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Differentiating emtricitabine (FTC) from lamivudine (3TC): what a "fine-tuning" of antiretroviral therapy might entail

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The HIV reverse transcriptase nucleoside inhibitors, including the nucleotide tenofovir, are commonly known with the acronym NRTI(s) and the nickname 'nukes'. Even though various attempts have been made to identify NRTI-sparing regimens, NRTIs are still the backbone of most HAART combinations, either first or later lines of treatment. When one takes into consideration the latest revised guidelines (EACS November 2009; DHHS January 2011), the role of this group of compounds is evident. In heavily pre-treated patients bearing viruses with multiple resistances, a NRTI-sparing combination is not a choice, but it's dependent on loss of activity of most antiretrovirals (ARVs), including NRTIs.

Currently NRTI therapies are prescribed largely as fixed-dose combinations (FDCs) for the sake of convenience and regime compactness. The zidovudine/lamivudine FDC (AZT/3TC, Combivir®) is no more a preferred, first-line choice due to the thymidine analogue (AZT) toxicity. The place of the FDC AZT/3TC/abacavir –ABC- Trizivir® has been reduced as well due to AZT toxicity and insufficient antiviral strength when this FDC was used alone. More interesting are the two most used FDCs (emtricitabine/tenofovir, FTC/TDF, Truvada® ; 3TC/ABC, Kivexa®), whose components appear to be well differentiated as far as TDF and ABC are concerned. What is definitely less clear are the differences between FTC vs. 3TC: they often are perceived as equivalent in terms of potency and for the ability to generate resistance mutations at failure. The aim of this article is to analyse the evidence on possible differences between these two drugs.

Actually, since the early 1990's a wealth of data have been generated from in vitro studies, short-term monotherapy studies, clinical trials (ASSERT, HEAT,ARIES, BICOMBO, GS934, ACTG 5202), cohort studies (ARCA, GNOMO), meta-analyses (Hill & Sawer) and others contributions available in the scientific literature, all suggesting in a direct or indirect way that differences in pharmacokinetics and pharmacodynamics between FTC and 3TC do exist. These data can be examined first from the latest available obtained in the study ACTG 5202.

ACTG 5202 is a strategic study that randomized an elevated number of naïve patients (n=1858) in four treatment arms described in the Fig. 1. The prospective, double blind, randomized, placebo-controlled study was designed to evaluate the efficacy and the tolerability of the two main FDCs (FTC/TDF vs. 3TC/ABC), associated either with efavirenz –EFV- (600 mg QD) or with atazanavir/ritonavir –ATV/r-(300/100 mg QD). A pre-planned analysis on efficacy according to baseline plasma HIV RNA (above or below 100.000 cps/ml) was included in the study design. In December 2009 a paper in the "New England Journal of Medicine" reported on the analysis of around 800 patients with baseline HIV-RNA levels > 100.000 copies/ml. The demographic and viro-immunological parameters were evenly distributed among the 389 patients treated with 3TC/ABC, and those 399 receiving FTC/TDF. In January 2008 the Data Safety and Monitoring Board (DSMB) that monitored the study noted an increased rate of virologic failure in patients with high viremia who received 3TC/ABC, independently from the third drug of the combination. Patients were followed for a median time of 60 weeks (0-112) with 90% (718) remaining in the study. Virologic failure, as defined by the protocol, occurred in 57 subjects treated with 3TC/ABC and in 26 treated with FTC/TDF. A decision was then taken to break the study blinding and to offer those with high baseline viremia and treated with 3TC/ABC to switch to the other FDC.

The Kaplan-Meier curve illustrating the proportion of patients free from virologic failure showed

