BRIEF REPORT

Predictors for the Emergence of the 2 Multi-nucleoside/nucleotide Resistance Mutations 69 Insertion and Q151M and their Impact on Clinical Outcome in the Swiss HIV Cohort Study

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The 69 insertion and Q151M mutations are multi-nucleoside/nucleotide resistance mutations (MNR). The prevalence among 4078 antiretroviral therapy (ART)-experienced individuals was <1.3%. Combined ART fully prevented MNR in subtype B infections. Case-control studies were performed to identify risk factors. Control subjects were patients with ⩾3 thymidine-analogue mutations. The 69 insertion study (27 control subjects, 14 case patients) identified didanosine exposure as a risk (odds ratio, 5.0 per year; $P = .019$), whereas the Q151M study (which included 44 control subjects and 25 case patients) detected no associations. Following detection, individuals with Q151M tended to have lower suppression rates and higher mortality rates, relative to control subjects. Additional studies are needed to verify these findings in non-subtype B infections.

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The introduction of highly-active antiretroviral therapy (HAART) reduced morbidity and mortality of human immunodeficiency virus (HIV) infected patients. However, drug resistance continues to emerge in association with treatment failure [1].

The 69 insertion and Q151M mutation are multi-nucleoside/nucleotide resistance (MNR) mutations on the reverse transcriptase that affect the activity of all approved nucleoside reverse transcriptase inhibitors (NRTIs). Although 69 insertion confers full resistance to all drugs, tenofovir retains some activity when Q151M is present [2–4]. MNR mutations occur rarely in European settings (prevalence, <1% to 3.6%). The prevalence in resource-limited countries has not been analyzed, but recent reports indicate that it has increased [5–8]. The possible increase in MNR HIV strains is of great concern because of the very limited options for salvage treatment in resource-limited settings and the general lack of understanding as to how to optimally treat patients who have MNR infections [9].

We aimed to identify predictors for the emergence of the 69 insertion and Q151M mutation in the Swiss HIV Cohort Study (SHCS) and studied outcomes of salvage regimens applied for treatment of MNR HIV infections.

METHODS

Data and Patient Selection

Our analysis included data from the SHCS and the SHCS drug resistance database up to February 2010 [10, 11]. The SHCS has been approved by the ethical committees of all participating institutions, and written informed consent has been obtained from participants.

Prevalence of Acquired and Transmitted MNR Mutations

The prevalence of the 69 insertion and the Q151M mutation was analyzed among treatment-experienced (at least 30 days exposure) and treatment-naive patients. Among treatment-naive patients, possible transmission clusters were identified through phylogenetic methods. These analyses were performed with PHYLIP 3.6 (distributed by J. Felsenstein), using the F84 nucleotide substitution model and the neighbor-joining tree algorithm with 1000 bootstraps. To avoid interference of treatment history, all major International AIDS Society–USA drug resistance–associated amino acid positions were deleted from the sequences prior to analysis [12].

Case-control Study to Determine Predictors for MNR

We compared patients with MNR detected with patients who carried viruses with ⩾3 thymidine analogue mutations (TAMs), either from the TAM 1 (M41L, L210W, T215Y) or the TAM 2 pathway (D67N, K70R, T215F, K219K/E). The rationale was to establish a control group consisting of highly NRTI-experienced individuals with comparable characteristics, except for the occurrence of 69 insertion or Q151M. Separate matched case-control studies were performed for each of the 2 MNR mutations. Control patients were matched 2:1 on the basis of the first antiretroviral therapy (ART) received and the time between ART initiation and the detection of MNR mutations (for case patients) or ⩾3 TAMs (for control subjects). Inclusion was restricted to individuals infected with HIV subtype B who started ART with single-class NRTI therapy.

