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# Safety and efficacy of regimens containing emtricitabine in HIV-infected patients taking highly active antiretroviral therapy

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**SUMMARY**

Emtricitabine FTC is a cytosine analogue, recently introduced in clinical practice for the treatment of HIV patients. In order to evaluate the safety and efficacy of antiretroviral regimen containing emtricitabine in the clinical practice, we performed an observational study on all patients starting a regimens containing emtricitabine in a clinical unit. Data were collected from clinical charts and inserted into a computerized database. We evaluated the following outcome measures: probability of interruption of FTC-regimen due to side effects; time to virologic suppression in patients with detectable viral load at baseline; time to loss of virologic efficacy in patients with virologic suppression at baseline, immunologic variations. In the period January 2005- March 2006, overall 150 patients started a FTC-regimen; 16.7% of them were naïve to antiretroviral treatment. The median period of observation was 80 days (IQR 26-190) and 26.7% of patients had a longitudinal observation longer than 24 weeks. At last observation, 82% of patients were still continuing baseline regimen and 13.3% interrupted FTC. Efficacy analysis in viremic patients showed that 6 months-probability of virologic success during treatment with FTC was 74.7%. Our preliminary observation show that FTC-regimens seems effective and tolerable in real practice.

*KEY WORDS:* human immonodeficiency virus, emtricitabine, antiretroviral therapy

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## INTRODUCTION

Highly active antiretroviral therapy (HAART) has significantly changed the natural history of human immunodeficiency virus (HIV) infection reducing related morbidity and mortality (Palella *et al.*, 1998).

In order to obtain a persistent virologic suppression, antiretroviral regiment must be potent. Adherence to treatment is one of the most relevant factor since a correct assumption of drugs assures a high pharmacological pressure on virus and prevents the emergence of drug-resistance virus (Friedland *et al.*, 1999).

Nowadays, several drugs are available and multiple HAART regimens are possible. Choosing the appropriate regimen both in naïve and experienced patients is crucial in order to obtain a therapeutic success; besides, an appropriate choice could represent a strategy to preserve possible future therapeutical options.

Emtricitabine (FTC), a synthetic nucleoside analogue of cytosine, inhibits the activity of the HIV-1 reverse transcriptase by competing with the

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natural substrate deoxycytidine 5'-triphosphate; it is incorporated into nascent viral DNA resulting in chain termination. It is structurally similar to lamivudine but with a greater in vitro activity against HIV (Schinazi *et al.*, 1992, Rousseau *et al.*, 2001).
Guidelines on treatment of HIV patients recommend the following drugs as preferred nucleoside reverse transcriptase inhibitors (NRTI) to be included in HAART regimen: zidovudine or tenofovir with lamivudine or emtricitabine (DHHS).
Emtricitabine demonstrated potent activity against HIV and HBV viruses. Clinical trials showed its high degree of efficacy and tolerability in combination therapy (Saag 2006). Its administration schedule allows simplification strategies and once-a-day treatments.
Based on these considerations, the objective of our study was to evaluate the use of emtricitabine in clinical practice, its efficacy and tolerability.

## MATERIAL AND METHODS

This was a prospective longitudinal observational study performed in a unit of the Clinical Department of National Institute for Infectious Diseases "Lazzaro Spallanzani" in Rome. We observed adult patients with HIV-infection starting a HAART regimen containing emtricitabine. We considered all consecutive outpatients visiting our department and starting HAART regimen with emtricitabine in the period from January 1st, 2005 to March 31th, 2006. We defined the date at which FTC was started as baseline visit for each patient.
From clinical chart the following parameters were taken: demographic characteristics, risk factor for HIV infection; date of HIV test positivity; clinical classification based on CDC criteria; all antiretroviral (ARV) regimens performed in the past and period of exposition; drugs associated with emtricitabine. For follow-up period evaluation, interruption of emtricitabine regimen and reasons for discontinuations, available CD4+ and HIV-RNA values, and clinical events were collected.
All available data were inserted in a computerized database.
To be included in the analysis on treatment efficacy patients needed to have at least one viro-immunological determination during follow-up. Nevertheless, patients who received at least one dose of FTC-regimen and discontinued it soon after were included in the safety analysis even if they didn't have a viro-immunological determination in the follow-up.
Relating to FTC-regimen we have distinguished patients previously naive to ARV (N-pts) from those who have experienced second or successive lines of treatment (E-pts). Considering ARV-experienced patients, we classified them into 2 groups based on plasmatic HIV-RNA value at baseline:

1) patients with undetectable HIV-RNA who switched to FTC-regimen due to toxicity on previous scheme or to simplification (E-und-pts);
2) patients with measurable levels of plasmatic HIV-RNA presenting failure to previous regimen (E-det-pts).