Figure 1

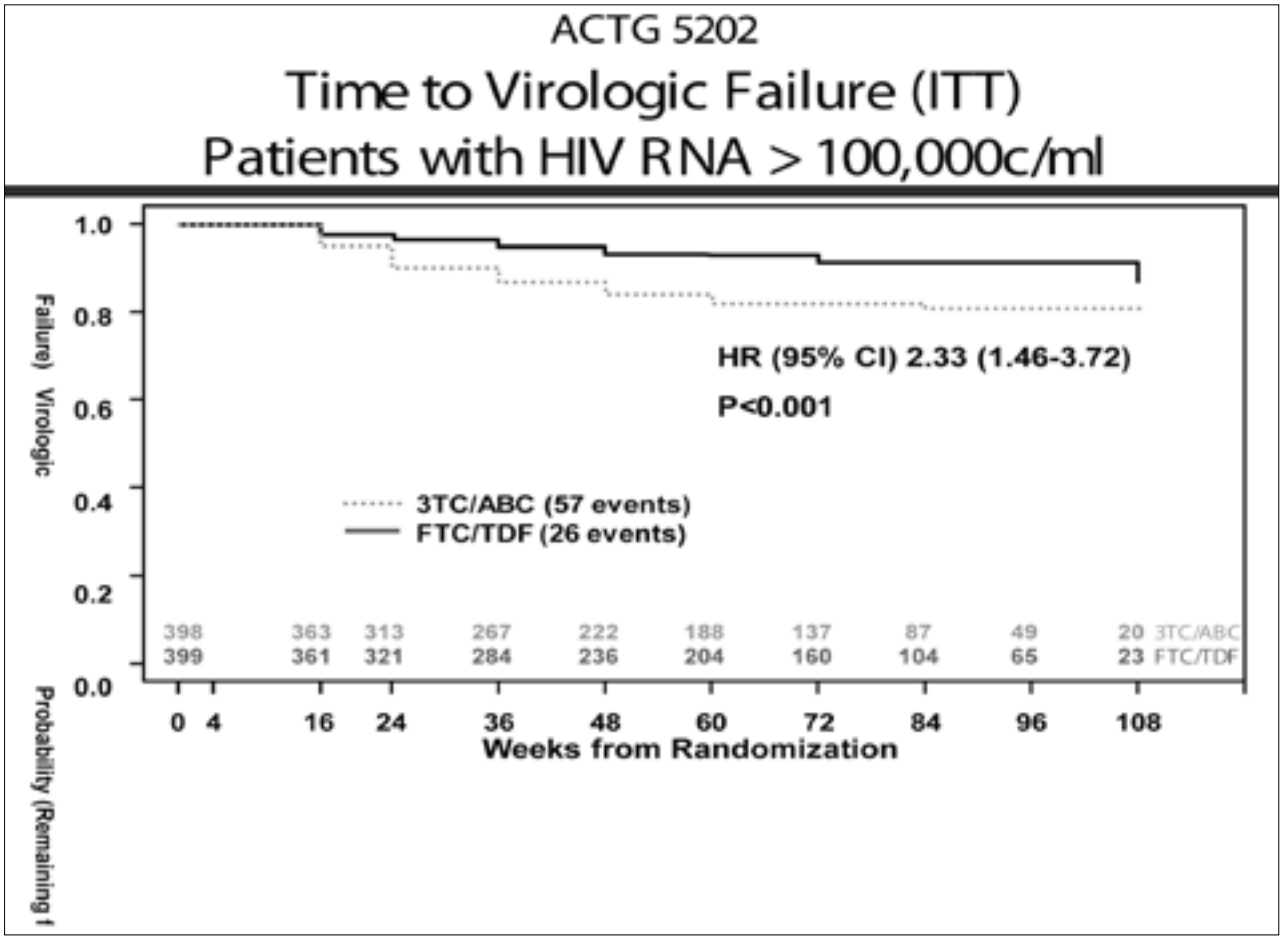
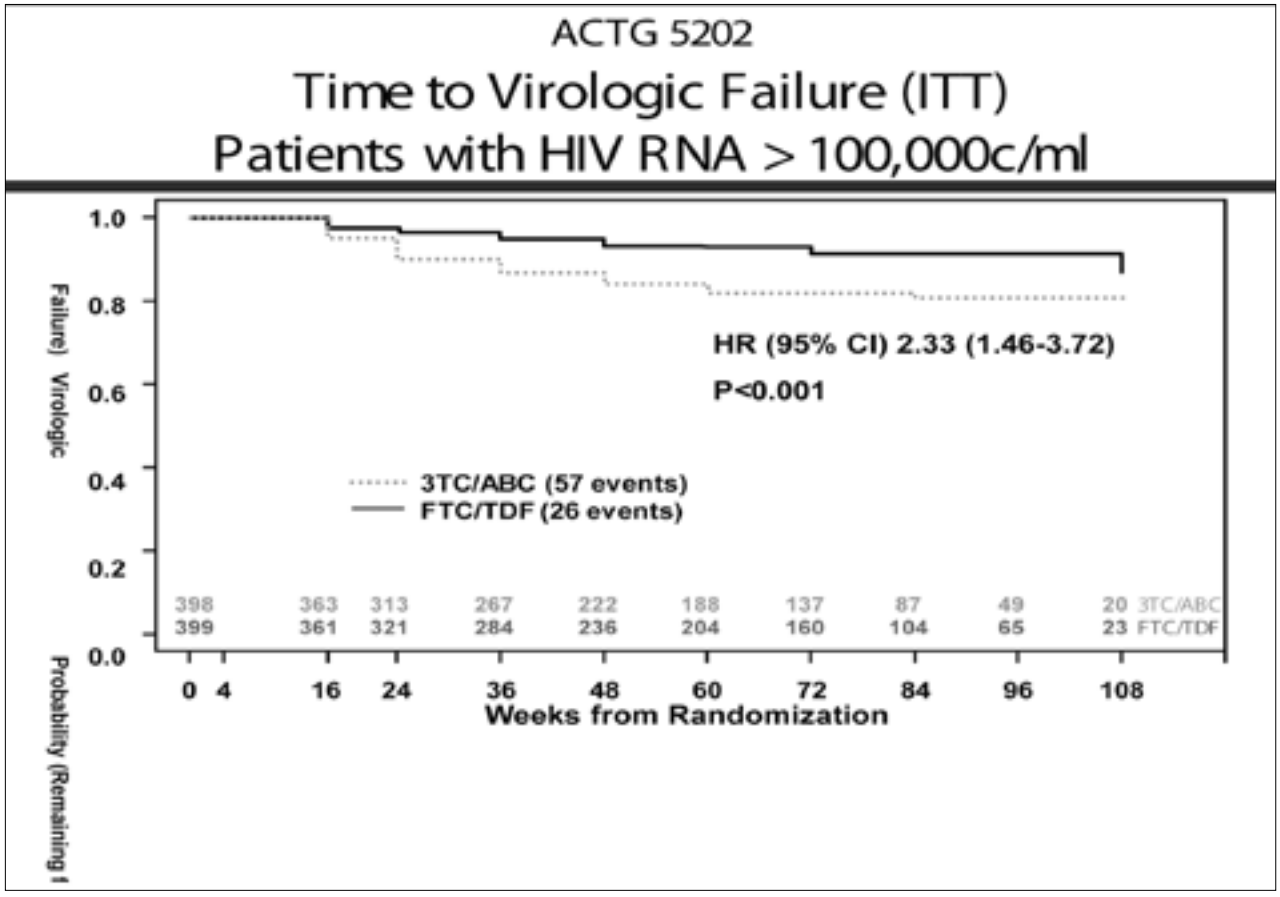


Figure 2



(Fig. 2) a statistically significant risk with 3TC/ABC (Hazard Ratio 2.33, 95% Confidence Interval [95% CI] 1.46 - 3.72, p<0.001) when compared to FTC/TDF. The Authors (1) gave some possible explanations for this finding. Potency of 3TC/ABC in patients with a high viremia cannot be sufficient for controlling HIV replication due to pharmacokinetic characteristics of its components. Otherwise, some pre-existing resistance mutations may have a different impact on the two FDCs. In essence, elevated viremia might emphasize differences in potency between two or more molecules which ordinarily would not show in patient populations with lower HIV RNA levels

NRTI PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE

Currently as the NRTIs used in most HAART combinations are formulated into two FDCs, the choice between FTC and 3TC is mainly based on characteristics of the FDC as a whole rather than on features of the single cytidine analogue. However some differences in the pharmacokinetics/pharmacodynamics do exist between FTC and 3TC, with a possible impact on virologic response and on the potential to induce resistance mutations. A more detailed analysis of available data from in vitro and in vivo studies (Fig. 3) could show to a greater extent what differences may be found not only between FTC and 3TC but also among NRTIs as a class.

One of the most common parameters employed in virology is the EC50, defined as the drug concentration that inhibits 50% of viral growth, including HIV-1 (2). When the activated metabolite FTC-triphosphate (FTC-TP) activity was studied in mononucleate cells harvested from peripheral blood (PBMCs), FTC-TP showed a potency 11 times greater than 3TC-TP measured in micromolars. Another parameter associated to antiviral efficacy is drug ability to bind itself to the catalytic site of the enzyme to inhibit. The greater this ability, the more likely would be the virologic potency of the drug. The binding affinity of FTC-TP is 10-fold larger than 3TC-TP (3).

