Week 48 Analysis of a Phase IV, Randomised, Open-label, Multi-centre Trial to Evaluate Safety and Efficacy of Continued Lamivudine Twice Daily Versus Discontinuation of Lamivudine in HIV-1 Infected Adults With Virological Failure on Ongoing Combination Treatments Containing Lamivudine: The COLATE Trial

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U. B. Dragsted [1], Z. Fox [1], L. Mathiesen [2], C. Katlama [3], M. Youle [4], J. Gerstoft [5], J.N. Bruun [6], and J. D. Lundgren [1] for the COLATE trial group
1 Copenhagen HIV Programme (Copenhagen, Denmark), 2 Hvidovre University Hospital (Copenhagen, Denmark), 3 Hopital de la Pitié-Salpêtriére (Paris, France),
4 Royal Free Hospital (London, UK), 5 Rigshospitalet (Copenhagen, Denmark), 6 Ullevål Hospital (Oslo, Norway)

Ulrik Bak Dragsted, MD, PhD
Copenhagen HIV Programme
Hvidovre University Hospital
DK-2650 Hvidovre, Denmark
Phone: +45 3632 3015
Fax: +45 3647 3340
Email: ubd@cphiv.dk

BACKGROUND

Lamivudine (3TC, Epivir®) is commonly used as a component of HIV-1 treatment regimens both prior to and following virological failure (VF). VF on a 3TC containing regimen is associated with emergence of the M184I/V mutation. Previous studies suggest:

- Deficiency of the mutant virus
- Enhanced efficacy of other antiretrovirals when M184V is present
- Higher fidelity of the mutant reverse transcriptase

The hypothesis of the COLATE trial is that continuation of 3TC treatment in patients with virological failure on a 3TC containing regimen would lead to better virological efficacy of the underlining HAART regimen compared to discontinuation of 3TC.

Objectives

Primary objective

To compare the log_{10} reduction in plasma HIV-RNA following 48 weeks of treatment.

Secondary objectives

- To assess the proportion of patients with renewed suppression of pVL
- To assess the CD4 lymphocyte count response
- To assess the safety and tolerance of the two treatment arms
- To assess changes in genotypic resistance in plasma HIV-RNA

METHODS

Randomised (1:1), phase IV, open-label, and multi-centre. All patients were followed for 48 weeks. Randomised treatment (r-Tx): Patients with HIV-RNA > 1000 c/ml while on a 3TC containing regimen were randomised to either

- continued (150 mg twice daily) (r-Tx=3TC) or
- discontinued 3TC (r-Tx=No 3TC)

The concomitant use of =3 drugs other than 3TC was decided by the treating physician prior to randomisation.

Stratification of enrolment: Stratum A failure on the first antiretroviral combination treatment and Stratum B second or later failure.

Analyses: Intention-to-treat on patients exposed to the r-Tx (ITT/e ("switch included")), "ITT/e/discontinuation of r-Tx=failure" and on treatment (OT) including patient remaining on r-Tx. The primary efficacy analysis – renewed viral suppression – was determined by the average area under the curve changes from baseline (AAUCMB). Further, protocol-defined VF was assessed (see below for definition). Finally, the % with HIV-RNA below 50 or 400 copies/ml were determined. With a sample size of 160 patients the trial will be powered to detect a difference in HIV-RNA reductions (AAUCMB) between treatment arms of at least 0,5 log_{10} within each of the study arms with one interim analysis, 90% power and a significance level of 0.05. Recruitment was terminated prematurely based on a recommendation from the DSMB due to futility. The enrolled patient number resulted in reduced power but this was 83 %.

Genotypic resistance analysis was performed on all available cryopreserved plasma samples at baseline and during follow-up (samples with HIV-RNA > 500 c/ml).

Definition of virological failure

From week 4 and thereafter

- a less than 0,5 log_{10} decrease in HIV-RNA compared to baseline value

or

- increase in HIV-RNA of more than 1 log_{10} compared with nadir (provided that the HIV-RNA that constitutes VF is more than 1.000 copies/ml)

Assessment of virological failure should be based on two consecutive measurements performed at least one week apart, and should not be taken during an intercurrent illness or within 4 weeks after the subject has received an immunisation. Once reconfirmed, the time of virological failure is defined as the time of the first measurement.

