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Evolution of HIV Resistance Mutations in Patients Maintained on a Stable Treatment Regimen After Virologic Failure

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Abstract

Objective— We compared the rate of emergence of thymidine analogue mutations (TAMs) and major protease inhibitor mutations in adherent patients who remained on stable treatment with a thymidine analogue and/or protease inhibitor after the onset of virologic failure.

Design— Follow-up genotypic resistance testing was done using archived plasma obtained from patients having 0 or 1 TAM and/or 0 or 1 major protease inhibitor resistance mutation at the onset of virologic failure.

Results— The median duration of observed failure was 691 days. There were 41 thymidine analogue regimens and 34 protease inhibitor regimens; concomitant ritonavir was used 4 times. New major protease inhibitor mutations emerged more rapidly than did new TAMs ($P = 0.0019$); new TAMs emerged more rapidly in thymidine analogue regimens that did not include lamivudine ($P = 0.0073$). The emergence of TAMs and major protease inhibitor mutations did not differ if lamivudine was not part of the thymidine analogue regimen. The evolution of CD4⁺ cell counts and plasma viral loads (pVLs) during virologic failure was similar regardless of whether or not a new TAM or major protease inhibitor mutations emerged or, for thymidine analogue-containing regimens, whether lamivudine was or was not used.

Conclusions— Major protease inhibitor mutations arose more frequently and rapidly than did TAMs in patients with sustained virologic failure who received lamivudine.

Keywords

HIV resistance; protease inhibitors; resistance mutations; reverse transcriptase inhibitors

Notwithstanding the continued development of new antiretroviral agents with unique profiles of resistance mutations and simpler dosing schedules,^{1–6} the development of multiclass antiretroviral resistance remains a serious problem for HIV-infected patients.^{7–12} With the

failure of each regimen, the number of remaining effective choices decreases and the virologic threshold for changing antiretroviral therapy necessarily increases.^{13,14}

For persons with clinical and virologic treatment failure, the benefits of changing therapy are evident. Many patients continue to demonstrate prolonged immunologic benefit from treatment, although achieving only partial viral suppression.^{9,15–21} For these patients, one option is to continue on a stable failing regimen and accept the risk of emergence of further resistance mutations, treatment failure, and the consequent reduction in future treatment choices.^{13,14} The primary alternative is to change therapy using new agents that are predicted to be effective. If the number or potency of new agents is small, however, application of the latter strategy may fail to suppress viral replication, and thus again lead to the emergence of new resistance mutations and yet further reductions in the number of subsequent viable treatment opportunities. Other options such as complete or partial structured treatment interruptions have failed to show consistent benefit or not undergone careful scrutiny in clinical trials.^{22–24} Complicating these decisions is the relative paucity of data regarding the rate at which anti-retroviral resistance develops after the onset of virologic treatment failure in patients receiving highly active anti-retroviral therapy (HAART).^{25–27}

The purpose of this study was to define the time to accrual of genotypic resistance mutations, particularly thymidine analogue mutations (TAMs) and major protease inhibitor mutations, in persons with a persistently detectable plasma viral load (pVL) despite being on a stable antiretroviral regimen. We also sought to evaluate the impact of co-administration of lamivudine on the emergence of TAMs given the detrimental effect of the 184V mutation on HIV replication capacity, especially in combination with TAMs.^{28,29}

METHODS

The comprehensive electronic medical records of the Veterans Affairs (VA) Greater Los Angeles Healthcare System were reviewed to identify HIV-infected patients who had a prolonged period of virologic failure while adherent to treatment with HAART, which was defined by the administration of 2 nucleoside reverse transcriptase inhibitors and a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor. Adherence was evaluated per retrospective review of the medication refill records, clinic appearances, and progress notes. All assessments of adherence were performed before performance of resistance genotypes on archived plasma specimens. All treatment decisions had been independently made by the patients' physicians without intervention by the study team.

To be included in the analysis, patients were required to be receiving at least 3 antiretroviral agents, including a thymidine analogue or a protease inhibitor, despite the onset of virologic treatment failure between August 1996 and February 2002. In addition, at least 2 plasma samples, separated by at least 120 days, had to have been obtained during virologic failure and to be available for analysis. The time of virologic failure was the earliest date that one of the following criteria were satisfied: failure to achieve a 1.0 log₁₀ decrease in the pVL after 1 month of treatment with HAART or, after 3 months of treatment, the first of 2 consecutive pVLs > 1000 copies/mL or the first pVL > 5000 copies/mL. Patients who did not have sufficient medication supplies to allow for 75% adherence during the study period were excluded, as were patients for whom progress notes indicated < 75% of their medications or nonadherence to an unspecified degree. Subjects were allowed to change their antiretroviral therapy while the pVL was < 400 copies/mL, to substitute stavudine for zidovudine (or vice versa), or to add low-dose ritonavir. Courses of therapy were otherwise censored to further follow-up when the antiretroviral regimen was altered.