Figure 3

Virologic Activity of FTC vs. 3TC

- **FTC exhibits greater potency than 3TC against HIV-1 *in vitro*[1]:**
  - **FTC EC_{50} = 0.02 µM (PBMC)**
  - **3TC EC_{50} = 0.23 µM (PBMC)**
- **FTC-TP Is Incorporated Quickly with High Binding Affinity During HIV-1 RT Catalyzed Viral DNA Synthesis[2]**

dCTP Analogs	k_{pol} (s^{-1})	K_d (µM)	k_{pol}/K_d ($µM^{-1}s^{-1}$)	Relative Substrate Specificity
dCTP	22.9	30	0.76	13
ddCTP	0.92	5.3	0.17	2.8
(–)FTC -TP	0.082	1.4	0.060	1
(–)3TC -TP	0.033	5.0	0.0067	0.1

Kpol is the rate of polymerization Kd is the dissociation constant, which reflects the binding affinity

[1] Schinazi RF et al. JAIDS 2003;34(2):243-245
[2] Feng JY et al. 14th ICAR, Seattle, 2001, Poster # 65.

Figure 4

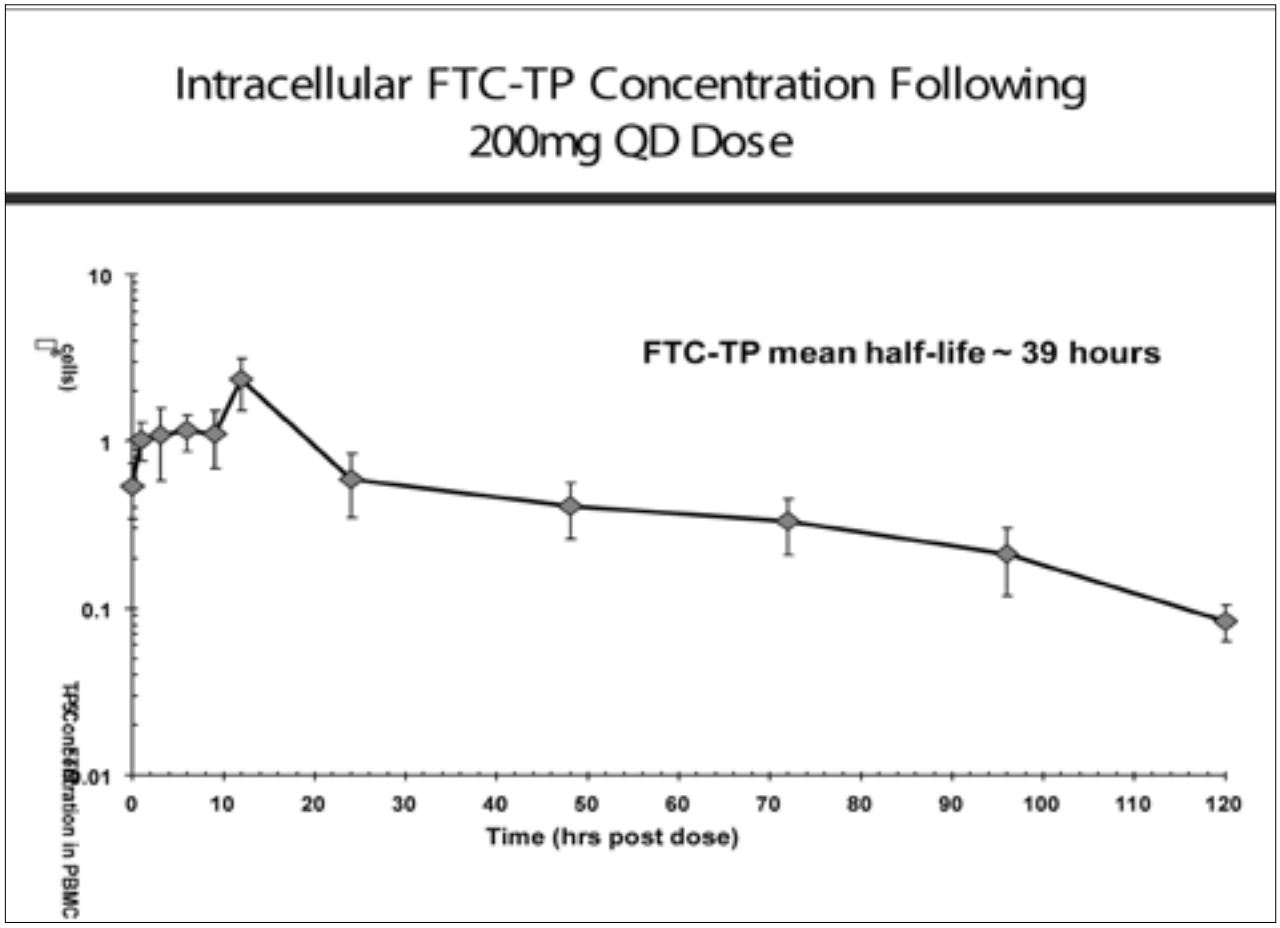
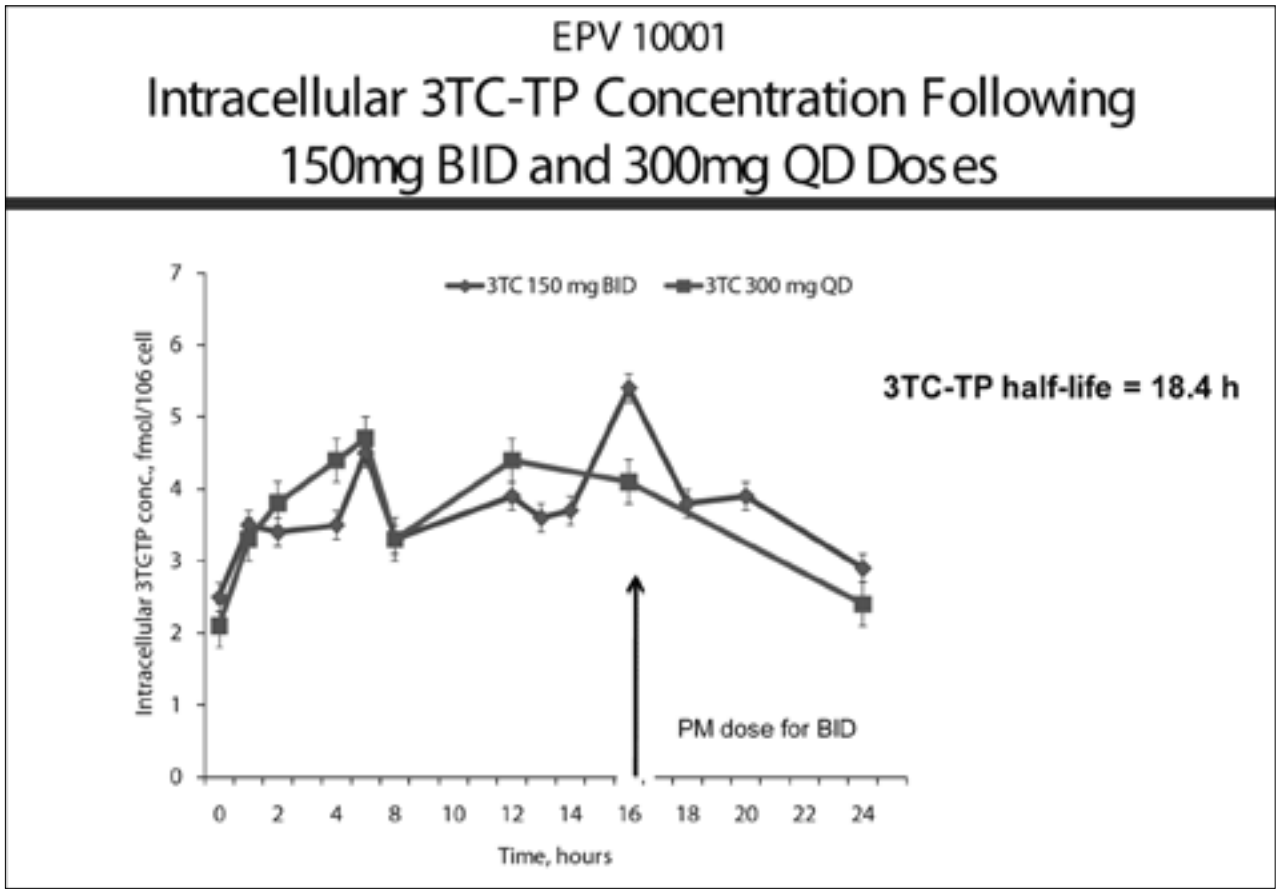