PRINCIPAL INVESTIGATORS

Belgium: N. Clumeck
Denmark: J. Gerstoft, L. Mathiesen, C. Pedersen
France: P. Dellamonica, C. Katlama
Germany: F.-D. Goebel, S. Staszewski
Greece: G. Panos
Ireland: F. Mulcahy
Italy: A. d'Arminio Monforte
Norway: J. N. Bruun
Poland: A. Horban
Spain: J. M. Gatell, B. Clotet
Sweden: K. Gyllensten
United Kingdom: D. Churchill, M. Fischer, B. Gazzard, M. Johnson, C. Leen

RESULTS

From June 1999 to May 2002, 133 patients were randomised from 18 sites, 55 patients in Stratum A and 76 patients in Stratum B. The randomised treatment was initiated in 131 (98%) patients and the percentage of patient lost to follow-up was only 5 %. 19 (15%) patients had a baseline HIV-RNA < 1000 c/ml, 11 (8%) < 400 c/ml, and 0 < 50 c/ml. Patients characteristics were well matched at baseline except for CD4 cell count, which was higher in the 3TC arm (Table 1).

At 48 weeks, 54 (83%) in the 3TC arm and 60 (91%) in the No-3TC arm were still on the randomised treatment (Table 2). No difference was observed in the rate of discontinuation of the randomised treatment (p = 0.2, log rank test)(Figure 1). Seventeen patients prematurely discontinued the r-TX, 11 in the 3TC arm and 6 in the No 3TC arm. This was due to non-fatal AEs (6), lost to follow-up (5), VF (4) withdrawn consent (1), and death (1).

The mean number of ARV drugs other than 3TC was comparable between arms at baseline and during the study period (Figure 2).

Resistance testing was successful in 102/115 (89 %) baseline samples with HIV-RNA > 500 c/ml (Table 3). No differences were seen between the study arms in the number (%) of primary NRTI, NNRTI or PI mutations at baseline (Table 3).

The M184V (and/or I) mutation was detected in 93/102 (91 %) at baseline (Figure 3). This mutation remained detectable in patients with HIV-RNA > 500 c/ml in the 3TC arm but gradually disappeared in the No 3TC arm (Figure 3).

No differences were seen in the proportion of patients with renewed suppression of HIV-RNA <50/<400 copies/ml (Figure 4). The relatively limited number of patients with HIV-RNA < 50 c/ml at Week 48 allowed for assessment of the primary efficacy analysis AAUCMB HIV-RNA decreased by 1.4 log10 c/ml (ITT/e and OT)(Figure 5).

Difference in mean AAUCMB between 3TC vs. No 3TC (95% Confidence Interval):

0.1 (-0.2 to 0.4, p=0.51) log_{10} c/ml (ITT/e),
0.1 (-0.2 to 0.4, p=0.52) log_{10} c/ml (OT)

Comparable results were seen after adjustment for baseline CD4 cell count.

No difference between the study arms in the time to protocol-defined virological failure (log rank test, p=0.65 - data not shown).

No difference between the study arms in change from baseline in CD4 cell count at 48 weeks or time to a rise of > 100 CD4 cells/µl (data not shown)

No difference between the study arms in number of patients experiencing an adverse event (AE), a grade 3/4 AE or the organ distribution of these (data not shown)

SUMMARY

Among patients failing a 3TC containing regimen and being switched to a new regimen where 3TC was added or not:

- Most patients adhered to the study assignment of continuing or discontinuing 3TC
- The number of drugs in the background HAART regimen was comparable between arms and maintained during the study period
- The M184V (and/or I) mutation in RT was present in most patients at baseline, was maintained in patients randomised to continue 3TC but tended to disappear after 12-24 weeks in patients randomised to discontinue 3TC
- About half of the population became re-suppressed and the HIV-RNA decreased by 1.4 log_{10} copies/ml in both arms
- Based on available sample size, and with power > 80 % to detect a difference, no superior virological effect could be demonstrated for patients randomised to continue 3TC

Under current investigation – evaluate per arm:

- More detailed analysis of utilisation of other ARTs than 3TC and how they influence virological outcome
- Evolution of genotypic resistance other than at codon 184 in RT gene

Table 1
Baseline characteristics (ITT/e)

Baseline parameter		3TC N=65	No 3TC N=66	Total N=131
Trial Stratum	(No. in A, %)	28 (43)	27 (41)	55 (42)
Age	(Median, IQR)	42 (37-50)	40 (36-47)	41 (36-48)
HIV exposure group	(%)			
Homosexual/bisexual		60	56	58
IVDU		3	2	2
Haemophiliac		2	2	2
Transfusion		0	2	1
Heterosexual		28	30	29
Unknown/other		8	9	8
CDC, cat. C	(%)	35	30	33
HIV-1 RNA (c/ml log_{10})	(Median, IQR)	3.9 (3.3-4.4)	4.0 (3.4-4.6)	4.0 (3.3-4.5)
HIV-1 RNA<400 c/ml	(No., %)	12	5	8
CD cell count+ (10^6/l)	(Median, IQR)	360 (257-481)	280 (180-376)	310 (203-440)
CD4 cell nadir (10^6/l)	(Median, IQR)	133 (38-198)	122 (61-200)	125 (52-200)