To avoid a ceiling effect on the potential emergence of mutations, we limited our analyses to patients who lacked evidence of multidrug resistance or multiple TAMs.³⁰ Therefore, analysis for the emergence of TAMs was limited to persons with < 2 TAMs who did not have the Q151M or the T69 insertion complex at the time of the first resistance genotype obtained after virologic failure. Analysis of the emergence of major protease inhibitor mutations was limited to persons with < 2 major protease inhibitor mutations at the time of the first resistance genotype obtained after virologic failure. Resistance mutations were classified as per the November 2004 version of the International AIDS Society (IAS)–USA guidelines.³¹ Thus, TAMs were defined as the specified mutations at amino acid positions 41, 67, 70, 210, 215, and 219. Major protease inhibitor resistance mutations were defined as those at amino acid positions 30, 46, 48, 50, 82, 84, and 90, and minor resistance mutations were defined as those at amino acid positions 10, 20, 24, 32, 33, 36, 47, 53, 54, 63, 71, 73, 77, and 88.

This study used plasma specimens obtained from patients who had undergone HIV pVL testing at the VA Greater Los Angeles Healthcare System between August 1996 and August 2004. Since August 1996, aliquots of plasma from all patients undergoing pVL analyses at this facility have been routinely stored at -70°C . All genotyping was done using the TruGene assay (Bayer, Berkeley, CA). All pVLs were determined by reverse transcriptase polymerase chain reaction (PCR; Amplicor v1.0 or Amplicor v1.5; Roche Diagnostics, Nutley, NJ) with a lower limit of either 50 or 400 copies/mL. pVLs of < 50 or < 400 copies/mL were arbitrarily assigned values of 25 and 200 copies/mL, respectively. All pVL results were log-transformed before statistical manipulation. All data are presented as mean \pm SD or median (25%–75% inter-quartile range [IQR]) as appropriate. Statistical analyses utilized the χ^2 test with Yates correction, Student *t* test, or Cox-Mantel test as appropriate.

This study was approved by the Institutional Review Boards of the VA Greater Los Angeles Healthcare System, Los Angeles, CA, and the University of Texas Medical Branch, Galveston, TX.

RESULTS

Among the 582 individuals who had received at least 1 month of HAART as of February 2002, there were 396 episodes of virologic failure for which there were 120 days of subsequent follow-up. After 276 such episodes, antiretroviral therapy was promptly changed, whereas for the other 123 episodes of virologic failure, patients remained on a stable HAART regimen, and thus were eligible to be considered for inclusion in this study. Subsequently, 40 episodes were excluded because of poor adherence to the treatment regimen, 27 episodes were excluded because of the presence of multiple resistance mutations at the time of virologic failure, 2 episodes were excluded because the failing regimen did not include a thymidine analogue or protease inhibitor, and 8 episodes were excluded because of lack of adequate plasma samples.

The remaining 46 episodes of failing antiretroviral therapy that were eligible for analysis occurred in 41 patients; for 5 patients, the emergence of resistance was assessed during 2 separate episodes of failing therapy. There were 29 episodes that satisfied criteria for evaluation of the emergence of TAMs and major protease inhibitor mutations, 12 episodes that were assessed for the emergence of TAMs only, and 5 episodes that were assessed for the emergence of major protease inhibitor mutations only. Twenty-three episodes evaluated for the emergence of TAMs were in patients who had previously received a thymidine analogue (usually before HAART), and 6 of the episodes evaluated for the emergence of major protease inhibitor mutations were in patients who had previously been treated with a protease inhibitor (3 with indinavir and 1 each with nelfinavir, ritonavir, and saquinavir). Among the thymidine analogue regimens, 17 included zidovudine and 24 included stavudine. The protease inhibitor regimens used nelfinavir (18 regimens), indinavir (12 regimens), saquinavir (3 regimens, 2 with 400 mg

of ritonavir administered twice daily), and amprenavir (1 regimen). During the course of virologic failure, ritonavir boosting was initiated in 1 patient receiving indinavir and in 1 patient receiving amprenavir.

Figure 1 provides the duration of successful and failing antiretroviral therapy and the CD4⁺ cell count and pVL values before virologic failure, at the onset of virologic failure, and at the end of follow-up. Episodes monitored for the emergence of TAMs or major protease inhibitor mutations did not differ in regard to prior antiretroviral therapy, duration of successful or failing treatment, CD4⁺ cell counts, or pVL values. Data regarding the status of individual patients at the time of virologic failure are provided in Table 1. In 30 episodes, a pVL of < 400 copies/mL had been achieved before treatment failure. At virologic failure, no TAMs were present in 35 of 41 episodes evaluated for the emergence of TAMs, whereas no major protease inhibitor mutations were present in 13 of 34 episodes evaluated for the emergence of major protease inhibitor mutations ($P = 0.019$).

The median time between virologic failure and the first subsequent genotype was 218 (IQR: 126–370) days; a median of 5 (IQR: 3–6) genotypes was performed per course of virologic failure. Kaplan-Meier analyses indicated that new major protease inhibitor mutations subsequently emerged more rapidly than did new TAMs. This relation held true when all regimens involving thymidine analogues or protease inhibitors were evaluated (Fig. 2; $P = 0.026$) and when evaluation was limited to the 29 regimens in which there was concurrent use of a thymidine analogue and a protease inhibitor (Fig. 3; $P = 0.0019$). Finally, the emergence of TAMs was substantially slower in the 32 thymidine analogue-containing regimens that included lamivudine than in the 9 regimens that did not (Fig. 4; $P = 0.0073$). When regimens not including lamivudine were excluded, the rate of emergence of TAMs and major protease inhibitor mutations did not differ. To compensate for potential bias introduced by including a second course of therapy, we also assessed the time to onset of new TAMs and major protease inhibitor mutations after limiting the data set to each patient's first course of therapy. In these analyses, new TAMs were again shown to emerge more slowly than new major protease inhibitor mutations ($P = 0.0072$ for all treatment regimens and $P = 0.0024$ for patients receiving current therapy with a thymidine analogue and a protease inhibitor). The emergence of TAMs was not shown to differ in patients who received thymidine analogue regimens with or without concurrent use of lamivudine ($P = 0.203$), however, possibly because of the small residual sample size (30 patients with receipt of lamivudine and 6 patients without receipt of lamivudine).