Figure 5



It would make no sense to employ high-affinity metabolites if these compounds do not enter and stay in target cells infected with HIV. FTC-TP has an intracellular half-life of approximately 39 hours (4) based on a daily dose of 200 mg QD (fig.4). This half-life is more than double that of 3TC-TP.

Actually, intracellular half-life of 3TC-TP is approximately 18 hours, less than half the one determined for FTC-TP (Fig.5). Furthermore, 3TC-TP intracellular half-life is independent from the dosing schedule, i.e. no variation has been demonstrated whether 3TC was administered twice-daily (150 mg BID) or once-daily at the dosage of 300 md QD (5). NRTI intracellular concentrations of the active metabolites are however difficult to determine, as variations due the type of cells in which they are studied and activation state do occur and may markedly influence NRTI-TP levels.

However, notwithstanding technical hindrances, it's possible to establish sort of a pharmacokinetic gradient among the NRTIs available in clinical practice. It may be constructed by keeping account of both plasma concentrations and intracellular levels of active metabolites. Even though this data cannot be directly extrapolated to rank NRTIs for pharmacodynamic potency, some compounds may be more effective than others. FTC and TDF not only are the NRTIs whit highest plasma and intracellular concentrations, but also share similar half-lives making them ideal companions to be incorporated in a FDC (Fig.6). It must be said that 3TC and ABC as well show comparable half-lives, even if decidedly inferior with respect to FTC/TDF.