Patients were also grouped on the basis of type of regimen containing FTC:

a) regimen with protease inhibitor (PI);
b) regimen with non-nucleoside reverse transcriptase inhibitors (NNRTI).
3) regimen with only Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI).

Primary outcome measures were: probability of interruption of FTC-regimen due to side effects; time to virologic suppression in patients with detectable viremia at baseline; time to loss of virologic efficacy in patients with virologic suppression at baseline. Secondary outcomes measures were: variation of CD4 cells count from baseline to end of observation.
Virologic success was defined as reaching HIV-RNA levels below the threshold of 50 copies/ml in two consecutive determinations. In patients with suppressed viral load at baseline visit, virologic failure was defined as rebound of HIV-RNA values above 50 copies/ml.
All statistical analysis were performed using the package SPSS 11.0.1.
Regarding statistical analysis, non parametric Mann-Whitney test and Kruskal-Wallis test were used to compare continuous variables respectively between two or three groups of patients; Pearson Chi Square or Fisher's test was used for comparisons between categorical variables. Moreover we utilized Kaplan-Meier

method to estimate probabilities of virological success or rebound and log-rank test to assess differences among the curves.

## RESULTS

Since January 1st, 2005 a total of 150 patients started regimen containing FTC in our department. Patients were 68.7% male; median age was 43 years (IQR 38-47); most frequent risk factor for HIV infection was intravenous drug abuse (IVD) (41.3%); median duration of HIV infection was 11 (IQR 7-17) years and a diagnosis of AIDS was present in 26% of patients. Median nadir of CD4 was 150 (IQR 60-247) cells/mmc and median HIV-RNA zenith was 5.08 (4.44-5.57) $\log_{10}$ copies/ml. Basal CD4 count and HIV-RNA were respectively 381 (IQR 195-633) cells/mmc and 3.61 (IQR 1.69-4.89) $\log_{10}$ copies/ml.

In 25 of 150 patients (16.7%) FTC-regimen was started as first HAART scheme. Most of patients (83.3%) were antiretroviral-experienced with a median of 6 (IQR 2.5-8.5) previous regimens, and a long exposition to antiretroviral treatments (median: 101 months; IQR: 71-123). Almost half of experienced patients (49.6%) performed sub optimal regimens with 1 or 2 NRTI in previous treatment history. Reasons for interruption HAART regimen before starting FTC were: simplification (24.4%), virologic failure (39.2%), toxicity (14.9%), intolerance (11.9%), patient decision (7.2%), clinical failure (0.8%), and intensification (0.8%). Concerning experienced patients, 49/125 (39.2%) had achieved virologic suppression at baseline.

Epidemiological and clinical characteristics of patients are showed in Table 1.

The three groups of patients (N-pts, E-und-pts, E-det-pts) were compared according to gender, age, risk factor, AIDS diagnosis and HIV infection duration.

In naïve group, patients were younger then other groups (p=0.033). With reference to risk factor for HIV transmission, homosexual intercourses were most frequent in naïve patients while intravenous drug abuse was more often observed in experienced patients with detectable baseline viremia (p=0.016).

The two subgroups of ARV-experienced subjects (E-und-pts, E-det-pts) were also compared according to previous exposure to antiretroviral therapy. We observed a trend toward E-det-pts being more likely to be exposed to mono-dual therapy (p=0.067) and to a higher number of previous regimens (p=0.068). There was no differences in the length of previous drug exposition between the two groups.