The median follow-up was similar for episodes of failure evaluated for emergent TAMs and for major protease inhibitor mutations, 695 (IQR: 414–1014) days and 745 (IQR: 529–1018) days, respectively. During virologic failure, new TAMs were detected in 15 of 41 eligible episodes and new major protease inhibitor mutations were detected in 21 of 34 eligible episodes ($P = 0.20$). In the subset of courses with no detectable TAMs ($n = 35$) or major protease inhibitor mutations ($n = 21$) at the onset of virologic failure, new TAMs emerged 11 times and new major protease inhibitor mutations emerged 13 times ($P = 0.026$).

Among the 41 thymidine analogue-containing regimens, a single TAM was detected at virologic failure in 3 of 9 courses that did not include lamivudine versus 3 of 32 courses that did include lamivudine ($P = 0.072$). New TAMs later emerged in 6 of the 9 thymidine analogue regimens with lamivudine versus 9 of the 32 thymidine analogue regimens without lamivudine ($P = 0.034$). Of the 9 thymidine analogue regimens that did not include lamivudine, 3 included didanosine, 1 included zalcitabine, and 5 included a nonnucleoside reverse transcriptase inhibitor or full-dose ritonavir plus a protease inhibitor. Among the 3 courses in which stavudine was combined with didanosine, new TAMs were detected after 150, 161, and 218 days; for the 6 courses in which stavudine ($n = 5$) or zidovudine ($n = 1$) was the sole nucleoside

reverse transcriptase inhibitor, new TAMs were detected after 253, 336, and 757 days in 3 instances and were not detected at final follow-up (274, 728 and 767 days) in 3 instances. The frequency of protease inhibitors versus nonnucleoside reverse transcriptase inhibitors did not differ in thymidine analogue-containing courses that did or did not include lamivudine.

For 11 of the 15 episodes in which a new TAM emerged, further follow-up on the same course of therapy was available for a median of 553 (IQR: 262–762) days. During 8 of these 11 periods, additional TAMs emerged. Similarly, there was a median of 403 (IQR: 258–586) days of follow-up for 18 of the 21 episodes in which a major protease inhibitor mutation emerged; additional major protease inhibitor mutations emerged in 7 of these 18 periods. Figure 1 shows the final distribution of TAMs and major protease inhibitor mutations among the thymidine analogue- and protease inhibitor-containing regimens.

The 62V, 118I, and 184V mutations were the only non-TAM nucleoside reverse transcriptase inhibitor resistance mutations present at virologic failure or that arose during the subsequent period (Table 2). The 2 instances of 118I emergence were in persons receiving didanosine and stavudine, both of whom had previously accumulated 3 TAMs. The 151M, 44A/D, and T69 insertion mutations were not found in any patients. Although the 62V mutation can be found in association with the 69S insertion complex (with 41L, 70R, 210W, 215Y/F, and 219Q/E) or the 151 complex (with 75I, 77L, and 116Y),³¹ neither of these associations was observed in any of the 6 studied treatment courses in which this mutation was detected.

Minor protease inhibitor resistance mutations were present at virologic failure in 25 regimens, and new minor protease inhibitor resistance mutations were detected during the period of observation in 22 of the 34 regimens. In 7 of the 8 patients receiving nonnucleoside reverse transcriptase inhibitors, genotypic evidence of resistance to these agents was present at virologic failure.

Compared with the time of virologic failure, at final follow-up, there was an increase of 24 ± 137 CD4 cells/ μ L and an increase of 0.16 ± 0.72 log₁₀ copies/mL in the pVL; neither of these changes were statistically significant. There were no differences in the change of the CD4⁺ cell count or the pVL from the time of virologic failure to last follow-up regardless of the emergence of a new TAM or major protease inhibitor mutation or for thymidine analogue-containing regimens in which lamivudine was or was not used.

DISCUSSION

This study utilized an unusual opportunity to evaluate the rate of emergence of genotypic resistance to thymidine analogues and protease inhibitors retrospectively in patients who remained on stable HAART after the onset of virologic treatment failure. In these 46 studied episodes of prolonged virologic failure (mean duration of 110 weeks), there was a significantly greater rate of emergence of major protease inhibitor mutations than of TAMs. This difference was observed only when thymidine analogues were used in combination with lamivudine; importantly, dual-protease inhibitor therapy with ritonavir or ritonavir boosting was used in only 4 of the 34 evaluable courses of protease inhibitor therapy. In addition, the emergence of TAMs was substantially slower in lamivudine-containing regimens. Overall, the mean time to detection of a new TAM in treatment courses that included lamivudine was > 300 days longer than the mean time until the detection of a new major protease inhibitor mutation.