Conditional logistic regression analyses were performed to identify risk factors for the emergence of 69 insertion and Q151M. Variables tested included the time spent on specific NRTIs and adjustments for the following potential confounders: sex, age, ethnicity, risk group, HIV-1 RNA level, and CD4+ cell count at time of detection of MNR mutations (for case patients) or ⩾ 3 TAMs (for control subjects).

Factors Associated with Attaining Undetectable Viral Loads After Detection of MNR Mutations

Virological outcomes after detection of MNR mutations were analyzed for patients from the case-control studies with >1 follow-up HIV-1 RNA measurement. Characteristics and treatments were compared between patients who ever achieved 2 consecutive undetectable HIV-1 RNA levels <50 copies/mL and patients who did not. Fisher's exact test (categorical) and Wilcoxon rank-sum test (continuous variables) were used.

Association of All-cause Mortality with Detection of MNR Mutations

Cox proportional hazard models for matched case-control data were estimated to analyze the time to all-cause mortality after detection of MNR mutations (case patients) or ⩾3 TAMs (control subjects). Models were stratified by years of detection of MNR mutations or ⩾3 TAMs (1998, 1999–2003, after 2003). The proportional hazard assumption was verified by analyzing Schoenfeld residuals.

Statistical analyses were performed with Stata 11 SE (StataCorp), all confidence intervals (CI) are 95% CIs, and the level of significance was set at $P = .05$.

RESULTS

Prevalence of MNR Mutations in Treatment-experienced Patients

The SHCS included 19 (0.5%) of 4078 and 34 (0.8%) of 4078 treatment-experienced patients who carried viruses with the 69 insertion and Q151M mutation, respectively. Most patients in the 69 insertion and Q151M groups were treated with mono- or dual-NRTI therapy (14 [73.7%] of 19 and 30 [88.2%] of 34, respectively. MNR was never detected in patients who were exclusively treated with HAART (2 NRTIs and 1 boosted protease inhibitor [PI]/nonnucleoside reverse transcriptase inhibitor [NNRTI]). The median duration of ART until detection was 6.8 years for the 69 insertion group and 5.5 years for the Q151M group. The median years of detection were 2000.5 (range: 1995–2007) and 2000 (range: 1995–2006), respectively. Most individuals who carried viruses with MNR were infected with subtype B viruses (18 [94.7%] of 19 and 29 [85.3%] of 34, respectively). All additional analyses were restricted to this subtype.

Evidence for MNR Transmission among Treatment-naive Patients

We screened 5692 sequences from treatment-naive patients and detected the 69 insertion 3 times (0.05%) and Q151M once (0.02%). The phylogenetic analysis provided strong evidence of forward transmission of the 69 insertion from 1 index patient to 2 patients (100% bootstrap support). All of these patients were men who had sex with men and were from the same study center. For Q151M, no transmission cluster was detected.

Predictors for the Emergence of MNR in Patients Infected with HIV Subtype B

For the 69 insertion case-control study, matching criteria fitted for 14 case patients (69 insertion) and 27 control subjects (⩾3 TAMs). Interestingly, years spent receiving didanosine were significantly associated with the emergence of 69 insertion in univariable (odds ratio [OR], 3.4; 95% CI, 1.2–9.6; $P = .019$) and multivariable models (OR, 5.0; 95% CI, 1.3–19.3; $P = .019$).

For the Q151M case-control study, 25 case patients and 44 control subjects (⩾3 TAMs) were matched, but conditional logistic regressions failed to identify predictors for the emergence of Q151M.

Virological Response to Salvage Treatment upon Emergence of MNR

Virological outcomes for patients with >1 follow-up HIV-1 RNA measurement after MNR detection were analyzed. The probability of ever achieving viral suppression was comparable between the 69 insertion group (9 [69.2%] of 13; 95% CI, 38.6%–90.9%) and respective control subjects (15 [75.0%] of 20; 95% CI, 50.9%–91.3%). A large proportion of patients who received previously unseen drug classes achieved viral suppression (87.5% compared to 40.0% of other patients; $P = .217$). As shown in table 1, all patients detected without major NNRTI or PI mutations achieved viral suppression (patients 1, 4, and 8). Five of 7 patients with either NNRTI or PI mutations achieved viral suppression with the remaining active non-NRTI drug class (patients 2, 5, 6, 7, and 11).