Figure 6

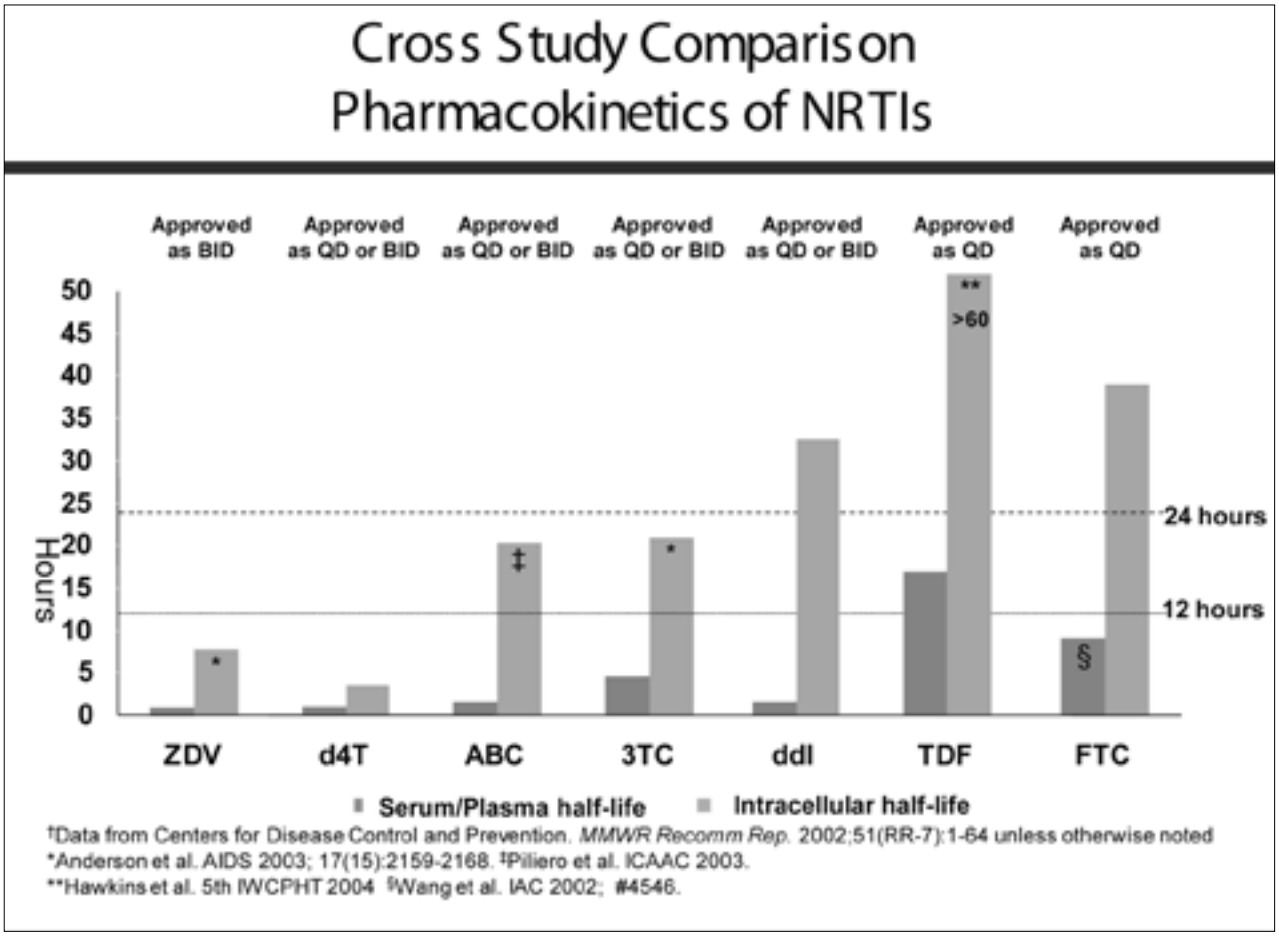


Figure 7

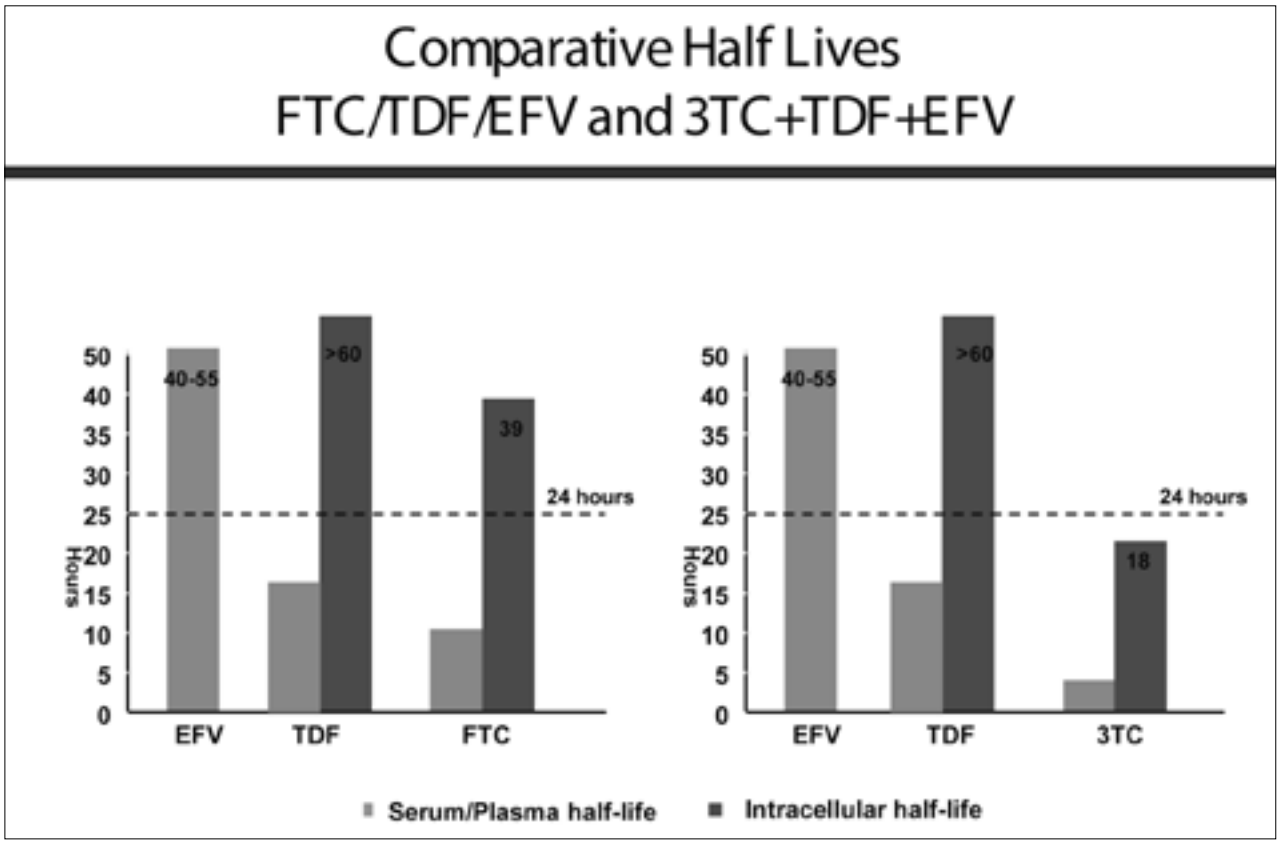
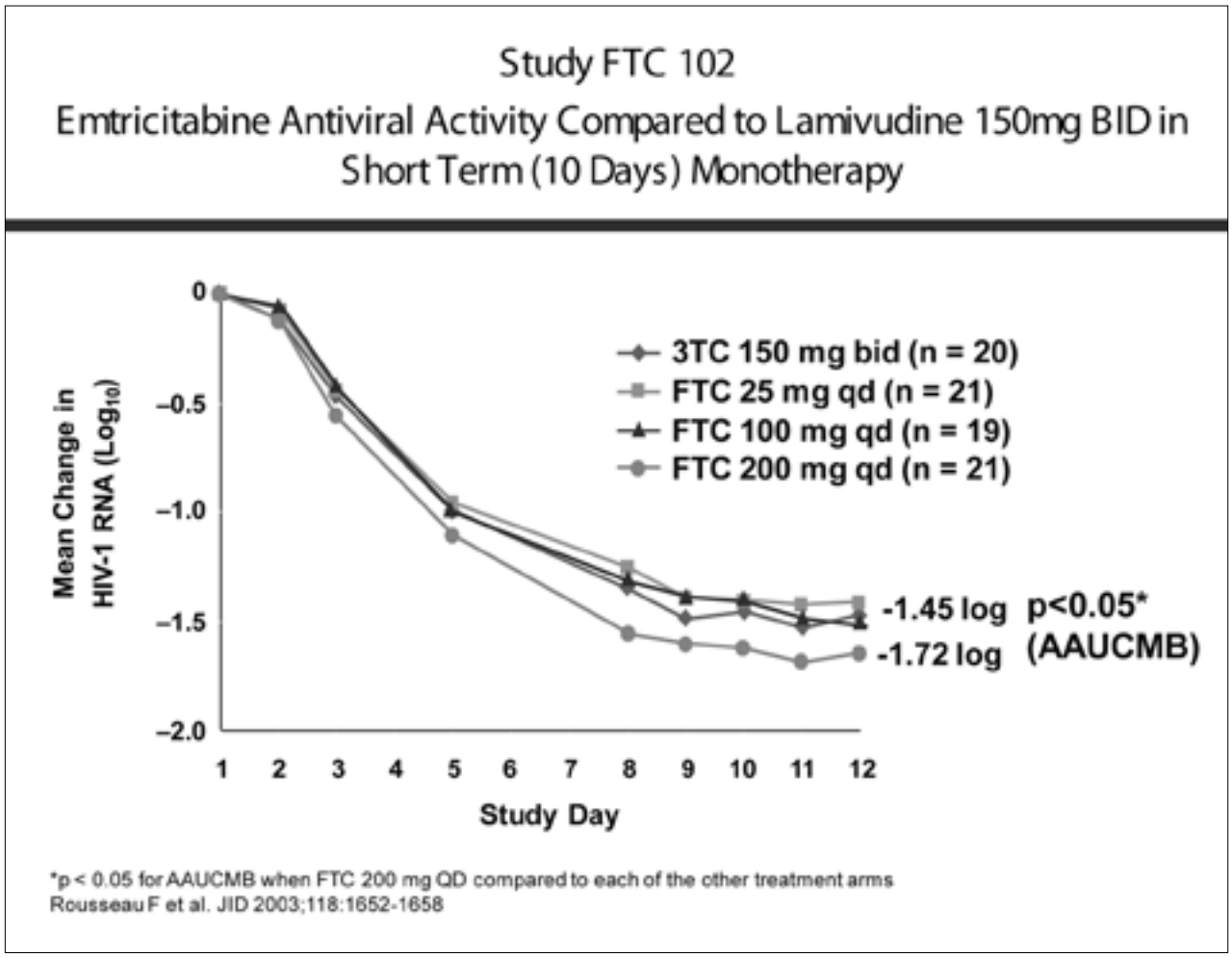


