

Early versus Deferred HAART Switch in Heavily Pre-treated HIV Patients with Low Viral Load Level and Stable CD4 Cell Count

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Background: When to switch HAART in heavily pre treated patients (pts) with detectable viral load (VL) and stable CD4cell count is still controversial
Methods: An open-label, randomised, 48-week(wk) prospective trial has been carried out. Pts, Lopinavir/rvtv(Lp/r) naive, with at least 2 previous HAART failed regimens, VL between 1000-20.000c/ml for at least 6 months and CD4cell count ≥ 200 cell/ml twice consecutively determined, were randomised to maintain current treatment (A) or to switch to an optimised Lp/r based regimen (B). VL increase above 30.000c/ml,CD4 decrease below 200 cell/ml and grade III/IV side effects, were considered primary end points. Rate of HAART interruption for any other reason (poor adherence and quality of life, patient's request) was also recorded. End points rate and time distribution was studied with Long-rank test and Spearman's rank multivariable analysis. The 48 wk data are here presented.
Results: Of 201 pts,102 were randomised in arm A and 99 in B. Mean previous failed regimens were 3, ARV exposure time 6 years. Arm A and B pts disposition at baseline (BL) was respectively: mean VL 3,5 and 3,7(SD)0,4c/ml;CD4 cell count 455(SD219) and 388(SD227) cell/ml .median resistance mutations 7,74(0-24) and 7,21(0-18). In arm A maintenance treatment was a PI sparing in 69% pts. At 48 wk, the mean VL change was -0,16 and -1,4c/ml and CD4 -37 and +67 cell/mm³ in arm A and B respectively. VL <50c/ml was obtained in 49% of arm B pts. Viro-immunological(V-I) end point was reached by 11 and 3 of arm A and B pts. Arm A pts with V-I failure switched to Lp/rvtv based regimen and all reached V-I success. No grade III/IV adverse events were recorded. Treatment interruption for any other reason was observed in 28 and 23 in arm A and B respectively(p<0,2).Arm A pts reached V-I end point more often than arm B pts in per protocol analysis(p<0,03),but in intention to treat (ITT) analysis (p<0,4).Variables related with: -therapy interruption were female sex (p<0,03)and VL at BL(p<0,01);-CD4 decrease <200 cell/mm³;nadir and at BL CD4 cell count (p<0,002 and 0,02) and to be randomised in arm A(p<0,02).-VL increase up 30.000c/ml:number of previous PIs and NRTIs(p<0,01)
Conclusions: To defer HAART switch in heavily treated HIV pts with low VL and high CD4 cell count could be an option to save new drugs. Further analysis is needed to characterize the profile of pts who preferentially could switch earlier because of severe risk of heavy V-I impairment

Key inclusion criteria

- Patients with ≥ 2 failed HAART regimens
- Lopinavir/ritonavir naive
- Currently receiving unmodified HAART for at least 6 months
- HIV-RNA plasma level between 1000-20.000 copies/ml for at least 6 months
- CD4 cell count ≥ 200 cell/mm³ confirmed in the last two blood examinations

Study design

Low viremic pts
(HIV-RNA 1000-20000 c/ml
with stable HAART)

