

# Early Virologic Response at 1 Month, and 8 Months Median Follow-up, of a New Triple NUCS Combination (Zidovudine, Lamivudine and Tenofovir) in 42 Antiretroviral Naïve, HIV-1 Infected Patients



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## Summary

- Background:** High rates of early virologic failure have been reported in naïve patients receiving triple NUCs combination containing tenofovir (TDF), with either lamivudine (LAM) and didanosine, or LAM and abacavir (ABC). However, a qd zidovudine (ZDV), LAM, ABC and TDF regimen showed acceptable virologic success rate, and the resistance pattern (less K65R or M184V) suggested a role of ZDV in resistance modulation in this quadruple NUCs combination.
- Methods:** Pilot prospective cohort study, conducted in the HIV outpatient clinic at Strasbourg University Hospital. Treatment naïve subjects were offered a fixed dose combination of ZDV/LAM (300 mg/150 mg) bid, and TDF 300 mg QD. CD4 cells count and HIV-1 viral load were assessed at baseline, after 1 and 2 months of treatment, and then every 2 months. Early virologic response was evaluated after 1 or 2 weeks of treatment.
- Results:** 42 patients were included between April 2002 and November 2004 (36 males; 6 females; median age of 39 years [22-73]). 2 had an AIDS diagnosis. At baseline, median CD4 count was 233/mm<sup>3</sup> (23-425/mm<sup>3</sup>), 17 subjects had CD4 < 200/mm<sup>3</sup>, median HIV-1 viral load was 4.88 log (3.14 - > 5.87 log), and 19 had a viral load > 5 log. Median follow-up was 8 months (1 week to 33 months).
- On treatment analysis showed a median HIV RNA decrease after 1-2 weeks of treatment of -1.56 log, and after 1 month of -2.34 log (1<sup>st</sup> quartile, -1.23 to -2.01 log; 4<sup>th</sup> quartile, -2.75 to -3.4 log). 30/35 patients had viral load < 1 000 copies/ml at month 1. At months 6, 25/27 (93%) had viral load < 50 copies/ml, and 14/18 (78%) after 12 months. Median time to HIV RNA < 50 copies/ml was 10 weeks (1-24 weeks).
- Median CD4 count increase at months 12 was + 82/mm<sup>3</sup>. 5/42 (12%) treatment interruptions for side effects were seen (abdominal pain and nausea: 3; anaemia: 2, probably due to ZDV). During the first 12 months of treatment, 4 viral failures occurred (due to poor compliance), 1 with K65R mutation, 2 with M184V + 2 or 3 TAMS, and 1 with 2 TAMS. Two of them successfully changed the ART treatment; the others remained on ZDV + LAM + TDF, with low viral loads.
- Conclusion:** Combination of ZDV + LAM + TDF in treatment naïve HIV-infected subjects induces a rapid and sustained HIV RNA decrease, associated with a good immunologic response and good safety profile. Despite recently recommendation on triple NUCs drugs association, the results of this evaluation suggest that this triple NUCs combination needs to be further evaluated.

## Introduction

- Availability of tenofovir (nucleotide analogue of RT, -1.7 log)
  - New triple NUCS combinations
- But early virologic failures with:
  - tenofovir + lamivudine + abacavir (once a day)<sup>1-3</sup>
  - tenofovir + didanosine + lamivudine (once a day)<sup>4</sup>
    - Convergent resistance pathways (K65R [abacavir, tenofovir, didanosine), M184V [lamivudine, abacavir])
- On the other hand, good results were obtained with the quadruple combination trizivir + tenofovir once a day<sup>5</sup>
  - Less K65R or M184V, suggesting a role of ZDV in resistance modulation
    - What about ZDV + 3TC + tenofovir?

## Methods

- Pilot, prospective, open-label and single site cohort-study
- Antiretroviral naïve HIV-1 infected patients with CD4 lymphocyte count < 350/μl (or < 15%)
- Treatment: fixed dose combination of ZDV/3TC (300/150 mg) twice a day, and tenofovir 300 mg once a day
- CD4 cells and HIV-1 viral load (Cobas Amplicor HIV Monitor V 1.5) were assessed at baseline, 1 or 2 weeks of ART, 1 and 2 months of treatment, and then every 2 months

## Results

### Baseline Characteristics

- 42 patients included between April 2002 and November 2004 (36 males, 6 females)
- Median age (range): 39 years (22-73)
- HIV risk group: CDC classification:
  - MSM: 20 – A: 31
  - heterosexual: 15 – B: 9
  - IV drug users: 2 – C: 2
  - unknown: 5
- Immunologic results:
  - median (range) CD4 cell count: 233/μl (23-425)
  - CD4 < 200/μl: 17/42 patients (40%)
- Virologic results:
  - median (range) HIV-1 RNA: 4.88 log (3.14 log - > 5.87 log)
  - HIV-1 RNA > 5 log: 19/42 patients (45%)