Figure 8



Indeed, weather inside a FDC or simply in a combination of ARVs, the homogeneity of pharmacokinetic parameters, namely plasma and/or intracellular half-life is of paramount importance. Any significant mismatching may result in dissimilar exposures to drugs included in the combination. This means that at some points of the time-concentration curve, a three-drug regimen would turn out as two- or even single-drug therapy, with the obvious consequence of generating resistance mutations. When EFV plasma half-life is plotted beside the same parameter relative to intracellular FTC/TDF active metabolite concentrations (Fig.7), it's evident how the FDC Atripla® which incorporates EFV/FTC/TDF offer a peculiar advantage in opposition to use 3TC as an alternative to FTC.

A good pharmacokinetic profile ought to be associated with an adequate virologic potency in order to contend that an ARV compound is effective. Antiviral potency is usually determined in vivo by plotting changes in HIV viremia across time at different drug concentrations. FTC-102 was a dose-ranging, 10-day monotherapy study to identify the optimal dosage of FTC (dosages tested: 25, 100 or 200 mg QD), in comparison with a control arm (3TC, 150 mg BID). The FTC 200 mg treatment arm (Fig.8) showed a significantly greater decrease of viremia compared to 3TC (-1.7 $\log_{10}$ vs. -1.45 $\log_{10}$) and this dosage was then chosen for further clinical studies with FTC.

Along with reduction in HIV RNA plasma viremia, the 200 mg QD dose of FTC was chosen based on comparative data from the same study looking at the percentage of patients in each arm showing a viremia <400 cps/mL or a reduction > 2 $\log_{10}$. FTC resulted more potent than 3TC for all doses tested in the study, even if a greatest effect was seen with the 200 mg dosage (Fig.9).

