 - adherence, grade 3-4 toxicity and non-HIV morbidity did not differ between arms
 - cost of care and cholesterol abnormalities were higher in C-ART;
 - the percentage of patients with resistant virus was higher in F-STI;
 - The difference between arms was maximal for resistance to NNRTIs, and still significant but lower for resistance to NRTIs. In contrast, resistance to PIs was significantly more frequent in CT arm. Table 3 shows the pattern of NNRTI resistance mutations
 - Timing of NNRTI resistance in patients randomised on Efavirenz, the % of patients with at least one NNRTI resistance mutation was
 - At 12 months, F-STI 10%, C-ART 2%, a 8% difference between groups after two cycles of interruption/reintroduction;
 - At 24 months, F-STI 23%, C-ART 3%, a 20% difference between groups after four cycles of interruption/reintroduction.

4. Conclusion

- The 2-months-off/4-months-on ART was clinically and immunologically non-inferior to C-ART and less costly than C-ART, but led to an unacceptable 5% additional risk of NNRTI resistance at each new efavirenz interruption.
- Whatever future the scientific community decides to give STI, no STI strategies should include NNRTI-based regimens.
- In sub-Saharan Africa where NNRTI regimens are recommended as the standard for first-line ART, these data provide strong arguments to warn against the risk of any potential cause of ART discontinuation that may occur out of the framework of a STI strategy. Factors that may lead to such discontinuation include patient-related factors, such as incomplete adherence, as well as program-related factors, such as drug stock outs.

Figure 1. Trial Profile

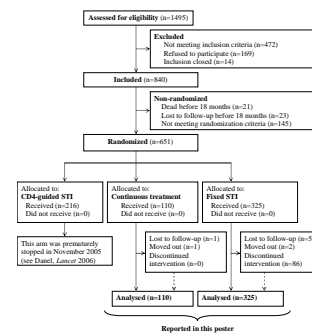


Table 1. Primary outcomes

	Intent to treat	Per Protocol
Death		
Continuities, rate/100 PY (95% CI)	0.45 (0.01;2.5)	0.45 (0.01;2.50)
Fixed STI, rate/100 PY (95% CI)	0.46 (0.1;1.3)	0.37 (0.04;1.32)
Difference between arms	-0.01	0.08
Lower bound of the 95% CI	-0.07	0.77
Protocol non inferiority bound	-.5	-.5
Conclusion	Non inferiority	Non inferiority
Overall severe morbidity⁽¹⁾		
Continuities, rate/100 PY (95% CI)	6.8 (3.7;11.4)	6.8 (3.7;11.4)
Fixed STI, rate/100 PY (95% CI)	9.2 (6.7;11.6)	9.4 (6.7;12.0)
Difference between arms	-2.38	-2.58
Lower bound of the 95% CI	-6.01	-6.30
Protocol non inferiority bound	-.15	-.15
Conclusion	Non inferiority	Non inferiority
CD4 below 350 mm³ at 24 months		
Continuities, percentage of patients (95%CI)	5.6 (1.3;10.0)	5.6 (1.3;10.0)
Fixed STI, percentage of patients (95%CI)	14.6 (10.7;18.5)	10.8 (2.0;6.8)
Difference between arms	-9.0	-5.2
Lower bound of the 95% CI	-13.9	-10.1
Protocol non inferiority bound	-.15	-.15
Conclusion	Non inferiority	Non inferiority

(1) The most frequent stage 3 or 4 morbidity events observed in both arms were oropharyngeal candidiasis (46%), invasive bacterial diseases (20%), tuberculosis (10%), severe unexplained syndrome leading to death (4%), oesophageal candidiasis (2%) and isosporosis (1%).

Table 3. Resistance to NNRTIs

Table 3. Pattern of resistance mutations for the 69 patients with at least one NNRTI resistance mutation at trial termination. Intent-to-treat.