Table 1: HIV RNA decrease during 48 weeks of Combivir + Viread Treatment

	Baseline	Week 1-2	Week 4	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48
Evaluable patients	42	40	36	36	29	27	22	19	18
Observed data	42	42	42	42	37	36	30	27	26
VL 1 <sup>st</sup> quartile	3.14 - 4.43	< 1.7 - 2.6	< 1.7 - 1.74	< 1.7	< 1.7	< 1.7	< 1.7	< 1.7	< 1.7
Median VL (log)	4.88	3.32	2.6	1.94	< 1.7	< 1.7	< 1.7	< 1.7	< 1.7
VL 4 <sup>th</sup> quartile	5.24 - > 5.87	3.7 - 4.54	2.89 - 3.75	2.55 - 2.96	1.71 - 2.87	< 1.7 - 2.49	< 1.7 - 2.49	< 1.7 - 2.38	1.97 - 3.09
Range	3.14 - > 5.87	< 1.7 - 4.54	< 1.7 - 3.75	< 1.7 - 2.96	< 1.7 - 2.87	< 1.7 - 2.49	< 1.7 - 2.49	< 1.7 - 2.38	< 1.7 - 3.09

- Median (range) follow-up (on treatment): 8 months (1 week - 33 months)
- Time to HIV RNA < 50 copies/ml (N = 30)
  - median (range): 10 weeks (1-24)
- HIV RNA < 1 000 copies/ml at W 4:
  - 30/35 = 86%

## Results (cont'd)

Figure 1. % of Patients with Undetectable Viral Loads at 48 weeks

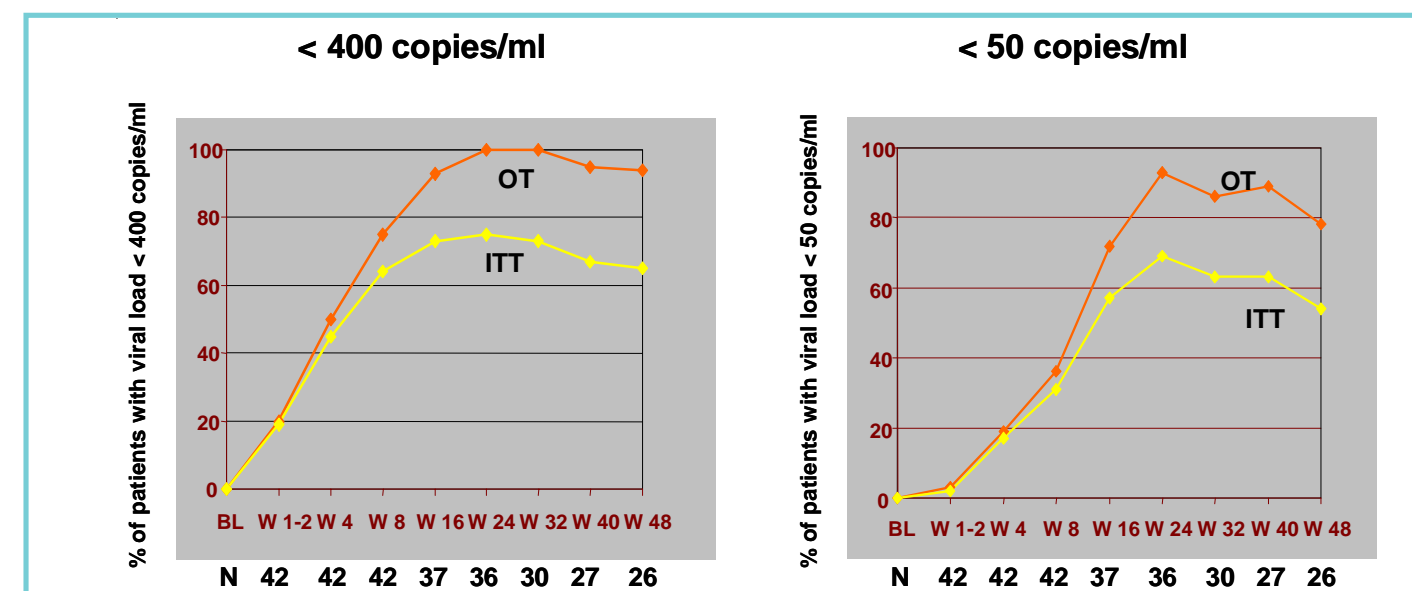
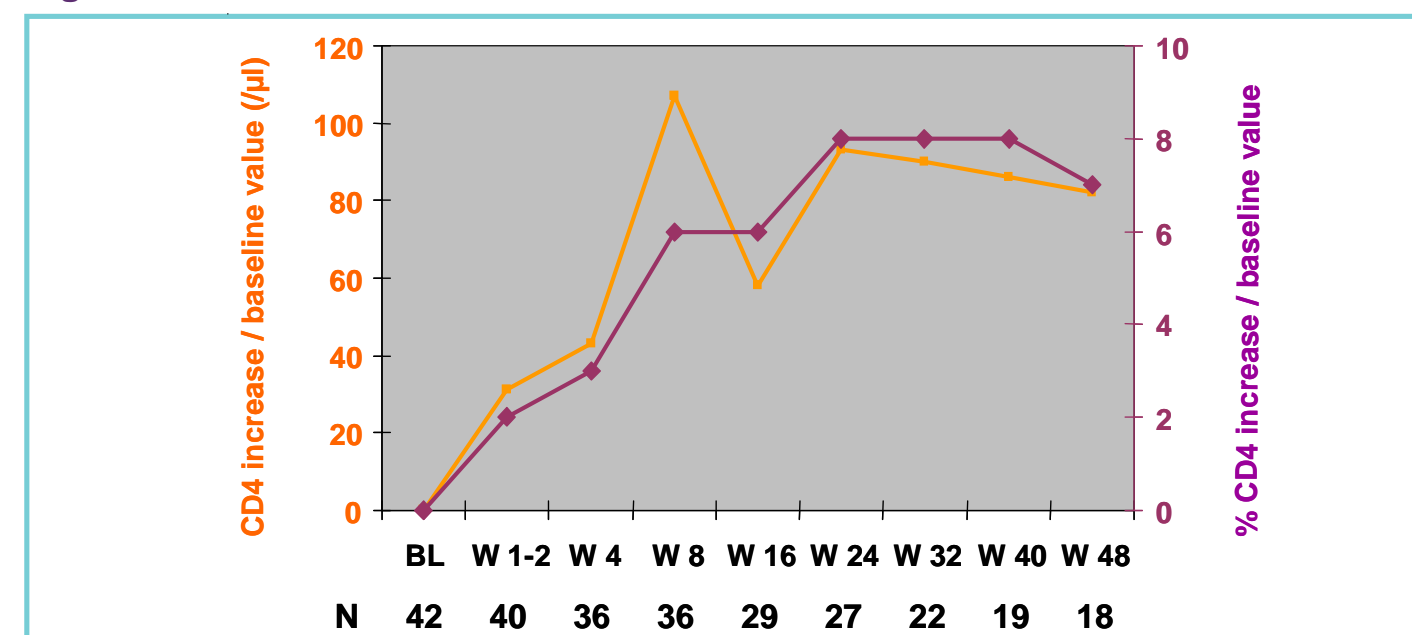


