Development of the M184V Mutation in HIV-1 and Outcomes of Antiretroviral Therapy Following its Development

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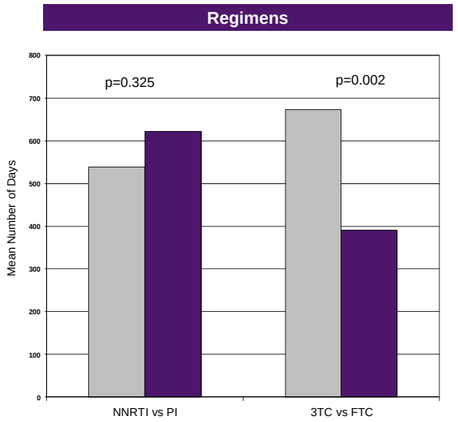
BACKGROUND

Highly active antiretroviral therapy (HAART), consisting of 3 antiretroviral drugs from 2 or 3 classes, has reduced morbidity and mortality due to HIV-1 infection since its introduction. Current standard of care in naïve patients consists of 2 nucleoside reverse transcriptase inhibitors (NRTIs), plus either a non-NRTI (NNRTI) or ritonavir boosted protease inhibitor (PI) or integrase inhibitor. Emergence of drug resistance is associated with increased mortality in patients who receive first line HAART. An estimated 10% of patients on HAART develop genotypic resistance after 2 years, and almost 30% develop virologic failure (VF) with at least 1 major mutation within 6 years of starting HAART. Although the most common mutations are to NNRTIs, which develop in approximately 50% of failing regimens, resistance to lamivudine (3TC) and emtricitabine (FTC) via the single resistance mutation, M184V, occurs in 35% of failing regimens. The purpose of this study was to describe the prevalence of the M184V mutation and the treatment outcomes following its development.

METHODS

This was a retrospective cohort study of all HIV-infected patients receiving care at the Washington University School of Medicine Infectious Disease Clinic between January 2001 and June 2010. Prevalence of the M184V mutation, outcomes of antiretroviral therapy in patients with M184V, as measured by time to virologic suppression (VS) and failure, and immune recovery were analyzed. VF was defined as a viral load >400 copies/mL after 6 months on a second line regimen (SLR).

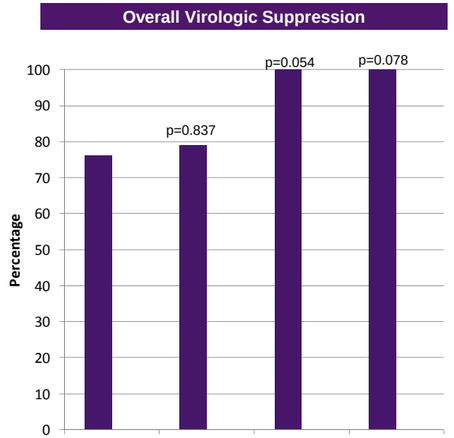
Development of M184V

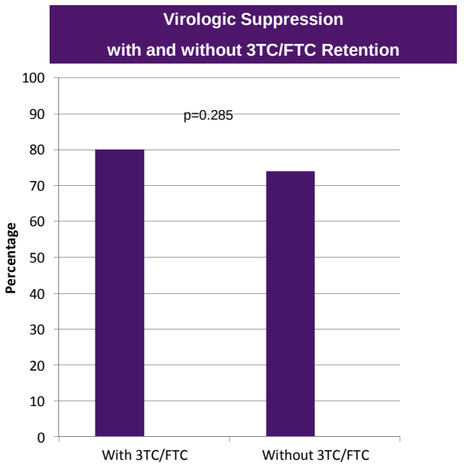


Demographics	Number (%)
Gender	
Male	158 (72%)
Female	62 (28%)
Race/Ethnicity	
African American	171 (78%)
Caucasian	43 (20%)
Hispanic	5 (2%)

Demographics	Number (%)
Sexual Orientation	
Heterosexual	85 (39%)
MSM	115 (52%)
Bisexual	9 (4%)
IVDU	9 (4%)
History of Monotherapy	38 (17%)
History of Dual Therapy	26 (12%)

Outcomes of Second Line Regimens





RESULTS

Of 2500 screened clinic patients, 220 had an acquired MI184V mutation (9%).

The mean time from the start of a regimen to the documented M184V mutation was 575 (0-3253) days. Independent of NRTI backbone, the mean time to development of M184V in NNRTI (n=109) and PI-based (n=84) regimens was 538 (±556) and 622 (±620) days, respectively (p=0.325).

Approximately 78% of patients achieved VS on SLR in a mean of 179 days. Of the 122 (57%) of patients whose SLR retained FTC/3TC, VS was achieved in 80% with FTC/3TC compared to 74% without FTC/3TC (p=0.285) with no significant difference in time to VS (152 (±187) and 181 (± 257) days respectively, p= 0.406). About 50% of these groups experienced VF after VS with a similar time to failure (273 (±188) days vs. 221 (±156) days).

There were no significant differences in achievement of VS in PI (n=158) and NNRTI (n=27) -based SLRs independent of the NRTI backbone, 76% vs. 78%, respectively (p=0.837) with a similar time to VS (180 (±228) vs. 128 (±158) days, p=0.313). All patients on PI+raltegravir (RAL) (n=10) and PI+NNRTI (n=12) –based regimens achieved VS (vs. 76% in PI+2NRTI (p=0.078 and p=0.054, respectively).

CONCLUSIONS

M184V mutation developed in 9% in a mean of 575 days with no significant differences between ART regimens. Following initiation of an SLR, the majority of patients achieved VS in approximately 179 days irrespective of the regimen. The addition of 3TC/FTC did not significantly affect VS. Although numbers were small, 100% of patients on fully active non-2 NRTI-backbone-based regimens were fully suppressed.