Mutations associated with resistance to NNRTIs	Patients on NNRTI-based regimen at randomization		Patients on a PI-based regimen at randomization	
	CT	F-STI	CT	F-STI
1 mutation				
K103N	-	39	-	-
G190A	-	1	-	-
Y106M	-	1	-	-
M230L	-	1	-	-
K101E	-	2	-	-
2 mutations				
K103N + P225H	3	15	-	-
K103N + Y188L/H	3	14	-	-
K103N + M230L	-	3	-	-
K103N + K101E	-	2	-	-
K103N + Y181C	-	1	-	-
Y106M + G190A	-	1	-	-
K101E + G190A	-	1	-	-
3 mutations				
K101E + K103N + G190A	-	1	-	-
4 mutations				
K101E + K103N + Y188L/F + G190A	-	1	-	-

Table 2. Secondary outcomes

	CT	F-STI	p
Biological outcomes at 24 months, % of patients			
Plasma HIV-1 RNA > 300 copies/ml	12%	27%	0.02
Resistance to at least one drug ⁽¹⁾	9%	24%	0.001
Resistance to at least one NNRTI	3%	21%	<0.0001
Resistance to at least one NRTI	8%	19%	0.01
Resistance to at least one PI	6%	1%	0.01
Resistance to at least two classes of drug ⁽¹⁾	7%	17%	0.02
HIV and lipodystrophy at 24 months, % of patients			
Blood pressure > 140/90 mmHg	11%	12%	0.87
Any sign of lipodystrophy	3%	1%	0.37
Any sign of lipodystrophy	2%	1%	0.25
Biological tolerance, rate/100 PY			
Any grade 3 or 4 biological abnormality	25.0	21.9	0.44
Asaemia < 50 g/L	1.8	5.0	0.04
Granulocytopenia < 750/mm ³	20.8	16.2	0.21
Thrombocytopenia < 50,000/mm ³	0.5	0.5	0.99
Transaminases > 5 x ULN	0.9	0.3	0.32
LDL cholesterolemia > 4.90 mmol/L	1.0	0.2	0.17
LDL cholesterolemia > 4.90 mmol/L	2.5	0.2	0.005
Hypertlyceridemia > 8.49 mmol/L	0.0	0.0	-
Hypoglycemia < 3.89 mmol/L	0.0	0.2	0.75
Non HIV morbidity, rate/100 Y			
Any non WHO stage 2, 3 or 4 classifying severe event ⁽²⁾	14.5	14.3	0.94
Adherence, % of patients			
Self reporting at least one pill intake missed at any visit	11.9%	11.4%	0.98
Cost of care, \$15/Person-years			
Overall	959.6	785.2	<0.0001
Antiretroviral drugs			
Non Antiretroviral drugs	96.3	99.9	0.73
Protocol visits	25.1	25.6	0.32
Protocol biological tests	154.9	157.0	0.99
Non Protocol visits	3.2	3.4	0.51
Non Protocol biological tests	21.6	25.0	0.09
Non Protocol non biological tests	8.8	9.6	0.33
Non Protocol hospital admissions	9.2	8.8	0.98

1. the number of viral load measurement available at 24 months was 315 in F-STI and 107 in CT. In F-STI, 76 patients had resistance to at least one drug, including 24 (32%) to one class (NNRTI+STC=n=17, STC=n=6, ZDV+4dF7C=n=1) and 52 (68%) to two classes (NNRTI+STC=n=48, NNRTI+ZDV+4dF7C=n=1, STC+PI=n=3). In CT, 10 patients had resistance to at least one drug, including 2 to one class (STC=n=1, PI=n=1) and 8 to two classes (NNRTI+STC=n=3, STC+PI=n=1)

2. [2] all morbidity events that led to death or/and hospital admission and that were not documented as a WHO stage 1, 2, 3 or 4 classifying events

Acknowledgments

- We are indebted to all patients who participated in this trial ;
- We gratefully acknowledge the valuable contributions of the SMIT, CeDReS, CEPREF, USAC, CIRBA, CNTS and INSERM U593 teams ;
- We thank Bristol-Myers Squibb for providing Zert® and Videx® during the study;
- This trial was supported by grants from the French Agence Nationale de Recherches sur le SIDA et les hépatites virales, Paris, France (ANRS 1269 and ANRS 12104).