Figure 2. CD4 Results at 48 weeks of Combivir + Viread Treatment



### Side Effects

- 5 patients discontinued the study regimen because of side effects:
  - Abdominal pain, nausea, loss of appetite: 3 (after 1 or 2 weeks of treatment)
    - NNRTI or PI-containing new regimen
  - Acute hemolytic anemia (?): 1 (after 3 weeks)
    - ddl + 3TC + lopinavir/r new regimen
  - AZT-related anemia: 1 (after 3 weeks)
    - 3TC + ABC + TDF new regimen
- 1 pre-existing, moderate renal failure
- Transient hypophosphatemia (n = 24), always > 0.65 mmol/l

### Virologic Failures (n = 4)

- At weeks 24, 32 and 48 (n = 2)
- Genotypic analysis at failure (on treatment):
  - K65R (virologic success after EFV switch)
  - M41L + T215N (present at baseline)
  - D67N (mixture) + K70R + K219E (mixture) + M184V (virologic success with ddl + ABC + ATV/r)
  - K70R (mixture) + T215F (mixture) + M184V

## Discussion

Two studies of quadruple combination, containing zidovudine and tenofovir, showed good immunologic and virologic results:

- Trizivir (OAD) + tenofovir: 123 patients (COL 40263)<sup>6</sup>**
  - BL VL < 5 log
  - BL VL > 5 log
- HIV RNA < 50 copies/ml (W 24) 85%**
- CD4 (W 24) + 90/μl**
- Trizivir (twice a day) + tenofovir (vs Combivir + Efavirenz)<sup>7</sup>**
  - n = 56 (vs n = 57)
  - HIV RNA < 50 copies/ml (OT) (W 48) 97% - CD4 (W 48) + 165/μl

One study evaluated the association of zidovudine, lamivudine and tenofovir in patients who switched from a previous therapy<sup>8</sup>:

- 23/27 (85%) with HIV RNA < 50 copies/ml at baseline, remained in virologic success at 24 weeks**
- Database of genotypic drug resistance (Madrid, Spain)<sup>9</sup>:
  - **K65R inversely associated with the number of TAM**
    - role of AZT in resistance modulation ?
    - role of AZT twice a day ?

## Conclusions

- AZT + 3TC (twice a day) + Tenofovir (once a day), in ART-naïve patients:**
  - induces a rapid (- 1.56 log at 1-2 weeks) and sustained (78% < 50 copies/ml at 48 weeks) HIV RNA decrease
  - is associated with a good immunologic response (+ 82 CD4/μl at 48 weeks)
  - has a good safety profile (12% of treatment interruptions for adverse events)
  - deserves further evaluations

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