Our results extend and generally corroborate the observations of previous studies regarding the rate of emergence of TAMs and protease mutations after virologic failure but provide a substantially longer period of follow-up. Kempf et al²⁶ reported that genotypic evidence of resistance to lamivudine, stavudine, and nelfinavir emerged in 100%, 15%, and 74%, respectively, of 80 previously treatment-naïve individuals with up to 48 weeks of ongoing

virologic failure. Similarly, Aleman et al²⁵ reported that among 10 patients with fewer than 2 TAMs at the time of initial virologic failure who continued to receive a thymidine analogue and protease inhibitors, 2 developed 1 or more TAMs and 8 developed new major protease inhibitor resistance mutations over a mean follow-up period of 103 weeks. In contrast, Napravnik et al³² found that the incidence of new major protease inhibitor mutations was lower than the incidence of nucleoside reverse transcriptase inhibitor-associated mutations in persons who remained on stable combination antiretroviral therapy with detectable viremia for a median of 9.3 months. Importantly, the rate of development of new resistance mutations was greater among persons who maintained an average viral load of 3 to 4 HIV RNA log₁₀ copies/mL than in persons whose average viral load was lower or higher. These authors also found that the adjusted incidence rate of new mutations was lowest among persons who had 1 to 3 resistance mutations (including minor protease inhibitor mutations) at baseline or whose viral load was stable during follow-up (slopes ≤ 0.2 per month). Unlike our study, however, Napravnik et al³² did not specifically assess the emergence of TAMs. In addition, the proportion of patients receiving thymidine analogues (with or without lamivudine) or ritonavir-boosted protease inhibitor regimens was not specified. Other analyses of the emergence of resistance mutations during virologic failure fail to describe the specific emergence of TAMs or major protease inhibitor resistance mutations, include patients with high levels of preexistent resistance, or do not provide separate analyses of patients with few mutations at baseline.^{30, 33–37}

Our observations regarding the slower rate of emergence of TAMs after treatment failure in persons receiving lamivudine are consistent with and extend previous observations. In particular, Kuritzkes et al³⁸ previously reported that in 49 treatment-naive patients given 52 to 72 weeks of nonsuppressive therapy, TAMs emerged more often with zidovudine monotherapy than with zidovudine plus lamivudine. Other studies have shown that 184V is usually the first nucleoside reverse transcriptase inhibitor mutation to arise in failing zidovudine plus lamivudine regimens but have not examined the long-term evolution of TAMs after initial treatment failure.^{39–44}

The relatively gradual rate of accrual of TAMs in patients receiving lamivudine may be related to the observation that in the presence of the 184V mutation, the emergence of TAMs decreases viral fitness as measured by replication capacity.²⁹ Thus, in the presence of M184V, mutations that diminish nucleoside reverse transcriptase inhibitor activity (TAMs) may not be favored. In contrast, the emergence of multiple minor protease inhibitor mutations may improve replication capacity and allow for the development of further major protease inhibitor mutations.⁴⁵ Of note, the emergence of TAMs in patients not receiving lamivudine was similar to the rate of emergence of major protease inhibitor mutations. We were not otherwise able to determine predictors of the emergence of antiretroviral resistance. In particular, the CD4⁺ lymphocyte count tended to remain stable and the magnitude of pVL changes before or after treatment failure did not correlate with the presence or absence of antiretroviral resistance mutations at the time of first failure or the subsequent emergence of these mutations. As previously shown, there was no difference in the emergence of TAMs in subjects who received zidovudine versus stavudine.⁴⁶

The strengths of this study are the prolonged period of observation during virologic failure on a stable antiretroviral regimen and the frequency with which resistance genotypes were obtained. We believe that the differential rate of emergence of TAMs and major protease inhibitor mutations is not likely to be attributable to variances in adherence to these medications, especially because there was no correlation between the emergence of resistance mutations and the observed virologic responses.^{46,47} Furthermore, at the time of final follow-up, in all but 5 patients, the pVL was less than the pre-HAART level, and in all but 2 patients, the CD4⁺ lymphocyte count was greater than the pre-HAART value (data not shown). Although

other studies have examined differences in the presence of TAMs and major protease inhibitor mutations at the time of initial treatment failure, few studies have evaluated the subsequent course of patients who remain on stable nonsuppressive regimens^{25–27} and none, to our knowledge, have followed as large a cohort of failing patients with low rates of baseline resistance who continue to receive a stable regimen for as long a period.

The principal limitation of this study is the retrospective and potentially biased case selection. In particular, persons with virologic failure that is progressive or accompanied by immunologic and/or clinical deterioration are much more likely to have had their antiretroviral therapy rapidly changed, and thus would not have been eligible for inclusion in this study. Such individuals may have more rapidly developed resistance than did the individuals we studied. Furthermore, exclusion of persons with 2 or more TAMs or major protease inhibitor mutations at the time of virologic failure may bias the analysis by eliminating patients in whom resistance emerges particularly quickly. Our results may also be relevant only for the specific regimens received by our subjects, particularly because few patients received ritonavir-boosted protease inhibitor regimens,^{26,27} and for the resistance profiles observed at the time of virologic failure. Previous studies have shown that the rate of emergence of major protease inhibitor mutations is less in persons receiving a ritonavir-boosted protease inhibitor than when ritonavir boosting is not used.^{26,27} In addition, our ability to assess the time of onset of anti-retroviral resistance was limited by our reliance on having access to sufficient stored plasma that had been obtained for clinical reasons; thus, we were not able to assess the emergence of resistance at regular fixed intervals. Our results should also be interpreted in the context of our definition of virologic failure. This relied principally on reproducibly demonstrating a pVL > 1000 copies/mL. This was based on treatment recommendations for changing antiretroviral therapy^{13,14} and on the practical consideration of the pVL threshold for reliably performing genotypic assays for anti-retroviral resistance.

