HIV/AIDS RESEARCH AND TREATMENT

Openventio PUBLISHERS

ISSN 2377-8377 Open Journal http://dx.doi.org/10.17140/HARTOJ-2-114

Brief Research Report

***Corresponding author**
Alexandria Garavaglia Wilson, PharmD, BCPS
Division of Infectious Disease
Department of Internal Medicine
St. Louis College of Pharmacy
4588 Parkview Place
St. Louis, MO 63110, USA
Tel. 314-446-8510
Fax: 314-446-8500
E-mail: awilson@stlcop.edu; Alexandria.Wilson@stlcop.edu

Volume 2 : Issue 3
Article Ref. #: 1000HARTOJ2114

Article History
Received: October 13th, 2015
Accepted: October 16th, 2015
Published: October 16th, 2015

Citation
Wilson AG, Cross S, Nurutdinova D, Presti R. Development of the M184V mutation in HIV-1 infection and subsequent treatment outcomes. *HIV/AIDS Res Treat Open J*. 2015; 2(3): 86-89. doi: 10.17140/HARTOJ-2-114

Development of the M184V Mutation in HIV-1 Infection and Subsequent Treatment Outcomes

Alexandria Garavaglia Wilson[1,2*], Sara Cross[1], Diana Nurutdinova[1] and Rachel Presti[1]

[1]Division of Infectious Disease, Department of Internal Medicine, 4570 Clayton, Box 8051, St. Louis, Missouri 63110, USA

[2]St. Louis College of Pharmacy, 4588 Parkview Place, St. Louis, Missouri 63110, USA

ABSTRACT

Objective: The purpose of this study was to describe the occurrence of the M184V mutation in a single clinic setting over a period of 10 years. We examined the combination Antiretroviral Therapy (cART) being taken at the time of first identification of the M184V mutation as well as Second Line Regimens (SLR) started immediately after the documentation of M184V. SLR were evaluated for frequency and time to Virologic Suppression (VS) as well as frequency and time to subsequent Virologic Failure (VF).

Design: This was a retrospective cohort study of all Human Immunodeficiency Virus (HIV)-infected patients receiving care at the Washington University School of Medicine Infectious Disease Clinic in St. Louis, MO, USA between January 2001 and June 2010.

Methods: Prevalence of the M184V mutation, ART regimen leading to M184V acquisition, and outcomes of SLR in patients with M184V (as measured by time to initial VS and subsequent VF on SLR) were analyzed in a retrospective cohort study of all HIV-infected persons receiving care at a university clinic.

Results: Of 2500 screened clinic patients, 220 had an acquired MI184V mutation (8.8%). There were 158(72%) male and 171(78%) African-American patients. The mean time from the start of a regimen to the documented M184V mutation was 575(0-3253) days. Independent of Nucleoside Reverse Transcriptase Inhibitor (NRTI) backbone, the mean time to development of M184V in Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) (n=109) and Protease Inhibitor (PI) based (n=84) regimens was 538(+/- 556) and 622 (+/- 620) days, respectively (p=0.325) approximately, 78% of patients achieved VS on a SLR in a mean of 179 days. Of the 122(57%) of patients whose SLR retained FTC/3TC, VS was achieved in 80% 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). 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). Regardless of SLR, about 50% of each group experienced VF after VS with a similar time to failure.

Conclusions: M184V mutation developed in 9% of patients 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 two fully active non-NRTI-backbone-based regimens attained VS. Approximately half of all patients subsequently failed on SLR, regardless of regimen used, suggesting that the development of M184V is a marker of noncompliance to therapy.

KEYWORDS: HIV; Drug resistance; Lamivudine; Antiretroviral therapy; HIV drug resistance.

HIV/AIDS RESEARCH AND TREATMENT

Openventio PUBLISHERS

ISSN 2377-8377 Open Journal http://dx.doi.org/10.17140/HARTOJ-2-114

ABBREVIATIONS: VS: Virologic Suppression; SLR: Second Line Regimens; cART: combination Antiretroviral therapy; VF: Virologic Failure; NRTI: Nucleoside Reverse Transcriptase Inhibitors; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; FTC: Emtricitabine; 3TC: Lamivudine; RAL: Raltegravir; PI: Protease Inhibitor.