Table 1. Characteristics of Patients who Achieved Viral Suppression and Characteristics of the First Successful Treatment following Detection of 69 Insertion or Q151M

Mutation, patient	Year of detection	Log_{10} HIV-1 RNA level at detection, copies/mL	CD4+ cell count at detection, cells/μL	CDC stage	NRTI mutations at detection	Major[a] NNRTI mutations at detection	Major[a] PI mutations at detection	Year of first successful treatment	Successful treatment	Year of loss of follow-up
69 insertion										
1	1995	4.4	50	C	M41L, 69 insertion, L210W, T215Y			2003	TDF EFV ddI	2009
2	1995	4.2	118	B	M41L, 69 insertion, K70R, M184V, L210W, T215Y	Y188C		1999	NFV ZDV 3TC	2009
3	1997	5.9	32	C	M41L, 69 insertion, L210W, T215Y		M46L, V82A, L90M			2001[b]
4	1997	3.3	472	B	M41L, 69 insertion, M184I, T215Y			1997	SQV RTV NVP D4T	2009
5	1997	4.3	315	C	M41L, 69 insertion, T215Y		I84V	2000	LPV IDV D4T 3TC	2009
6	1999	3.1	180	B	M41L, 69 insertion, L210W, T215Y		M46I, T74P, I84V, L90M	2001	LPV EFV ddI 3TC	2009
7	1999	5.1	139	C	M41L, 69 insertion, M184I, T215Y		M46L, V82A, I84V	2002	EFV ddI ABC	2009
8	2001	4.2	415	B	D67N, 69 insertion, K70R, K219Q			2004	RTV EFV ATV 3TC	2009
9	2002	4.8	542	B	M41L, 69 insertion, T215Y	Y181C	M46I, G48V, I84V, N88S, L90M			2009
10	2003	5.7	13	B	M41L, 69 insertion, L74V, L210W, T215Y	L100I, K103N	M46I, L76V, V82F, L90M			2003[b]
11	2004	4.8	198	B	M41L, 69 insertion, M184V, L210W, T215Y		M46I, I84V, L90M	2005	LPV EFV ZDV 3TC	2009
12	2004	5.1	367	C	M41L, 69 insertion, L210W, T215Y		M46L, V82A, L90M			2009
13	2007	2.9	358	B	M41L, 69 insertion, M184V, L210W, T215Y	K103N	I54L, I84V, L90M	2008	TDF RAL ETV ABC 3TC	2009
Q151M										
1	1995	5.4	160	A	V75I, F77L, Y115F, F116Y, Q151M		Q58E			2001[b]
2	1996	5.7	50	C	F77L, F116Y, Q151M		G48V, L90M			1997[b]
3	1996	4.2	100	C	D67N, K70R, F77L, Q151M, T215F, K219E	V108I				2000[b]
4	1996	3.5	162	B	F116Y, Q151M,			1999	NFV D4T 3TC	2009
5	1996	4.4	133	C	K65R, V75I, F77L, Y115F, F116Y, Q151M, K219Q			2008	TDF RTV RAL MVC ETV DRV ZDV 3TC	2009
6	1997	5.2	75	C	M41L, A62V, V75I, F77L, F116Y, Q151M, M184V					1998[b]
7	1997	2.6	464	A	D67N, Q151M, K219Q					2001[b]
8	1997	3.6	61	C	Q151M, M184V					2001[b]
9	1997	3.8	476	C	D67N, F116Y, Q151M		Q58E	1997	IDV D4T 3TC	2009
10	1998	5.1	15	C	A62V, V75I, F77L, F116Y, Q151M, M184V	K103N	M46L, G48V, V82A			2003[b]
11	1998	5.0	8	C	M41L, D67N, F77L, F116Y, Q151M, M184V, L210W, T215Y		M46I, V82A			2000[b]