Finally, in comparison between naive patients and experienced viremic patients there was diversity in viro-immunological parameters. As expected, naive group presented lower CD4 cell count (P<0.001) and higher HIV-RNA values (p<0.001).

Considering backbone combination of baseline regimen, most frequent NRTIs used in association with FTC were tenofovir (94.0%), didanosine (5.3%), abacavir (0.7%). Third drug of scheme was NNRTI in 31.3% of patients (efavirenz: 42 patients, nevirapine: 5); PI in 66.0% of cases (nelfinavir: 3, fosamprenavir: 2, fosamprenavir/ritonavir: 21, lopinavir/ritonavir: 35, atazanavir/ritonavir: 35, tipranavir/ritonavir: 1); NNRTI plus PI in 1.3% (efavirenz+ atazanavir/ritonavir: 1, efavirenz+lopinavir/ritonavir: 1); only NRTI in 1.3%. The median period of observation was 80 days (IQR 26-190), and 26.7% (40/150) had a longitudinal observation longer than 24 weeks.

At last observation 123 (82%) patients were still continuing baseline assigned regimen, 7 (4.7%) switched to another FTC containing-regimen, and 20 (13.3%) patients have interrupted FTC. Reasons for discontinuation were intolerance in 9 patients, patient decision in 7, toxicity in 3, virologic failure in 1, and progression to clinical event in 1. In the analysis of treatment interruption probability, patients were followed for 577.2 person-months from beginning to interruption of the drug for any causes or last viral load. The 3-months probability of discontinuing FTC for any reason was 14% and increased to 17% by 6 months, estimated by Kaplan-Meier method. The group of E-und-pts had an estimated treatment interruption probability of 3% by 3 months, N-pts 13%, E-det-pts 21% (p=0.047 at log rank) (Figure 1).

In order to evaluate virologic efficacy, eligible patients were 113 with at least one follow up HIV-RNA determination. We first considered 74 patients with HIV-RNA ≥50 copies/ml at baseline with longitudinal data (N-pts and E-det-pts),

to assess probability of reaching undetectable viral load during treatment. Over a follow up of 231 person-month, 43/74 (58.1%) patients reached undetectable viral load.
The 6 months-probability of virologic success during treatment with FTC was 74.7%. There were no significant differences in probabilities of virological response between N-pts and E-det-pts (p= 0.2 at log rank test).
Within the group starting FTC-regimen with HIV-RNA <50 copies/ml, 11/39 (28.2%) patients had virologic rebound after a follow up of 165 person/months, with a 6-months probability of rebound of 30%.
Concerning immunological analysis, CD4 changes from baseline to last follow-up values were significantly different among three groups of patients (N-pts, E-und-pts, E-det-pts)

TABLE 1 - *Epidemiological and clinical characteristics, and laboratory values of all groups of patients*

| | *All patients* | *Naïve patients* | *Experienced patients* | | *P value* |
|---|---|---|---|---|---|
| Baseline variable | | | Pts with suppressed VL at baseline | Pts with not-suppressed VL at baseline | |
| | N=150 | N=25 | N=49 | N=76 | |
| Male, n (%) | 103 (68.7) | 16 (64.0) | 32 (65.3) | 55 (72.4) | 0.608* |
| Age, median (IQR) | 43 (38-47) | 38 (34-45) | 44 (39-50) | 43 (40-47) | 0.033* |
| Risk factor for infection, n (%)<br>a) IDU<br>b) Heterosexual<br>c) Homosexuals<br>d) Blood transfusions<br>e) Unknown | 62 (41.3)<br>45 (30.0)<br>23 (15.3)<br>2 (1.3)<br>15 (15.0) | 2 (8.0)<br>9 (36.0)<br>6 (24.0)<br>-<br>8 (32.0) | 17 (34.4)<br>19 (38.8)<br>9 (18.4)<br>1 (2.0)<br>3 (6.1) | 43 (56.6)<br>17 (22.4)<br>8 (10.5)<br>1 (1.3)<br>7 (9.2) | 0.016* |
| AIDS diagnosis, n (%) | 39 (26.0) | 6 (24.0) | 13 (26.5) | 20 (26.3) | 0.997* |
| HIV infection length, median (IQR) | 11 (7-17) | 1.5 (0-6) | 10 (7-16.5) | 15 (10-18) | <0.001* |
| Previous ARV regimens, median number (IQR) | 6 (2.5-8.5) | NA | 5 (2-8) | 6 (3-9) | 0.068# |
| Length of ARV exposition, median months (IQR) | 101 (71-123) | NA | 92 (57-129) | 106 (79-120) | 0.131# |
| Mono-dual therapy before FTC, n (%) | 62 (41.3) | NA | 19 (38.8) | 43 (56.6) | 0.067# |
| Nadir CD4 value, median (IQR) | 150 (60-247) | 139 (80-246) | 180 (38-285) | 150 (67-240) | 0.892+ |
| Zenith Viral load, median log (IQR) | 5.08 (4.44-5.57) | 5.35 (4.82-5.61) | 4.62 (3.72-5.29) | 5.14 (4.55-5.65) | 0.305+ |
| Baseline CD4 value, median (IQR) | 381 (195-633) | 139 (77-288) | 663 (461-804) | 355 (184-537) | <0.001+ |
| Baseline Viral load, median log (IQR) | 3.61 (1.69-4.89) | 5.19 (4.61-5.53) | 1.69 (1.69-1.69) | 4.24 (2.95-4.95) | <0.001+ |

