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LETTER TO THE EDITOR

The multifactorial pathways towards resistance to the cytosine analogues emtricitabine and lamivudine: Evidences from literature

Letter – The article by Bulteel et al.,¹ published in the September issue of the journal, has investigated the rate of M184V emergence in patients receiving HAART combinations containing efavirenz (EFV), tenofovir (TDF) and lamivudine (3 TC) or emtricitabine (FTC) within the UK Collaborative HIV Cohort. By analyzing 304 genotypic resistance tests, the authors asserted that, although patients receiving 3 TC-based regimens were more likely to develop M184V than those receiving FTC-based regimens (event rate: 0.55 [95%CI: 0.28–0.96] for 3 TC versus 0.34 [95%CI: 0.21–0.46] for FTC), this association was not statistically significant in both univariable and multivariable models. These results are different from those reported in previous studies from our and other groups^{2–4} showing a significant decrease in M184V emergence in patients failing FTC + TDF-based compared to 3 TC + TDF-based HAART (Table 1). The lower prevalence of M184V in FTC-containing regimen was also supported by a recently published letter showing a strong trend ($P = 0.051$) towards higher rates of resistance to the 3 TC containing regimen 5.5 (1.8–12.8) per 1000 patient years when compared with the FTC containing regimens 1.7 (0.8–3.2) per 1000 patient years.⁵

Such discrepancy in M184V prevalence can be explained by the profound differences in the dataset of patients analyzed. The most striking difference is represented by the fact that the studies by our and other groups^{2–4} have analyzed viremic patients at the time of starting a FTC + TDF- or 3 TC + TDF-containing HAART. Conversely, Bulteel et al.¹ have analyzed a quite heterogeneous population composed for around 50% by patients starting FTC + TDF- or 3 TC + TDF-containing regimen during virological suppression (Table 1). In Bulteel's study, 49.9% of 3 TC-treated patients and 46.1% of FTC-treated patients had a plasma HIV-1 RNA <50 copies/ml at the time of starting 3 TC/FTC-containing therapy. The negative correlation between baseline viremia and drug resistance emergence is well known,⁶ and it is supported also by Bulteel's study¹ showing that a viremia >50 copies/ml at the time of starting 3 TC/FTC containing therapy correlates with an

increased rate of M184V detection. This result supports the critical role of first phases of viremia decay during treatment in drug resistance emergence. In this light, it is conceivable that the different impact of FTC versus 3 TC may be better appreciated in the setting of a higher baseline viremia, and not in the setting of undetectable or low level viremia.

In addition, the studies by our groups^{2,4} have analyzed patients starting a first line FTC + TDF- or 3 TC + TDF-containing HAART. Conversely, Bulteel et al.¹ also included patients not at the first prescription of FTC/3 TC + TDF-based regimen. In a previous analysis presented at 16th CROI 2009 (abs#642), including also patients previously treated with 3 TC, Svicher et al. showed that a previous 3 TC exposure was an independent factor correlated with an increased rate of M184V detection in multivariate analysis (Odds Ratio [CI]: 2.28 [1.74–2.98], $P = 0.001$). This highlights the existence of a viral reservoirs enriched with the M184V mutation that can re-emerge despite FTC use. This is in line with a previous study⁷ showing that 3 TC-resistant HIV-1 variants can persist (as minority species) despite highly unfavorable conditions *in vivo* and *in vitro*.

Furthermore, the studies by our and other groups^{2–4} have included patients receiving as third drug either EFV or a Protease Inhibitor boosted with ritonavir (PI/r) (Table 1). Conversely, Bulteel et al.¹ have included only patients receiving EFV as 3rd drug (Table 1). The protective role of PIs/r in delaying drug resistance emergence is well known. We showed that the use of a PI/r is an independent factor correlated with a lower M184V detection at virological failure.^{2,4} In addition, Gupta et al.⁸ (in a systematic review of clinical trials) showed that the prevalence of M184V was 35.3% in patients starting NNRTI-based HAART compared with 21.0% in those receiving PI/r.