Table 1. (*Continued*)

Mutation, patient	Year of detection	Log_{10} HIV-1 RNA level at detection, copies/mL	CD4+ cell count at detection, cells/μL	CDC stage	NRTI mutations at detection	Major[a] NNRTI mutations at detection	Major[a] PI mutations at detection	Year of first successful treatment	Successful treatment	Year of loss of follow-up
12	1998	3.9	412	B	A62V, K65R, V75I, F77L, Y115F, F116Y, Q151M, M184V		D30N	1999	SQV RTV EFV D4T ABC	2007[b]
13	1999	5.8	5	C	D67N, Q151M		V82A, I84V, L90M			2000[b]
14	1999	5.3	23	C	D67N, K70R, F116Y, Q151M, M184V, K219E		V82A, L90M	2007	RTV RAL ETV DRV 3TC	2009
15	2000	5.3	36	C	M41L, D67N, K70R, Q151M, M184V, T215F, K219E	K103N, V108I	I54L, V82A, L90M			2002[b]
16	2000	4.9	481	B	A62V, V75I, F77L, F116Y, Q151M			2002	LPV EFV ZDV ABC 3TC	2009
17	2001	2.5	259	C	A62V, F116Y, Q151M, M184V,		M46I	2002	EFV D4T 3TC	2003[b]
18	2001	4.7	229	A	A62V, V75I, F77L, F116Y, Q151M		I84V, L90M	2003	LPV EFV APV 3TC	2009
19	2001	5.0	253	C	A62V, K65R, D67N, V75I, F77L, Y115F, F116Y, Q151M, M184V, K219E		D30N, M46I, I54M	2002	SQV NVP LPV	2009
20	2002	4.8	77	B	K65R, K70R, V75I, F77L, Y115F, F116Y, Q151M, K219E	K101E, Y181C, G190A	M46I, V82A	2004	TDF RTV ETV ABC	2009
21	2003	3.9	191	C	D67N, K70R, F116Y, Q151M, M184V, K219Q	K103N	M46I, Q58E, V82F, L90M			2006[b]
22	2003	3.0	5	B	A62V, D67N, K70R, V75I, F77L, F116Y, Q151M, M184V, K219E	K103N, V108I	I50V, V82A, L90M	2004	TPV TDF T20 LPV DDI ZDV APV 3TC	2009
23	2004	4.5	84	B	D67N, K70R, Y115F, F116Y, Q151M, M184V, K219Q	Y181C, Y188L	M46I, V82A	2006	TPV TDF RTV RAL ZDV 3TC	2009
24	2004	3.9	461	B	F116Y, Q151M,		M46I, L90M	2007	RTV DRV	2008[b]
25	2006	4.8	773	A	F116Y, Q151M	K103N, Y188L		2006	TDF RTV FTC ATV	2009

NOTE. Viral suppression was defined as 2 consecutive viral loads <50 copies/mL. 3TC, lamivudine; ABC, abacavir; APV, amprenavir; CDC, Centers for Disease Control and Prevention; D4T, stavudine; ddI, didanosine; DRV, darunavir; EFV, efavirenz; ETV, etravirine; HIV-1, human immunodeficiency virus type 1; IDV, indinavir; LPV, lopinavir; MVC, maraviroc; NFV, nelfinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir; RTV, ritanovir; SQV, saquinavir; T20, enfuvirtide; TDF, tenofovir; TPV, tipranavir; ZDV, zidovudine.

[a] Mutations printed in bold on the International AIDS Society-USA list [12].

[b] Year of death.