INTRODUCTION

Combination active antiretroviral therapy (cART), consisting of 3 antiretroviral drugs from 2 or 3 classes, has reduced morbidity and mortality due to HIV-1 infection since its introduction. Current guidelines for the treatment of HIV 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.[1] Due to its tolerability, relative ease of administration, and availability in fixed combination products, either lamivudine (3TC) or the related drug emtricitabine (FTC) are a part of all recommended initial cART regimens, and are commonly included in second line regimens (SLR) after virologic failure (VF).[1] However, lamivudine and emtricitabine have relatively low barriers to the development of virologic resistance, most commonly through the emergence of a single mutation in the reverse transcriptase gene, M184V.[2] Emergence of drug resistance is associated with increased mortality in patients who receive first-line cART.[3] An estimated 5% of patients on cART develop genotypic resistance after 1 year, 10% after 2 years, and almost 30% develop virologic failure (VF) with at least 1 major mutation within 6 years of starting cART.[3,4] Although the most common mutations are to NNRTIs, which develop in approximately 50% of failing regimens, resistance to 3TC and FTC *via* the single resistance mutation, M184V, occurs in 35% of failing regimens.[3-5] This mutation impairs the fitness of the virus, and therefore discontinuation of 3TC/FTC in a regimen results in apparent reversion to wild type genotype, although the mutation remains archived, and will re-emerge once 3TC/FTC are restarted. Currently there are no guidelines directing second line therapy after developing the M184V mutation. Previous studies have demonstrated that continuing to maintain FTC or 3TC in the backbone of the second line regimen (SLR) has similar activity to using regimens with at least 2 other active NRTIs;[6,7] several studies suggest that SLR with protease inhibitors (PI) may be more effective.[8,9] Several reports have suggested that failure of second line therapy after developing M184V is due more to non-adherence, and not primarily to virologic failure (VF),[7,10] and that even the initial failing regimen may be used if adherence is improved. The purpose of this study was to describe the occurrence of the M184V mutation in a single clinic setting over a period of 10 years; to examine second line therapy choices, regarding VS, time to VS, and VF following virologic suppression (VS).

MATERIALS AND METHODS

This was a retrospective cohort study of all HIV-infected patients receiving care at the Washington University School of Medicine Infectious Disease Clinic in St. Louis, MO, USA 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 were analyzed. VS was defined as HIV viral load <400 copies/mL after initiation of SLR. VF was defined as VL>400 either after a period of VS or persistent HIV VL>400 for 6 months on a second line regimen (SLR). Differences between the groups were compared using χ^2 and Fisher exact test for categorical data and Mann-Whitney tests for continuous variables; statistical significance was defined as $P<0.05$. The study was approved by Washington University School of Medicine Human Research Protection Office.

RESULTS

Of 2500 screened clinic patients, 220 were identified as having acquired M184V mutation (9%). Similar to the clinic population as a whole, 158(72%) patients were male and 171(78%) were African-Americans. HIV was acquired predominantly through sex, with 124 men reporting sex with men and 85 reporting only heterosexual encounters. Nine patients were injection drug users. Concurrent resistance to other antiretrovirals was common, with 172 patients having other NRTI resistance, 136 with genotypic NNRTI resistance, and 35 with PI resistance. The mean time from the start of a regimen to the documented M184V mutation was 575(0-3253) days. There was a significant difference in the time to development of M184V when 3TC was used (mean 706 days, SD 673 days) compared to FTC (mean 394 days, SD 304 days) (p=0.002) (Figure 1). Despite changing cART prescribing patterns over time, no significant differences were seen in the time to develop M184V between different NRTI backbone partners to 3TC or FTC (other NRTIs used included zidovudine (AZT), tenofovir (TDF), abacavir (ABC), didanosine (ddI), stavudine (d4T)), and no significant differences were seen between NNRTI or PI based regimens. 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).

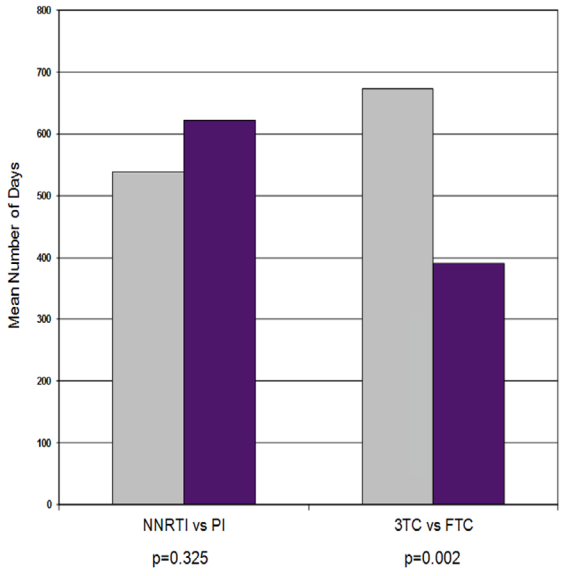
Following initiation of an SLR, approximately 78% of all study patients (n=171) achieved VS in a mean of 179 days. Of the 122(57%) patients whose SLR retained FTC/3TC, VS was achieved in 80% compared to 74% without FTC/3TC (p=0.285) with no significant difference in mean time to VS (152(±187) and 181(±257) 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) (p=1).