*comparison between all 3 groups; #comparison between the two subgroups (viremic and not-viremic) of ARV-experienced patients; + comparison between naive patients and experienced patients with baseline detectable viremia. Legend: VL = viral load; NA = not applicable

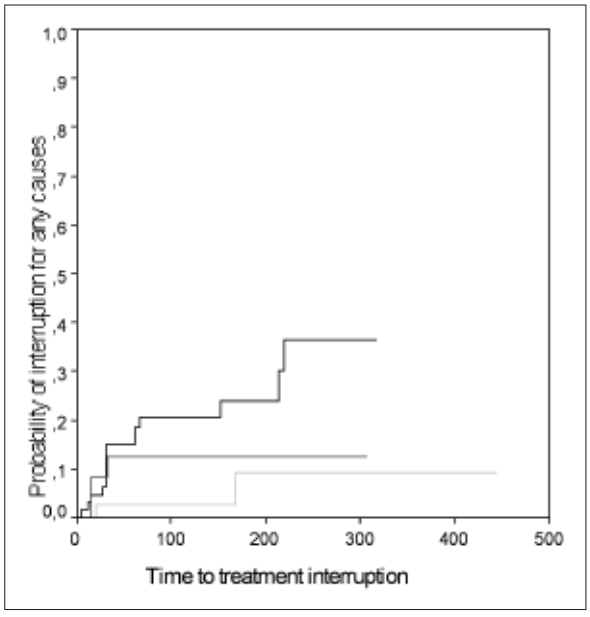


FIGURE 1 - *Probability of interrupting of FTC-regimen for any cause. Legend: pink line: patients naïve to ARV (N-pts); blue lines: patients ARV-experienced with measurable baseline viral load (E-det-pts); green line: patients ARV-experienced with undetectable baseline viral load (E-undet-pts).*

(p<0.001). Median CD4+ changes were 99 (IQR 55-169) for N-pts, -25 cells (IQR -85; -55) for E-und-pts, and 36 cells (IQR -13-108) for E-det-pts.

We did not performed statistical analysis on resistance mutations because of low incidence of virologic failure during follow-up.

## DISCUSSION

Data from clinical trials demonstrated a good tolerability and efficacy of FTC-regimens both in naive and experienced patients. According to preliminary results, the administration of regimens containing emtricitabine, didanosine, and efavirenz in patents who had not previously received antiretroviral treatment was associated with a rapid declination of HIV-RNA levels. The proportion of patients achieving virological suppression was very high at 24 weeks: 93% considering cut-off of 50 copies/mL and 98% for cut-off of 400 copies/mL (Molina *et al.*, 2000). Similar results were achieved by Gallant, et al. (2006) in a randomized non-inferiority trial comparing the regimens of tenofovir, emtricitabine and efavirenz and a fixed dose of zidovudine and lamivudine plus efavirenz in HIV naïve patients. In this clinical trial, proportions of patients with virologic suppression (HIV-RNA <400 cp/ml) were 84% in tenofovir-emtricitabine group and 73% in zidovudine-lamivudine group (p=0.002) at 48 weeks. Proportion of patients reaching less than 50 copies/ml were respectively 80% and 70% for two arms of the study. Once a day regimen was associated with greater adherence, as measured on the basis of pill count (90% versus 87%;P=0.004) (Gallant *et al.*, 2006).