Viral suppression rates between the Q151M group (14 [56.0%] of 25; 95% CI, 34.9%–75.6%) and the respective control subjects (27 [73.0%] of 37; 95% CI, 55.9%–86.2%) were similar. Generally, patients who achieved viral suppression had a higher median CD4+ cell count at detection (241 cells/μL vs 61 cells/μL; $P = .030$), a lower viral load (median $\log_{10}$ RNA level, 4.5 copies/mL vs 5.1 copies/mL; $P = .089$), a higher percentage of a previously unseen drug class (88.9% vs 37.5%; $P = .033$), and were detected later (median year, 1997 vs 2001; $P = .027$). As illustrated in Table 1, most patients with Q151M detected before the introduction of HAART never achieved viral suppression (patients 1–3 and 6–8). Four of 11 patients detected in the HAART era prior to the approval of enfuvirtide (T20) (1998–2002) never had a successful treatment (patients 10, 11, 13, and 15). All of these patients had low CD4+ cell counts (<50 cells/μL) and extensive PI and/or NNRTI mutations. Most of the other patients had PI mutations but achieved viral suppression with a regimen containing NNRTIs (patients 12, 14, and 16–20).

Survival after Detection of MNR

The crude incidence of mortality after detection of the 69 insertion was 1.9 deaths (95% CI, 0.2–6.9) per 100 person-years of follow-up, compared with 6.3 deaths (95% CI, 2.9–12.0) per 100 person-years of follow-up among control subjects (≥3 TAMs) [Figure 1]. Of the 2 deaths noted in the 69 insertion group, 1 death was HIV-related, and the cause of the other death was unknown. The risk of mortality was not significantly different between patients with the 69 insertion and those with ≥3 TAMs (univariable hazard ratio [HR], 0.3 [95% CI, 0.1–1.6]; $P = .178$). The small number of events did not allow stratified or multivariable models.

Patients with Q151M detected tended to have a higher crude incidence of 9.8 deaths per 100 person-years (95% CI, 5.3–16.4), compared with 5.8 death per 100 person-years (95% CI, 3.3–9.4) in control subjects (with ≥3 TAMs) [Figure 1]. HIV infection was the cause of death for 6 (42.9%) of 14 patients from the Q151M group and 7 (43.8%) of 16 control subjects. Additional causes of death reported in the Q151M group were neoplasm (14.3%), cardio-vascular diseases (14.3%), chronic hepatitis C (7.1%), suicide (7.1%), or unknown (14.3%). The detection of Q151M was associated with increased mortality but was of marginal statistical significance in the univariable (HR, 2.7 [95% CI, 0.9–8.0]; $P = .075$) and multivariable model, adjusted for sex, ethnicity, risk group, CD4+ cell count, and age (HR, 7.5 [95% CI, 0.9–64.6]; $P = .068$).

Sensitivity analyses including only those deaths associated with HIV infection (univariable HR, 2.6 [95% CI, 0.6–10.4]; $P = .189$) or by additionally matching case patients and control subjects by CD4+ cell count at time of detection of Q151M or ≥3 TAMs showed similar results (univariable HR, 3.2 [95% CI, 1.0–10.9]; $P = .058$; and multivariable HR, 6.2 [95% CI, 0.7–56.0]; $P = .105$).