Thus, based on the above-mentioned differences, it is likely that the criteria used by Bulteel et al.¹ to select patients may not allow to extrapolate conclusive information on the rate of M184V emergence between 3 TC and FTC. It should be also noted that when Bulteel et al.¹ focused on a subgroup of patients experiencing virological failure for the first time, the M184V prevalence was 13.5% for FTC + TDF + EFV treated patients and 22.6% for 3 TC + TDF + EFV treated ones (Table 1). While prevalence of M184V in patients failing FTC + TDF + EFV was nearly close to that observed by our studies,^{2,4} its prevalence in 3 TC + TDF + EFV is much lower. Beyond the above-mentioned factors, it might be thought

Table 1 Studies characteristics.

	Svicher et al., JAIDS 2010; 55:336–344	Marcelin et al., JAC 2012; 67:1475–1478	Maserati et al., AIDS 2010; 24:1013–1018	Bulsteel et al., J Infect 2014; 68:77–84
Number of patients analyzed with GRT available	352	880	859	304
NRTI backbone with:				
3 TC + TDF	40	345	473	65
FTC + TDF	42	535	123	239
3 TC/FCT + others	270	0	263	0
Third drug:	Either EFV or PI/r	Either EFV or PI/r	Either EFV or PI/r	Only EFV
Baseline viremia (log₁₀ copies/ml)				
3 TC-based HAART	5.0 (4.6–5.5)	4.2 (2.1–5.3)	Not available	1.7 (1.7–4.9)
FTC-based HAART	5.2 (4.2–5.5)	4.1 (2.5–5.2)	Not available	2.5 (1.7–4.8)
% of patients with baseline viremia <50 copies/ml	0	0	Not available	3 TC: 49.9%; FTC: 46.1%
Prevalence of M184V^a				
3 TC + TDF	40.0%	37.1%	52.7%	22.6% ^b
FTC + TDF	14.3%	17.2%	34.5%	13.5% ^b
Factors associated with M184V emergence	3 TC↑; FTC↓; TA or ABC↑; TDF↓; NNRTI↑; PI/r↓	3 TC↑; FTC↓; NNRTI↑; PI/r↓; Viral load at the time of virological failure↑	3 TC↑; FTC↓	Black ethnicity↑, Viral load >50 copies/ml at therapy start↑; Trend for 3 TC TC↑ and FTC↓

GRT: Genotypic resistance test; Lamivudine: 3 TC; Emtricitabine: FTC; Highly active antiretroviral therapy: HAART; Non-nucleoside reverse transcriptase inhibitors: NNRTI; Tenofovir: TDF; Thymidine analogues: TA; Abacavir: ABC; Protease inhibitor boosted with ritonavir: PI/r. ↑ Factors positively associated with M184V emergence; ↓ Factors negatively associated with M184V emergence.

^a The study by Marcelin et al., *JAC 2012; 67:1475-1478* reports the prevalence of M184V/I mutations.

^b Analysis performed on a subset of 210/304 patients receiving either 3 TC, TDF and EFV or FTC, TDF and EFV experiencing virological failure for the first time.

that the 3 TC-failures observed in Bulsteel's study¹ could be due to the poor adherence resulting from high pill burden, adverse events, or long-term toxicity, and not by the selection of drug resistance.

The lower M184V prevalence in patients failing FTC + TDF-based than 3 TC + TDF-based HAART relies on both basic and clinical bases. Indeed, it can be explained by the higher potency of FTC than 3 TC, and/or by the higher intracellular half-life of FTC triphosphate than 3 TC triphosphate due to FTC ability to inhibit the cellular efflux proteins.⁹ The higher potency and intracellular half-life of FTC can increase its ability to inhibit the reverse transcriptase enzyme, thus reducing the probability of M184V emergence. The lower M184V prevalence in patients failing FTC + TDF-based than 3 TC + TDF-based HAART can also be explained by the co-formulation of FTC + TDF as Truvada or Atripla. This concept was supported by a recent study¹⁰ analyzing 9586 patients failing their antiretroviral-based regimens from 2005 to 2010. The authors found that the M184V/I prevalence decreased significantly, and this decrease was associated with an increased use of a TDF + FTC + EFV single-tablet regimen over time. This supports the critical role of simplifying drug intake and maximizing adherence in preventing drug resistance emergence.

Overall, multiple factors cooperate in mechanisms underlying drug resistance emergence. Their knowledge is mandatory for the achievement of long term virological success, thus improving the quality of life of patients and optimizing the costs related to public health.

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