Arm B:
Switch to an
optimised HAART
containing Lopinavir/rvtv

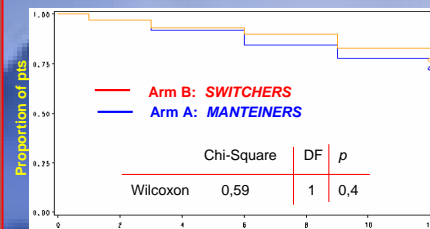
Arm A:
Continue
the current HAART

BASELINE CHARACTERISTICS

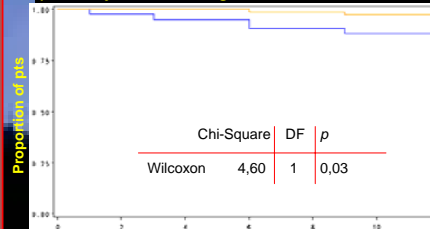
	Total(n=201)	Arm A (n=102)	Arm B (n=99)
Sex ratio (male/female) [n(%)]	139(70)/62(31)	66(64)/36(35)	73 (74)/26(25)
Mean age [years(SD)]	3,6 (7,3)	39,3 (7,2)	40 (7,3)
AIDS defining events [n(%)]	29 (14)	11 (10,8)	18 (18,1)
Mean CD4 cell count nadir [cell/ml(SD)]	202(146)	210,7(132,8)	194,9(159)
Pts undetectable at least once [n(%)]	114(56,7)	58 (56,8)	56 (56,5)
Mean duration ARV drugs [years(SD)]	6,6(3)	6 (3,1)	6,6 (2,8)
Mean no of ARVs exposure (SD)	2,9(1,4)	2,9 (1,6)	2,9 (1,2)
No NRTIs exposure (SD)	4,8(2,9)	4,6 (2,9)	4,8 (2,9)
No NNRTIs exposure (SD)	0,9(0,7)	1,03(0,7)	0,8 (0,7)
No PI exposure (SD)	2 (2,1)	1,7 (2,1)	2,3 (2)
Last treatment before randomisation [n(%)]			
2NRTIs+PI	75 (37,3)	31 (30)	44 (40)
2NRTIs+NNRTI	90 (44,7)	49 (48)	41 (41)
3NRTIs	36 (17,9)	22 (21)	14 (14)
Mean CD4 cell count [cell/ml (SD)]	422 (225)	455 (219)	388 (227)
Mean % CD4 [cell/ count (SD)]	21,1(9,3)	22,4 (8,4)	19,8 (9,9)
Mean HIV-RNA [log10copies/ml (SD)]	3,6(0,4)	3,5 (0,4)	3,7 (0,4)
Mean No of total DRM (range)	7,48(0-24)	7,74 (0-24)	7,21 (0-18)
Mean No of NRTIs RM (range)	3,39(0-10)	3,46 (0-9)	3,32 (0-10)
Mean No of NNRTI RM (range)	0,93(0-4)	1,01 (0-4)	0,93 (0-4)
Mean No of PI RM (range)	3,16(0-12)	3,26 (0-12)	3,16 (0-12)
Mean GSSMT [score(SD)]	1,5(1,1)	1,12 (0,9)	2,04 (0,7)
Mean GSSFT [score(SD)]	6,6(3,9)	7,6 (3,9)	6,5 (3,8)

TREATMENT'S INTERRUPTION RISK AT WEEK 48

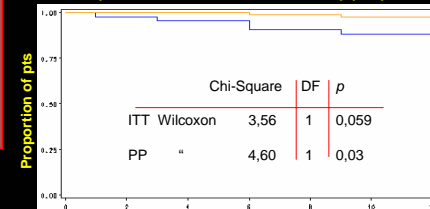
Treatment's discontinuation for any reason (ITT data censored at last study visit)



(PP analysis all missing are considered as failure)



Treatment's discontinuation because Viral (HIV-RNA >30.000 c/ml) AND/OR immunological failure (CD4 cell count <200 cell/mm³) (ITT)



Data Analysis

Patients were followed for 48 months

Immunological and virological assessment were detected at baseline, 1st and every 3 months

Resistance mutations were identified according to IAS Resistance-USA panel

Genotypic susceptibility score (GSS)
drugs score was calculated with on-line HIV drug resistance data base, Stanford University

Maintenance regimens GSS (GSS-MT)
was calculated by summing up scores of current HAART drugs (0=most resistant; 3=less resistant)

Future options GSS (GSS-FI)
summing score of drugs not included in the maintenance regimen (0=most resistant 13=less resistant)

PATIENTS DISPOSITION AT WEEK 48

	Total No (=201)	Arm A (=102)	Arm B (=99)
N° pts on study at 48 week (%)	150(74,6)	74(72,5)	76(76,6)
Pts dropped for any reason (n-%)	51(25,3%)	28(27,4%)	23(23,2%)
Pts who reach viro immunological end point (VL >30.000 c/ml and/or CD4 <200 cell/mm ³)	14(6,9)	11(10,7)	3(3,03)
Adverse events	5(2,4)	2 (1,9)	3(3,0)
Lost to follow up(n-%)	9(4,4)	4(3,9)	5(5,1)
Death (n-%)	2(0,9)	1(0,9)	1(1,0)
Treatment change as patients wish (n-%)	9(4,4)	6 (5,8)	3(3,0)
Lack of adherence (n-%)	11(5,4)	4 (3,9)	8(8,0)
Change of VL (Δ c/ml)		+0,16	-1,4
Change of CD4 cell count (Δ cell/mm ³)		-37	+67
Patients with undetectable viral load (<50 copies/ml)	50	0	50 (49)