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 mean time to VS (180(±228) *vs.* 128(±158) days, p=0.313). However, all patients with two non-NRTI class agents in the regimen (PI+raltegravir (n=10) or PI+NNRTI (n=12)) achieved VS (*vs.* 76% in PI+2NRTI (p=0.078 and p=0.054, re-

HIV/AIDS RESEARCH AND TREATMENT

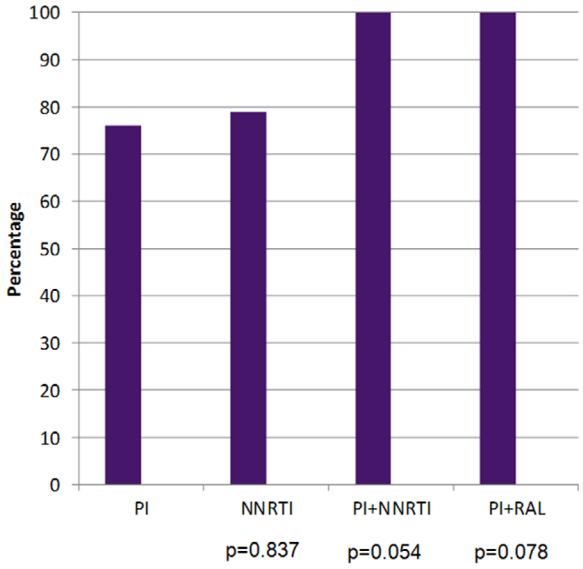
Openventio PUBLISHERS

ISSN 2377-8377 Open Journal http://dx.doi.org/10.17140/HARTOJ-2-114



PI: Protease Inhibitor; NNRTI: Non nucleoside Reverse Transcriptase Inhibitor; 3TC: Lamivudine; FTC: Emtricitabine.

Figure 1: Time to the development of the M184V mutation.



PI: Protease Inhibitor; NNRTI: Non nucleoside Reverse Transcriptase Inhibitor; RAL: Raltegravir

Figure 2: Virologic suppression (VS) with second-line regimens (SLRs).

spectively) (Figure 2).

Of the 171 subjects that achieved virologic suppression on SLR, 84 subsequently failed and 87 maintained suppression. There were no differences in the regimens which maintained virological success *versus* those that that met the definition of virological failure. Fifty percent of the patients on PI-based SLRs met virologic failure compared to 52% of patients on NNRTI-based regimens, 51% on PI+RAL, and 42% on PI+NNRTI. Of the SLR regimens which failed, 22 had further Reverse Transcriptase (RT) resistance mutations, and 16 had further protease resistance mutations.

DISCUSSION

Despite its early development as an antiviral, lamivudine, and its related drug emtricitabine, are among the most successful and well-tolerated antiviral agents used in cART. Resistance to these NRTI *via* the M184V mutation impairs viral fitness, but is extremely common. Despite this, all currently recommended regimens for treatment-naïve patients include either 3TC or FTC. A review of the literature does not reveal guidelines, consensus, or much data recommending second-line regimens after the development of the M184V mutation.

We examined the development and consequences of the M184V mutation in patients seen in the Washington University Infectious Disease Clinic. Of the approximately 2500 unique patients seen from 2001-2010, the M184V mutation developed in 9% in a mean of 575 days with no significant differences between cART regimens. A difference was seen between 3TC and FTC in the development of M184V, which is potentially due to the different pharmacokinetics of the two agents, with FTC being more forgiving of intermittent adherence.[11] However, this difference might also be due to shifts in other antiretrovirals given concurrently, as regimens containing 3TC (and especially the use of the combination pill combivir or AZT/3TC) tended to occur on average between 2003-2004, while regimens containing FTC (and especially the combination pill Truvada, or TDF/FTC) tended to occur between 2007-2008. Following initiation of a SLR, the majority of patients achieved VS in approximately 179 days irrespective of the regimen. There was no significant benefit to the addition of 3TC/FTC as it did not significantly affect VS. Although numbers were small, 100% of patients on regimens containing two active agents in classes other than NRTIs (i.e. PI+NNRTI or PI+RAL) were virologically suppressed. The patients may or may not have been on a single active NRTI. This may be due to increased potency of these regimens, although studies of NRTI sparing regimens have not been proven to be better than NRTI containing regimens in naïve patients.[12-14] It is possible that the use of additional drugs is beneficial in the setting of NRTI resistance. Alternatively, the additional pill burden may have induced higher rates of adherence, at least upon initiation of the regimen.