The relatively slow rate of accrual of TAMs in our subjects provides support for further studies to understand better the determinants of the pattern of emergence of anti-retroviral resistance mutations and of strategies to delay the emergence of resistance in the context of virologic failure. We strongly caution that these results should not be used to make clinical management decisions in persons with virologic failure while receiving HAART, however, especially for those persons who have access to remaining effective antiretroviral agents. Although TAMs emerged slowly in most patients, our data clearly indicate that continued failing therapy is likely to result in the ultimate emergence of TAMs and major protease inhibitor mutations, with resultant cross-resistance that limits future treatment options and leads to poor clinical outcomes. Finally, regardless of whether there is initial immunologic benefit, patients with virologic treatment failure ultimately develop immunologic failure and, where excellent treatment options exist, have been shown to have worse clinical outcomes than do persons who achieve full virologic suppression.^{17,48}

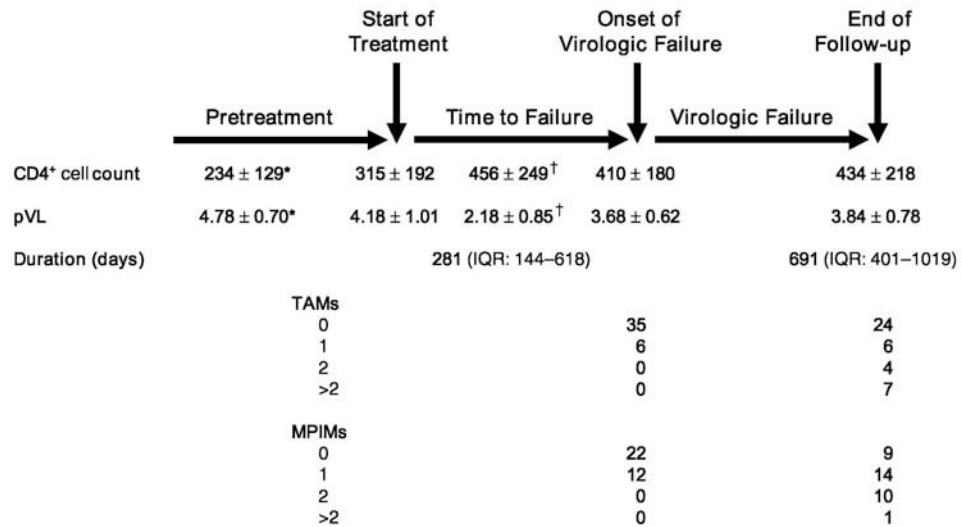
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**FIGURE 1.**

Relation between treatment, virologic failure, CD4⁺ cell count, pVL, and detection of TAMS and major protease inhibitor mutations (MPIMs). TAMS and MPIMs are shown at the first detection of virologic failure and at the end of follow-up. All data are presented as mean ± SD except for the duration of observation, which is presented as the mean and IQR. *CD4⁺ cell count is the minimum known value before treatment, whereas pVL is the maximum known value. [†]CD4⁺ cell count is the maximum value achieved on the treatment regimen of interest before virologic failure, whereas pVL is the minimum value.

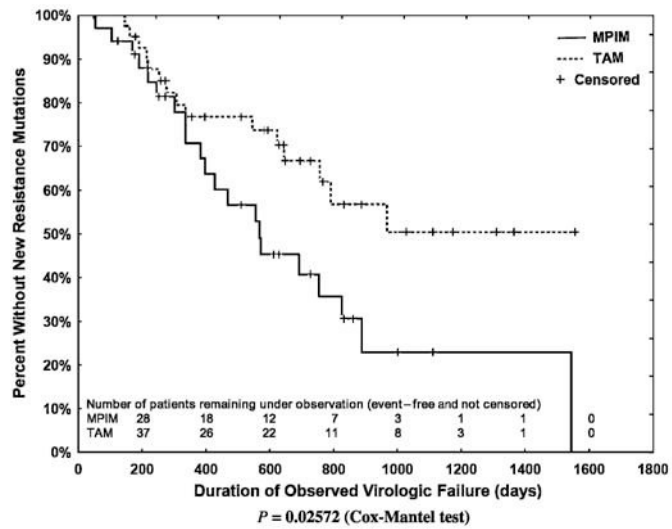


FIGURE 2. Kaplan-Meier plot of the emergence of a new TAM among the 41 thymidine analogue regimens and of a new major protease inhibitor mutation (MPIM) among the 34 protease inhibitor regimens (Cox-Mantel test, $P = 0.026$).

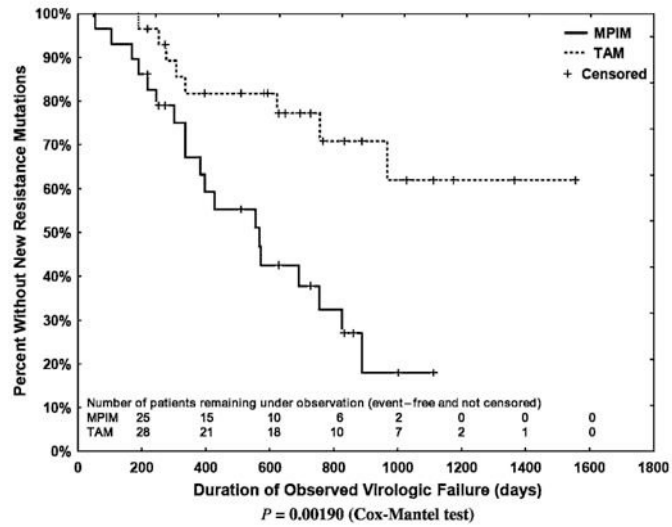


FIGURE 3.