Figure 9

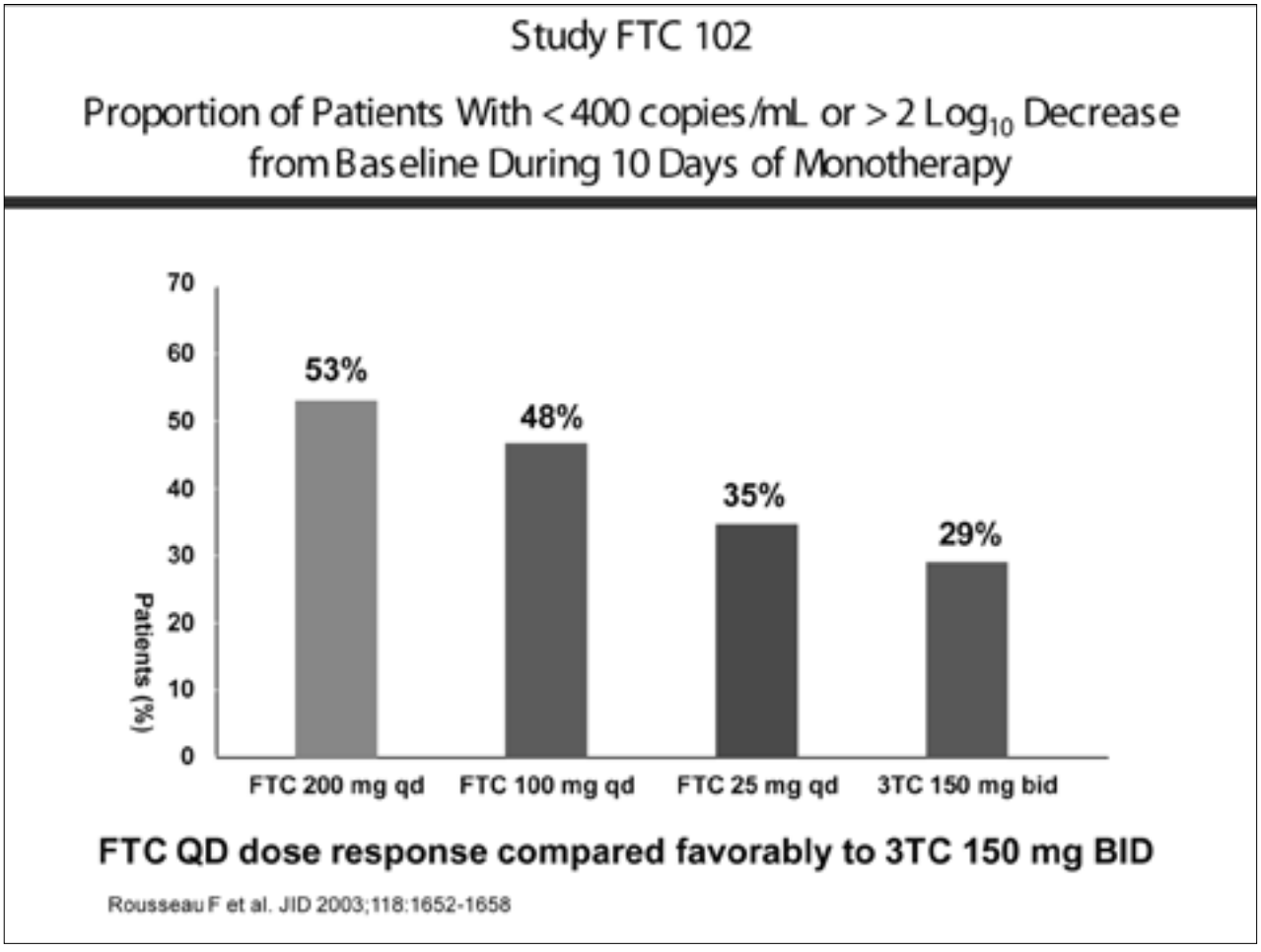


Figure 10

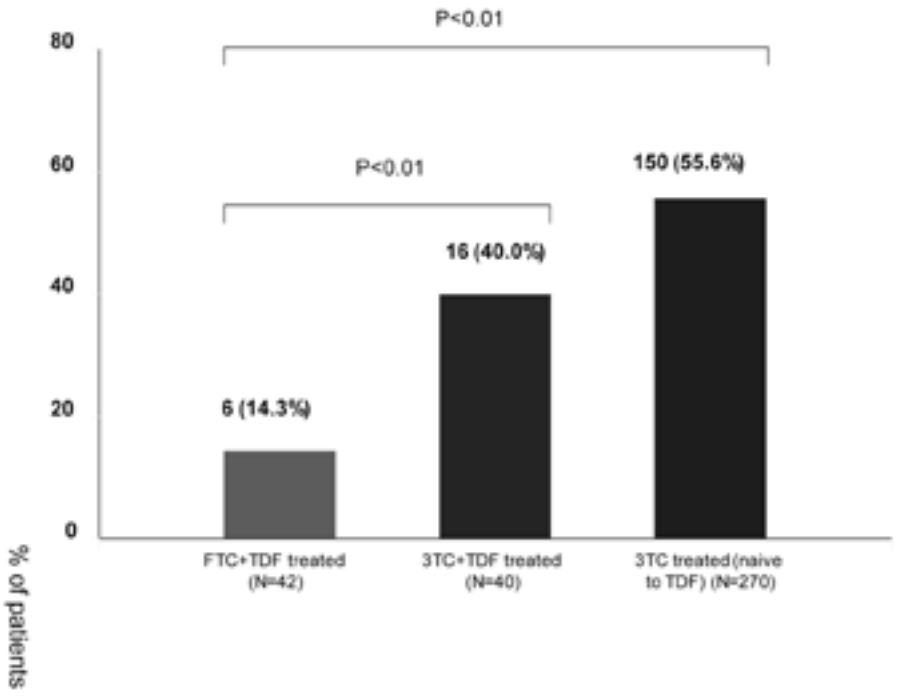
Relative Potency of Approved NRTIs

NRTI/NtRTI	Nadir Response*	Study
AZT	-0.5	NUCA 3001
D4T	-0.6	ACTG 298
DDI	-0.7	ACTG 175
3TC	-1.3 to -1.45	NCUA 2001/FTC 102
ABC	-1.6	CNAB 2002
TDF	-1.6	GS 917
FTC	-1.7 to -1.9	FTC 102/FTC 101

*Log_{10} HIV RNA decreases from baseline

Figure 11

Different Evolution of Genotypic Resistance Profiles to FTC Versus 3TC in TDF Containing Regimens



The efficacy of FTC as determined in the FTC 102 study is better put in perspective (Fig.10) when one considers the data available on the potency of NRTIs when studied in functional monotherapy studies. In the study NUCA 3001, monotherapy with AZT (200mg TID) reduced the viral load by -0.52 ± 0.04 $\log_{10}$ copies/ml in 24 weeks (6). In ACTG 298 monotherapy study, d4T 40mg BID reduced HIV-RNA by -0.59 log copies/ml in 12 weeks (7). Monotherapy with didanosine (200 mg BID) reduced the viremia in ACTG 175 to -0.65 ± 0.07 $\log_{10}$ after 8 weeks of treatment (8). In the studies NCUA 2001 (9) and FTC 102 (10), the 3TC monotherapy at 7 and 10 days decreased HIV RNA to -1.3 and -1.45 $\log_{10}$ copies/ml, respectively. The reduction of the baseline viremia after monotherapy with ABC (300mg BID) was -1.55 $\log_{10}$ copies/ml after 4 weeks in the CNAB 2002 study (11). The TDF activity after 21 days of treatment with a 300mg OD dosage was measured as -1.6 $\log_{10}$ copies/ml by the GS-917 investigators (12). Finally, FTC 200mg OD reduced the medians of plasma HIV-RNA between -1.72 (13) and -1.92 $\log_{10}$ copies/ml (14) in 2 weeks (FTC 101 and 102, respectively).
Even though there were differences in the design of these studies and NRTI monotherapy was not standardized, it might be observed how FTC treatment was associated with the more robust decrease in viremia from baseline.

Resistance Profile
The ARCA study (15) is a retrospective study that evaluated the resistance pattern at failure in 859 patients under treatment including 3TC/TDF (n=714) or FTC/TDF (n=145), after a period of virologic suppression (HIV RNA <50 copies/ml) of at least 6 months. Comparing the pre-treatment genotype and the one obtained at virologic failure allowed the study of emerging mutations (Fig. 11). More mutations were detected in the group treated with 3TC/TDF. At multivariate analysis appeared that not only the mutation M184V but also other mutations - NRTI-associated K70R and T215F; NNRTI-associated Y181C- were significantly more common in 3TC/TDF group than in FTC/TDF. This finding implies that failing a 3TC/TDF-containing HAART, compared to FTC/TDF, may increase the risk of limiting future options not only in the use of NRTIs but also for NNRTIs, including etravirine whose activity is significantly restricted by the presence of Y181C.

The GNOMO study (16) is a prospective, multicenter Italian study where resistance mutations found at virologic failure were studied in 1337 patients treated either with combinations: 1) including FTC/TDF, or: 2) including 3TC/TDF, or: 3) with 3TC but without TDF. As in the ARCA study patients were included in the study only if the pre-treatment genotype were available. Contrary to ARCA study though, patients were separately evaluated according to treatment lines (first vs. later lines). M184V resulted to be less frequent in FTC/TDF group, followed by 3TC/TDF and then in 3TC given with other NRTIs. This difference was significant for FTC/TDF vs. 3TC/TDF in treatment-experienced patients, and for FTC/TDF vs. 3TC/plus other NRTIs in both patient groups (Fig.12).

The lowest prevalence of M184V can be explained with a greater potency of FTC vs. 3TC as demonstrated by in vitro studies (17), and the different intracellular pharmacokinetics of FTC vs. 3TC. An extended intracellular half-life may limit more efficiently the HIV-1 reverse transcriptase activity, reducing the occurrence of M184V resistance mutation.