A randomized, placebo-controlled trial evaluating 2 HAART regimens containing didanosine, efavirenz associated with emtricitabine (200 mg QD) or stavudine (standard doses twice daily) in naïve patients showed that once daily FTC was statistically superior to twice daily d4T: virologic failure was present in 5,3% and 12.7%, respectively for FTC and d4T arms (p<0.05). Moreover, patient in FTC-arm had a significantly greater probability of persistent virologic response if compared to stavudine-arm (respectively 76% versus 54%; p<0.001) and a less probability of discontinuation due to adverse event (respectively 7% versus 15%; p=0.005) (Saag *et al.*, 2006).

Good results were achieved in simplification strategies too. In a prospective, open-label, multicenter study, in which 355 patients with sustained virologic suppression during PI-regimen were randomized to continue previous treatment or to receive a simplification with a once-daily regimen (FTC, ddI, and EFV, a total of 5 pills), switching therapy was associated with a larger proportion of patients with HIV-RNA <50 copies/ml at 48 weeks (87%) then maintaining the same regimen (79%, p=<0.05). Moreover, in this trial switching from zidovudine-lamivudine to emtricitabine-didanosine was associated to a statistical significant reduction of side effects as haematological toxicities (Molina *et al.*, 2005).

The data collected in our study indicate a high tolerability of combinations containing emtricitabine. At last observation, 82% of patients were still continuing baseline regimen. Interruption of emtricitabine for any reasons was present in 13.3% and primary reasons for discontinuation were subjective intolerance and patient decision. Only three patients interrupted regimen due to toxicity. In our patients, most frequent NRTI

used in association with emtricitabine was tenofovir (94.0%) and this backbone association could explain the tolerability as previously showed in clinical trials (Gallant *et al.*, 2006).
Considering analysis of efficacy, we observed that the probability of virologic success at 6 months during treatment with FTC was 74.7% and that it was similar according with different groups of patients.
The efficacy of regimen could be explained by the possibility of building very simple regimens with entricitabine. This may be pivotal, if we consider that high levels of adherence to HAART regimens are required to achieve optimal efficacy (Paterson *et al.*, 2000), and that simple and once-a-day regimens were related to less proportion of missing doses (Stone *et al.*). In our study we did not analyze the variations of patient's adherence to new regimen, but in a reasonable proportion of subject the switch to FTC-regimen was made after a request of simplification regimen.
One of the advantages of observational studies is the possibility of analyzing the real impact of a new drug in clinical practice where there are no criteria of patients selection and where several patients have access to drug. In this sense, the present study revealed high efficacy and tolerability of FTC-containing regimens in an unselected population, indirectly confirming results of controlled studies.
However, there are several limitations to our study. First of all, the short time of median follow-up, due to relatively recent registration of the drug in Italy, make difficult to evaluate long-term virological efficacy. In fact, in our study the median period of observation was 80 days and only 26.7% of patients had a longitudinal observation longer than 24 weeks.
Considering the type of study, no intervention on clinical management and data collection was planned. All information were taken from clinical charts after doctor had visited patients: data could be missing or nor very accurate in some cases. Besides, we had no systematic assessment of adherence both before and after starting FTC regimen.
In conclusion, preliminary results of our observational study indicate that antiretroviral regimens containing emtricitabine could represent an optimal therapeutic option in management of HIV infection, especially in first treatment lines. It is associated with a low risk of both virologic failure and treatment discontinuation due to toxicity. In particular, therapeutic success could be in part attributed to improved adherence increased by a simpler administration schedule with low pill burden. Long term observation is needed to evaluate the impact of backbone containing emtricitabine on efficacy and safety of HAART regimens.

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