MULTIVARIABLE ANALYSIS (Spearman's correlation)

Variables	Discontinuation Coef (p)	Maintain VL <30.000 c/ml Coef (p)	Maintain >200 cell/mm ³ Coef (p)
Arm enrolment	0,06 (0,3)	-0,03 (0,6)	0,1 (0,04)
Sex (female)	0,1 (0,04)	-0,1 (0,02)	-0,1 (0,01)
Age increase	0,03 (0,6)	0,06 (0,3)	-0,1 (0,1)
CD4 nadir	-0,06 (0,3)	0,03 (0,5)	0,1 (0,01)
AIDS event	0,07 (0,5)	-0,08 (0,2)	-0,1 (0,05)
Experience of undetectability	-0,1 (0,04)	0,1 (0,03)	-0,02 (0,7)
N° of previous ARVS	-0,03 (0,6)	-0,007 (0,9)	0,03 (0,5)
N° of PIs	0,04 (0,5)	-0,2 (0,002)	-0,08 (0,2)
N° on NNRTIs	0,02 (0,7)	-0,1 (0,1)	0,1 (0,7)
N° of NRTIs	0,02 (0,7)	-0,2 (0,0002)	-0,07 (0,3)
BL CD4 cell count	-0,01 (0,8)	0,04 (0,4)	0,2 (0,002)
BL HIV-RNA level	0,2 (0,03)	-0,1 (0,1)	0,003 (0,9)
N° of DRM at BL	-0,05 (0,4)	-0,04 (0,5)	0,05 (0,4)

Primary end-points

HIV RNA increase up to 30.000 copies/ml

T CD4+ cell count decrease < 200 cell/mm³

Grade III-IV WHO clinical adverse events and laboratory abnormalities

Efficacy evaluation at 24 and 48 weeks

Proportion of patients who discontinued HAART

Change in genotypic resistance mutations pattern from baseline

Change in GSSMT and GSSFI

Change of HIV-RNA log from baseline

Change in CD4 count from baseline

RESISTANCE MUTATIONS EVOLUTION IN ARM A PATIENTS (MAINTAINERS)

	BL (N=102)	6 ^m (N=91)	12 ^M (N=80)	Change (Δ BL-12m) (p*)
Total Mutations n° (median-range)	7,7(0-24)	7,1(0-20)	7,7(0-22)	0 (0,7)
NAM (median range)	3,4 (0-9)	3,1(0-9)	3,8(0,10)	+ 0,4 (0,4)
TAM(41,210,215,219,6 7,7) (median-range)	2,3(0-6)	2,0(0-6)	2,3(0-69)	0 (0,5)
NNRTI resistance mutations (median-range)	1,01(0-4)	1,01(0-4)	1,06(0-4)	+0,05 (0,5)
PI resistance mutations (median-range)	3,2(0-12)	2,6(0-11)	2,8(0-11)	- 0,4 (0,006)
Mean GSS-MT (SD)	1,12(0,9)	1,06(1,1)	1,04(1,2)	-0,08 (0,8)
Mean GSS-FI (SD)	7,6 (3,9)	7,3(3,8)	6,9 (4,8)	-0,7 (0,2)

CONCLUSIONS

Early or deferred switch in heavily pre-treated HIV infected patients Lopinavir/ritonavir naive, with low viral load and stable CD4 cell count, seems to have a similar outcome (p > 0,4).

The long term risk to reach a viro-immunological endpoint is higher among patients randomised to maintain failing HAART (p < 0,03 PP analysis).

The most of MAINTAINERS patients (69%) was in PI sparing regimen and a partial clearance of PI related resistance mutations was described at 48 week.

From BL to 48 week the NAMs seem to increase (+0,4), but not the total DRM and TAMs

GSSMT and GSSFI seem to be preserved in the short term outcome.

The future treatment options in heavily pre-treated patients with sustained Low Viral Load Level who are maintaining a failing PI sparing regimen, seem to be preserved in the short-term.

Further analysis are needed to characterize the profile of pts who preferentially could switch earlier because of severe risk of viral-immunological impairment