Table 2
Patient flow through Week 48

Status	3TC No. (%)	No 3TC No. (%)	Total No. (%)
Randomised (No.)	65	68	133
Never initiated r-Tx (No. (%))	0 (0)	2 (3)	2 (2)
Initiated r-Tx = ITT/e population (No. (%))	65 (100)	66 (97)	131 (98)
Initiated but permanently discontinued r-Tx (No. %))	11 (17)	6 (9)	17 (13)
Reason for discontinuation (No. (%)):			
Virological failure	3	1	4 (24)
Death	0	1	1 (6)
Clinical non-fatal AE	4	2	6 (35)
Laboratory AE	0	0	0 (0)
Patientchoice	1	0	1 (6)
Lost to follow-up	3	2	5 (29)
Other	0	0	0 (0)
Still on r-Tx at week 48 (No. (%))	54 (83)	60 (91)	114 (87)
Subjects with an outcome at week 48* (No. (%))	60 (92)	64 (97)	124 (95)

Figure 1
Adherence to the randomised treatment (ITT/e)

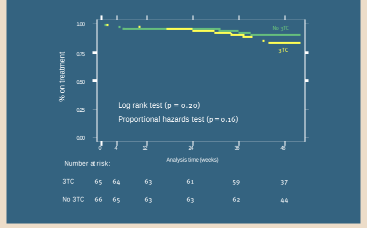


Figure 2
Mean (95% CI) number of ARTs (excluding 3TC) used during follow up (OT)

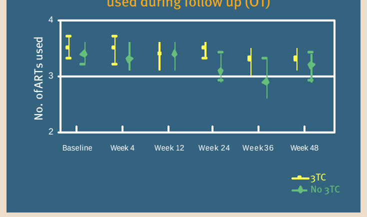
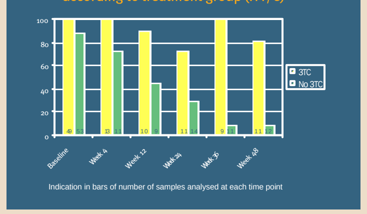


Table 3
Primary NRTI, PI and NNRTI mutations at baseline

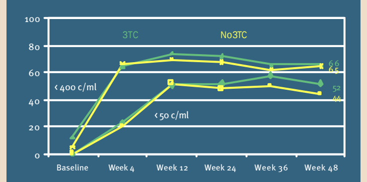
#primary resistance mutations		No 3TC N = 53 (No. %)	3TC N = 49 (No. %)	Overall N = 102 (No. %)	P-value
NRTIs	0	5 (9)	0 (0)	5 (5)	0.25
	1	14 (26)	11 (22)	25 (25)	
	2	3 (6)	5 (10)	8 (8)	
	3	8 (15)	7 (14)	15 (15)	
	4	7 (13)	8 (16)	15 (15)	
	5	6 (11)	3 (6)	9 (9)	
	>=6	10 (19)	15 (31)	25 (25)	
PIs	0	34 (64)	28 (57)	62 (61)	0.73
	1	9 (17)	11 (22)	20 (20)	
	>=2	10 (19)	10 (20)	20 (20)	
NNRTIs	0	34 (64)	31 (63)	65 (64)	0.52
	1	12 (23)	8 (16)	20 (20)	
	>=2	7 (13)	10 (20)	17 (17)	
# with > 1 primary resistance mutation (any class)		48 (91)	49 (100)	97 (95)	0.06

Figure 3
% of patients with the M184V (and/or I) mutation according to treatment group (ITT/e)



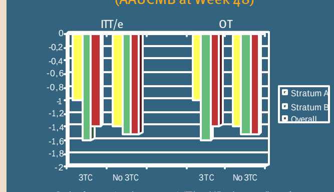
Indication in bars of number of samples analysed at each time point

Figure 4
% with HIV-1 RNA < 50/ < 400 copies/ml (ITT/e)



"ITT/e/discontinuation of r-Tx=failure" and "OT" analysis at week 48:
% w/ < 50 c/ml: 48% (3TC)/42% (No3TC); 58% (3TC)/47% (No3TC), respectively

Figure 5
Primary efficacy analysis (AAUCMB at Week 48)



P-values for comparisons between strata in ITT/e and OT analyses are all > 0.05 (t-test, values were normally distributed)

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