Kaplan-Meier plot of the emergence of a new TAM among the 29 regimens that included a thymidine analogue and a protease inhibitor (Cox-Mantel test, $P = 0.0019$).

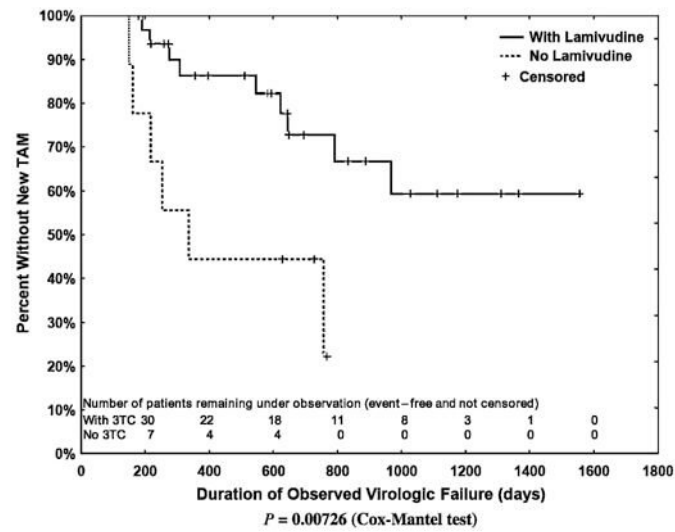


FIGURE 4. Kaplan-Meier plot of the emergence of a new TAM among the thymidine analogue-containing regimens that did (n = 32) or did not (n = 9) include lamivudine (Cox-Mantel test, $P = 0.0073$). 3TC indicates lamivudine.

TABLE 1

Status at Time of Initial Virologic Failure

Patient (Episode)	Course	Prior Therapy	Current Therapy	Days of Therapy	Current		Mutations	
					CD4	pVL	NRTI	PI
2 (1)	1	ZDV, 3TC, ddI, ddC	d4T/SQV/RTV	854	592	3.10	215Y	63P
5 (1)	1	ddI	ddI/3TC/IDV	126	349	3.12	WT	63P
5 (2)	2	3TC, ddI, IDV	ZDV/3TC/APV	161	343	3.19	WT	63P, 77I
6 (1)	1	None	ZDV/3TC/IDV	658	559	3.70	184V	46I
7 (1)	1	ZDV, 3TC, d4T, ddI	ZDV/3TC/IDV	112	371	3.75	184V	10L/R, 63P, 71A/T, 82T
11 (1)	1	None	d4T/3TC/NFV	397	330	3.12	WT	WT
13 (1)	1	ZDV, ddC	d4T/3TC/IDV	160	350	3.71	62V, 184V, 215Y	10I, 46I, 63P, 71V, 73S, 84V, 90M*
15 (1)	1	None	d4T/3TC/NVP	489	387	3.74	184V	63P, 71T
16 (1)	1	ZDV, d4T, ddI	d4T/3TC/IDV	112	169	3.94	184V	71T
21 (1)	1	ZDV, 3TC, d4T	ZDV/3TC/IDV	525	355	3.03	184V	63P, 71T, 77IV, 82AV
30 (1)	1	ZDV, 3TC, ddI	d4T/3TC/IDV	90	219	3.00	184V	10I, 71T
30 (2)	2	ZDV, d4T, 3TC, ddI, IDV	d4T/NVP/NFV	133	288	4.24	WT	10I, 24L/I, 46L/M
32 (1)	1	None	d4T/ddI/NVP	581	571	3.43	41L	63P
105 (1)	1	ZDV, d4T, ddI	ZDV/3TC/IDV	329	322	3.90	184V	WT
106 (1)	1	None	ZDV/3TC/NFV	442	729	3.48	62V, 184V	WT
107 (1)	1	None	ZDV/3TC/IDV	559	264	4.31	WT	46L, 54V, 82A*
108 (1)	1	ddI	ZDV/3TC/IDV	261	423	3.97	WT	63P
109 (1)	1	None	ZDV/3TC/NFV	273	498	4.69	184V	30N, 63P, 88D
110 (1)	1	ZDV, 3TC, d4T	ZDV/3TC/NFV	315	772	3.63	67N, 70R, 184V [†]	30N, 63HP
111 (1)	1	None	ddI/3TC/IDV	821	362	3.00	184V	46I, 63P
112 (1)	1	d4T, 3TC, ddI, NVP, IDV	ZDV/3TC/NFV	121	229	4.00	WT	20M, 63P
115 (1)	1	ZDV, 3TC, d4T	d4T/3TC/IDV	711	215	4.89	184V	82A
116 (1)	1	ZDV, 3TC, d4T	d4T/3TC/SQV	133	366	3.51	184V	No data*
116 (2)	2	ZDV, 3TC, d4T, NVP, SQV	d4T/NVP/NFV	49	246	3.94	184V	10I, 63P, 71T, 90M
133 (1)	1	ZDV, d4T	d4T/3TC/IDV	505	166	4.82	184V/M	WT
135 (1)	1	None	d4T/SQV/RTV	1170	437	3.34	WT	71T
142 (1)	1	None	d4T/3TC/NVP	216	316	2.91	WT	77I
143 (1)	1	d4T, 3TC, ddC	d4T/3TC/EFV/NFV	979	715	3.20	184V	No data
145 (1)	1	ZDV, d4T, ddI	d4T/3TC/NFV	196	405	4.08	184V	10I, 36I
146 (1)	1	ZDV	d4T/3TC/NFV	214	278	3.27	184V	10R, 63P, 77I
152 (1)	1	ZDV, 3TC, d4T, ddI	ddI/3TC/NFV	651	228	3.11	184V	36I, 88S
153 (1)	1	ddI	ddI/3TC/IDV	812	517	3.84	184V, 215Y	82A
154 (1)	1	None	ZDV/3TC/NFV	123	276	4.53	184V	63P
157 (1)	1	ddI	ZDV/3TC/NFV	630	444	3.52	184V	30N, 63P, 88D
158 (1)	1	ddI	ZDV/3TC/IDV	274	203	3.16	184V	63P, 77I
159 (1)	1	None	ZDV/3TC/NFV	95	128	5.78	184V	20R, 36I, 63P
161 (1)	1	ZDV, d4T	d4T/3TC/IDV	1599	620	4.23	41L, 184V	46I, 50I/V, 63P, 77I/V
162 (1)	1	ZDV	ZDV/ddC/NFV	1231	578	3.22	WT	36I
162 (2)	2	ZDV, ddC, 3TC, NFV	ZDV/3TC/NFV	288	662	3.01	184V	10V, 36I, 90M
164 (1)	1	None	d4T/3TC/SQV	139	336	4.28	184V	36I, 90M
164 (2)	2	d4T, 3TC, SQV	d4T/ddI/APV	68	499	3.37	184V	20R/T/K, 36I, 63P, 84V, 90M