Figure 12

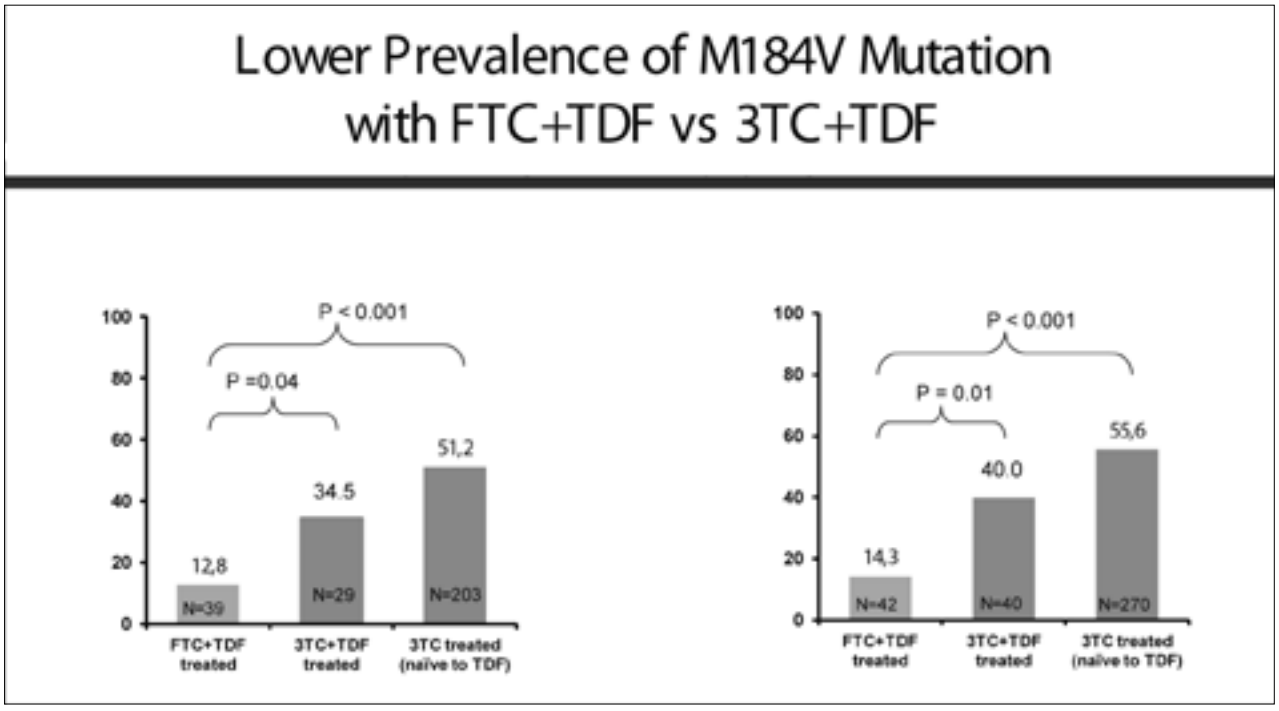
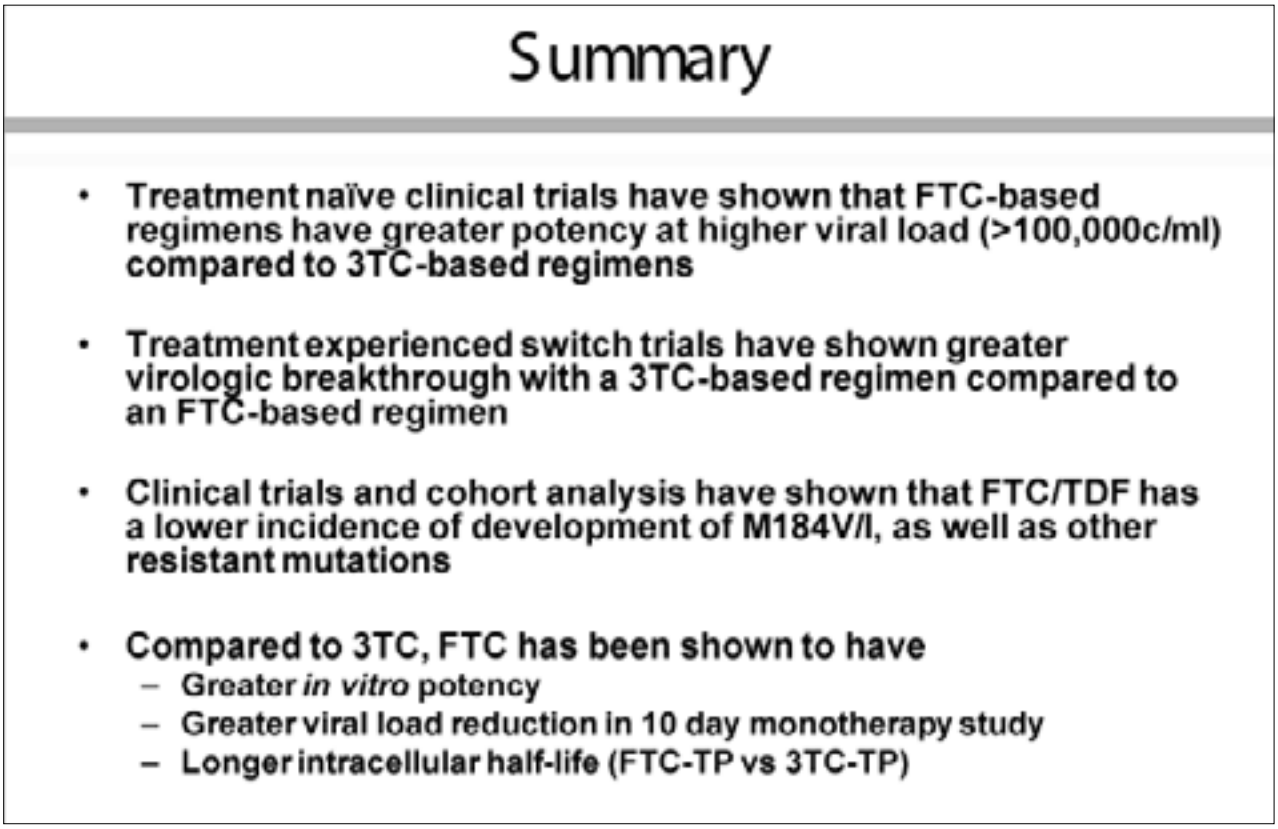


Figure 13



In conclusion, a series of data obtained from in vitro studies, observational trials, clinical trials and meta-analyses support the following statements:

1) FTC-based HAARTs commonly demonstrate an increased virologic potency – maybe more evident in, but not only limited to patients with baseline HIV RNA plasma viremia >100.000 copies/ml – if compared with those containing 3TC

2) In switch regimens this correlates with a reduced rate of virologic failures for FTC vs. 3TC

3) Resistance-associated mutations are selected less frequently at failure when FTC is used rather than 3TC

Differences in antiviral potency between these two cytidine analogues featured by similar mutational patterns could appear negligible in an era where there is a plenty of ARVs, most patients are virologically suppressed and a general decrease in the generation of resistance mutations is recorded. However a strong rationale still exists to consider very seriously a fine tuning of antiretroviral therapy where clinicians draw a distinction between FTC and 3TC. The perception of an intrinsic interchangeability between 3TC and FTC can lead to incongruent prescriptions of 3TC/TDF made also for curbing the cost of therapy. There will a cost to pay though, not only in terms of a reduced compliance associated to an increased number of pills, but mostly when facing elevated baseline viral loads or when virologic failures occur, generating resistance mutations that may extend to classes beyond NRTIs.

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