Although the data presented in this study is observational, the fact that no significant differences were seen between PI-based or NNRTI-based regimens, together with only an 80% success rate in obtaining virologic suppression, a subsequent 50% failure rate of maintaining virologic suppression, and low levels of further resistance mutations, suggests that failure of the SLR is likely due to subsequent non-adherence. As it has been shown in other studies, our data suggest that the appearance of the M184V mutation warrants further discussion and emphasis on strict adherence to the second line regimen regardless of how it is structured. Although, numbers were small, 100% of patients

ISSN 2377-8377 Open Journal http://dx.doi.org/10.17140/HARTOJ-2-114

on a fully active regimen containing two agents which are not in the NRTI class were virologically suppressed, suggesting that NRTI- sparing regimens may be preferable after the M184V mutation and other NRTI resistance mutations develop.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

ACKNOWLEDGEMENTS

We would like to acknowledge Toshibumi Taniguchi for assistance in the initial design of this study.

DISCLOSURE

The study was approved by Washington University School of Medicine Human Research Protection Office.

CONSENT

Our application for waiver of informed consent/authorization was approved by The Washington University Human Research Protection Office.

REFERENCES

1. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2009; 49(5): 651-681. doi: 10.1086/605292

2. Tang MW, Shafer RW. HIV-1 antiretroviral resistance: scientific principles and clinical applications. *Drugs.* 2012; 72(9): e1-e25. doi: 10.2165/11633630-000000000-00000

3. Hogg RS, Bangsberg DR, Lima VD, et al. Emergence of drug resistance is associated with an increased risk of death among patients first starting HAART. *PLoS Med.* 2006; 3(9): e356. doi: 10.1371/journal.pmed.0030356

4. Phillips AN, Dunn D, Sabin C, et al. Long term probability of detection of HIV-1 drug resistance after starting antiretroviral therapy in routine clinical practice. *AIDS.* 2005; 19(5): 487-494.

5. Gupta R, Hill A, Sawyer AW, Pillay D. Emergence of drug resistance in HIV type 1-infected patients after receipt of first-line highly active antiretroviral therapy: a systematic review of clinical trials. *Clin Infect Dis.* 2008; 47(5): 712-722. doi: 10.1086/590943

6. Sungkanuparph S, Manosuthi W, Kiertiburanakul S, Piyavong B, Chumpathat N, Chantratita W. Options for a second-line antiretroviral regimen for HIV type 1-infected patients whose initial regimen of a fixed-dose combination of stavudine, lamivudine, and nevirapine fails. *Clin Infect Dis.* 2007; 44(3): 447-452. doi: 10.1086/510745

7. Gupta RK, Goodall RL, Ranopa M, Kityo C, Munderi P, Lyagoba F, *et al.* High rate of HIV resuppression after viral failure on first-line antiretroviral therapy in the absence of switch to second-line therapy. *Clin Infect Dis.* 2014; 58(7): 1023-1026. doi: 10.1093/cid/cit933

8. Puthanakit T, Jourdain G, Suntarattiwong P, *et al.* High virologic response rate after second-line boosted protease inhibitor-based antiretroviral therapy regimens in children from a resource limited setting. *AIDS Res Ther.* 2012; 9(1): 20. doi: 10.1186/1742-6405-9-20

9. Scherrer AU, Boni J, Yerly S, *et al.* Long-lasting protection of activity of nucleoside reverse transcriptase inhibitors and protease inhibitors (PIs) by boosted PI containing regimens. *PLoS One.* 2012; 7(11): e50307. doi: 10.1371/journal.pone.0050307

10. Johnston V, Cohen K, Wiesner L, *et al.* Viral suppression following switch to second-line antiretroviral therapy: associations with nucleoside reverse transcriptase inhibitor resistance and subtherapeutic drug concentrations prior to switch. *J Infect Dis.* 2014; 209(5): 711-720. doi: 10.1093/infdis/jit411

11. Maserati R, De SA, Uglietti A, *et al.* Emerging mutations at virological failure of HAART combinations containing tenofovir and lamivudine or emtricitabine. *AIDS.* 2010; 24(7): 1013-1018. doi: 10.1097/QAD.0b013e328336e962

12. Allavena C, Ferre V, Brunet-Francois C, *et al.* Efficacy and tolerability of a nucleoside reverse transcriptase inhibitor-sparing combination of lopinavir/ritonavir and efavirenz in HIV-1-infected patients. *J Acquir Immune Defic Syndr.* 2005; 39(3): 300-306.

13. Riddler SA, Haubrich R, DiRienzo AG, *et al.* Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med.* 2008; 358(20): 2095-2106. doi: 10.1056/NEJMoa074609

14. Kozal MJ, Lupo S, DeJesus E, *et al.* A nucleoside- and ritonavir-sparing regimen containing atazanavir plus raltegravir in antiretroviral treatment-naive HIV-infected patients: SPARTAN study results. *HIV Clin Trials.* 2012; 13(3): 119-130. doi: 10.1310/hct1303-119