Patient (Episode)	Course	Prior Therapy	Current Therapy	Days of Therapy	Current			Mutations	
					CD4	pVL	NRTI	PI	
166 (1)	1	ZDV, ddI	d4T/3TC/NFV	1302	905	3.05	184V	WT	
167 (1)	1	No data	d4T/3TC/NVP	258	373	3.50	70K/R, 184V	63P, 77I	
169 (1)	1	ZDV, 3TC, d4T, IDV, DLV, SQV	d4T/ddI /APV	174	428	3.31	62V, 215F	10F, 20M, 24I, 36I, 46I, 54V, 63P, 82A	
170 (1)	1	ZDV, 3TC, d4T, ddI, RTV, SQV	d4T/NVP/NFV	160	281	3.00	WT	10I, 63P, 71V, G73S, 90M	
171 (1)	1	None	d4T/3TC/NVP	508	768	4.35	184V	WT	

In 5 patients, the emergence of resistance was assessed in 2 separate courses of therapy.

* Emergence of major protease inhibitor mutations while on protease inhibitor therapy was not evaluated because of the inability to sequence HIV protease [patient 116(1)] or the presence of 2 or more major protease inhibitor mutations at the time of virologic failure [patients 13(1), 107(1), 164(2), and 169(1)].

[†] Emergence of TAMS while on thymidine analogue therapy was not evaluated because of the presence of 2 or more TAMS at the time of virologic failure [patient 110(1)].

APV indicates amprenavir; CD4, CD4 cell count; ddI, didanosine; d4T, stavudine; EFV, efavirenz; IDV, indinavir; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir; 3TC, lamivudine; WT, wild type; ZDV, zidovudine.