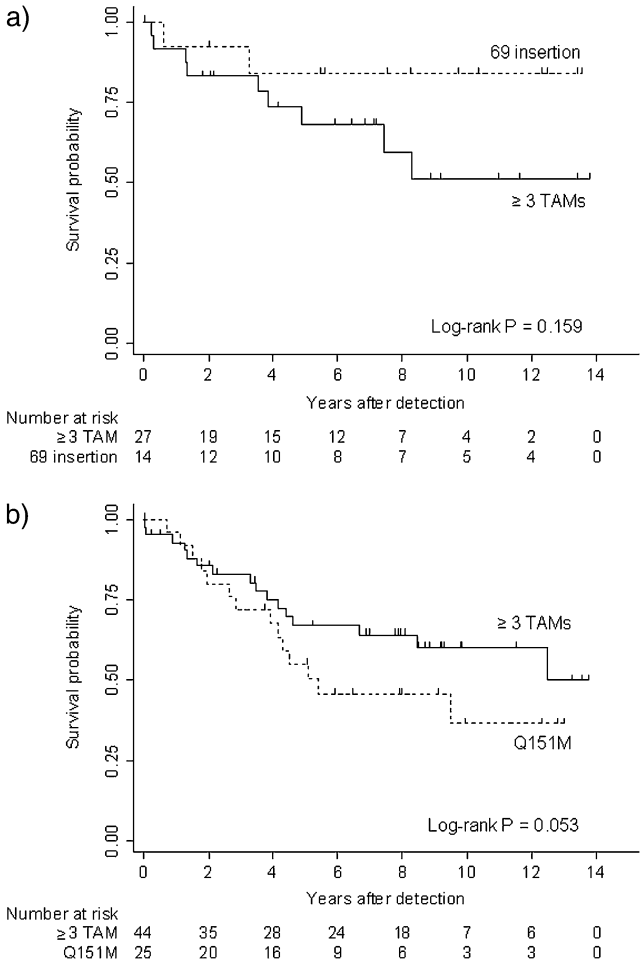

Figure 1. Kaplan-Meier curves showing survival after detection of 69 insertion (*a*) or Q151M (*b*). Patients detected with ≥3 thymidine analogue mutations (TAMs) were matched (2:1) for comparison. Log-rank test was stratified for matched pairs.

DISCUSSION

Because the prevalence of MNR is increasing in resource-limited countries, and because 69 insertion and Q151M affect the activity of an entire drug class, it is of great importance to identify risk factors and to optimize treatment strategies.

Our study currently represents the largest longitudinal dataset with full treatment history available. We found high evidence of forward transmission of 69 insertions. This finding is of relevance, because the presence of 69 insertion results in a substantial reduction of treatment options, which can be devastating in settings with limited access to potent salvage therapies.

Moreover, our study identified a significant association of ddI exposure with the emergence of the 69 insertion [13]. No specific NRTI was associated with the emergence of Q151M. Our study did not confirm a previously reported negative association of lamivudine with Q151M [2, 14], nor was d4T exposure correlated with an increased risk for Q151M (data not shown).

Of note, MNR mutations were never detected in patients who were exclusively treated with HAART. This is in contrast to the high prevalence of MNR mutations observed in resource-limited settings [7, 8]. Free access to potent antiretroviral drugs in Switzerland and close monitoring are the most likely explanations for this difference.

Moreover, this study widened the very limited knowledge for treatment strategies of patients detected with MNR. These patients can be successfully treated if potent drugs, such as boosted PI, raltegravir, or T20 are available. The descriptive analysis of therapy success further suggests that extensive resistance to NNRTIs and PIs, as well as a low CD4+ cell count at the time of detection of MNR mutations, were prognostically unfavorable [15].

Patients with viruses possessing Q151M tended to have an increased mortality risk, compared with patients with $\geqslant 3$ TAMs. Although this finding was robust throughout several sensitivity analyses, conclusions regarding causality between Q151M and death should be drawn with care.

This study has some limitations. Even though our sample is the largest study to date to address MNR, it is still limited in power [11]. Our study was restricted to subtype B–infected individuals, and results may therefore not be readily transferable to other subtypes.

Taken together, our data indicate that modern antiretroviral therapies in combination with adequate viral monitoring are able to prevent the emergence of MNR mutations in developed settings. In Switzerland, detected MNR mutations are mainly a relic of the mono- or dual-NRTI therapy era, although 2 cases of transmitted MNR were observed. This analysis further demonstrates that salvage treatment can be successful even when MNR mutations are present if at least 1 previously unused drug class is available. Today, the development of MNR seems to be becoming an emerging problem in resource-limited settings, where most patients are infected with non–subtype B strains. Thus, additional studies are needed to investigate whether our findings are also true for non–subtype B infections.

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