TABLE 2

Status at Final Follow-Up

Patient (Episode)	Final Therapy	Failure Days	Days to First New			Mutations		
			TAM	MPIM	CD4	pVL	NRTI	PI
			> 728*	> 728	600	3.69	215Y	36I, 63P
2 (1)	d4T/SQV/RTV	728	> 728*	> 728	600	3.69	215Y	36I, 63P
5 (1)	ddl/3TC/IDV	613	N/A	> 613	264	3.05	WT	63P, 77I
5 (2)	ZDV/3TC/APV/r	511	> 511	> 511	137	3.44	WT	63P, 77I
6 (1)	ZDV/3TC/IDV	648	> 648	556	570	3.03	184V	46I, 63P, 71V, 82A, 90M
7 (1)	ZDV/3TC/NFV	1988	645	N/A	534	3.31	67N, 70R, 184V, 219Q	10V, 36I, 54V, 63P, 71T, 82TA, 88S
11 (1)	d4T/3TC/NFV	1896	967	56	386	3.09	41L, 184V, 215Y	36I, 46I, 63P, 71V, 90M
13 (1)	d4T/3TC/NFV	1311	> 1311	N/A	524	3.23	62V, 184V, 215YC	10I, 46I, 63P, 71V, 84V, 90M
15 (1)	d4T/3TC/NFV	1556	> 1556	567	469	3.50	184V	10I, 46I, 54L, 63P, 71T, 90M
16 (1)	d4T/ddI/NFV	693	> 693	301	261	3.04	184V	30N, 46L, 63P, 71T, 88D
21 (1)	ZDV/3TC/IDV	763	623	336	556	4.45	41L, 67N, 70R, 184V, 219E	54V, 77I, 84V
30 (1)	d4T/3TC/IDV	218	> 218	> 218	273	3.06	184V	10I, 24I, 46L
30 (2)	d4T/NVP/NFV	253	253	> 253	229	4.43	70R, 215SYTN	10I, 24I, 36I
32 (1)	d4T/ddI/NVP	430	150	N/A	718	3.31	41L, 210W, 215Y	63P
105 (1)	d4T/3TC/IDV	1366	> 1366	826	385	3.50	184V	46L, 82A
106 (1)	ZDV/3TC/NFV	300	190	190	805	4.75	41L, 62V, 184V	46I, 77I
107 (1)	ZDV/3TC/IDV	179	> 179	N/A	295	4.68	184V	46L, 54V, 63P, 71V, 82A
108 (1)	ZDV/3TC/IDV	397	> 397	397	398	4.27	184V	82A
109 (1)	ZDV/3TC/NFV	833	> 833	> 833	543	4.70	184V	30N, 63P, 88D
110 (1)	ZDV/3TC/NFV	1218	N/A	469	472	4.33	67N, 70R, 184V, 219Q	30N, 63QHP, 71IV, 90M
111 (1)	ddl/3TC/IDV/r	1545	N/A	1545	349	3.53	184V	10I, 36I, 46I, 63P, 90M
112 (1)	ZDV/3TC/NFV	1020	> 1020	691	352	4.18	184V	71V, 90M
115 (1)	d4T/3TC/IDV/r	888	> 888	888	172	6.44	184V	10I, 24I, 46I, 63P, 82A
116 (1)	d4T/3TC/NVP/NFV	644	> 644	N/A	234	4.31	184V	10I, 63P, 71T, 90M
116 (2)	d4T/NVP/NFV	778	336	572	188	3.89	67N, 70R, 219E	30N, 36I, 63P, 71V, 88D, 90M
133 (1)	d4T/3TC/IDV	1112	> 1112	> 1112	166	4.03	184V	WT
135 (1)	d4T/SQV/RTV	767	> 767	383	210	4.25	WT	10I, 48V, 54V, 71T, 82A
142 (1)	d4T/3TC/NVP	357	> 357	N/A	474	4.32	WT	77I
143 (1)	d4T/3TC/NVP	259	> 259	N/A	1000	3.16	184V	30N, 36I, 46I, 77I, 88D
145 (1)	d4T/3TC/NFV	1029	> 1029	427	405	3.70	184V	10I, 20R, 30N, 36I, 88D
146 (1)	d4T/3TC/NFV	584	> 584	169	405	4.66	184V	30N, 63P, 71T, 77I, 88D
152 (1)	ddl/3TC/NFV	126	N/A	> 126	372	3.86	184V	36I, 88S
153 (1)	ddl/3TC/IDV	177	N/A	> 177	676	4.06	184V, 215Y	82A
154 (1)	ZDV/3TC/NFV	695	> 695	219	363	3.85	184V	30N, 63P, 71V, 77I, 88D
157 (1)	ZDV/3TC/NFV	861	308	> 861	364	3.40	41L, 184V, 215Y	30N, 36I, 63P, 88D
158 (1)	d4T/3TC/IDV/r	1175	> 1175	244	109	3.14	WT	10I, 63P, 73S, 77I
159 (1)	ZDV/3TC/NFV	276	276	105	124	5.17	70R, 184V	20R, 30N, 36I, 63P
161 (1)	d4T/3TC/IDV	214	214	N/A	318	4.18	184V, 210W, 215Y	10V, 46I, 63P, 71V
162 (1)	ZDV/ddC/NFV	628	> 628	> 628	625	2.43	WT	10V, 36I
162 (2)	ZDV/3TC/NFV	274	> 274	> 274	478	3.54	184V	36I, 90M
164 (1)	d4T/3TC/SQV/NVP	1014	> 1014	755	534	2.18	184V	20RT, 36I, 63P, 84V, 90M
164 (2)	d4T/DDI/APV/r	816	161	N/A	617	4.01	41L, 67N, 118I, 210W, 215FY	10F, 20R, 32I, 33F, 36I, 54L, 63P, 84V, 90M
166 (1)	d4T/3TC/NFV	595	> 595	337	826	3.11	184V	10F, 88S
167 (1)	d4T/3TC/NVP	545	545	N/A	265	3.36	67N, 70R, 184V, 219E	63P, 77I

Patient (Episode)	Final Therapy	Failure Days	Days to First New			Mutations		
			TAM	MPIM	CD4	pVL	NRTI	PI
169 (1)	d4T/DDI/APV	414	218	N/A	483	3.70	41L, 118I, 210W, 215F	20M, 24I, 36I, 46I, 54V, 63P, 82A
170 (1)	d4T/NVP/NFV	1002	757	> 1002	329	3.77	215FY	10I, 63P, 71V, 73S, 77I, 90M
171 (1)	d4T/3TC/NVP	1620	791	N/A	1100	5.58	70R, 184V	WT

* No mutation was observed at the end of the follow-up period.

APV indicates amprenavir; CD4, CD4 cell count; ddi, didanosine; d4T, stavudine; EFV, efavirenz; IDV, indinavir; ; MPIM, major protease inhibitor mutation; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; r, ritonavir; RTV, ritonavir; SQV, saquinavir; 3TC, lamivudine; WT, wild type; ZDV, zidovudine.