

## Rate of Virologic Failure and Selection of Drug Resistance Mutations Using Different Triple Nucleos(t)ide Analogue Combinations in HIV-Infected Patients

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### ABSTRACT

Virologic failure seems to occur more frequently in HIV-infected patients treated with triple nucleoside analogue (NA) combinations than with regimens including nonnucleoside reverse transcriptase inhibitors or protease inhibitors. However, the rate of failure and resistance profiles may differ with distinct triple NA combinations. A retrospective review of all HIV-infected individuals who received triple NA combinations at our institution was conducted. Virologic failure was defined as lack of achievement of plasma HIV-RNA <50 copies/ml at week 16 following initiation of antiretroviral therapy or as viral rebound in subjects with prior undetectable viremia. Genotypic analyses were performed at the time of first virological failure. Of the 261 patients identified, 13 were drug naive, 126 had undergone simplification, and 122 were antiretroviral-experienced patients with detectable viral load. Virologic failure was recorded in 95 (36.4%) after an average follow-up of 19 months. Rates were 0.67 in drug-naive, 0.55 in simplification, and 2.38 in rescue interventions for 100 persons-month follow-up. Factors associated with virologic failure in the multivariate Cox regression analysis were rescue vs naive or simplification strategies (OR 2.6; 95% CI 1.6–4.2) and using tenofovir as part of the combination (OR 2.04; 95% CI 1.3–3.2). In contrast, the use of AZT prevented virologic failure (OR 0.52; 95% CI 0.3–0.8). M184V was the most frequent resistance mutation (75.4%), followed by T215Y (52.5%) and K65R (14.8%). Of note, K65R did not develop in patients taking AZT nor in those with prior thymidine-associated mutations (TAMs). Conversely, subjects who developed K65R did not accumulate TAMs. Virologic failure is relatively frequent in patients treated only with triple NA regimens, particularly in the setting of rescue therapy. The use of TDF might be associated with a higher risk of virologic failure and, conversely, AZT might be protective. The presence of TAMs precluded the selection of K65R in patients treated with TDF. Resistance pathways for TDF and thymidine analogues seem to be divergent and could be the basis to explore a synergism between these drugs.

### INTRODUCTION

THERAPEUTIC FAILURE has been reported to occur more frequently in HIV-infected individuals treated with triple nucleos(t)ide analogue (NA) combinations than in those receiving regimens based on nonnucleoside reverse transcriptase inhibitors (NNRTI) or protease inhibitors (PI).<sup>1–7</sup> Triple NA combinations seem to be particularly less effective in patients with high viral load, low CD4 counts, or with a history of AIDS-defining events.<sup>3,7,8</sup> However, subjects with prior exposure to NA as mono or dual combinations may fail more

frequently than patients who have never been exposed to sub-optimal therapies.<sup>9–11</sup> Taking into consideration all these data, the most recent HIV treatment guidelines have discouraged the use of triple NA combinations as the sole treatment for HIV infection.<sup>12,13</sup> However, because these regimens lack the toxicity and metabolic interactions of NNRTI and PI, their use may still be justified in particular situations.<sup>14</sup>

Resistance has been demonstrated for all approved NA. Two main pathways seem to drive the loss of susceptibility to these drugs. The first mechanism decreases the affinity binding of

TABLE 1. MAIN CHARACTERISTICS OF THE STUDY POPULATION TAKING TRIPLE NUCLEOS(T)IDE ANALOGUES<sup>a</sup>

Variables	Values
No. of patients	261
Mean age (years)	40 ± 6.8
Gender (male)	178 (68%)
Risk group:	
IDU	134 (51.3%)
MSM	86 (33%)
Heterosexual	34 (14.9%)
Unknown	2 (0.8%)
Reason for using three nucleos(t)ides	
Naive	13 (5%)
Simplification	126 (48%)
Rescue therapy	122 (47%)
Mean CD4 count (cells/μl)	524 ± 292
Lowest historical nadir CD4 count (cells/μl)	
≤200	35 (13%)
>200	80 (31%)
Unknown	146 (56%)
Highest historical peak of plasma HIV-RNA (copies/ml)	
≤100.000	57 (22%)
>100.000	26 (10%)
Unknown	178 (68%)
Prior mono or dual suboptimal NA combination	133 (51%)

<sup>a</sup>IDU, intravenous drug users; MSM, men who have sex with men; NA, nucleoside analogue. Continuous variables are expressed as mean ± standard deviation.

NA for the viral reverse transcriptase (RT) enzyme. This is how the M184V or the K65R mutations act, typically linked to lamivudine (3TC) and tenofovir (TDF) resistance, respectively.<sup>15</sup> A second mechanism of NA resistance operates favoring the removal of the chain terminators in the newly synthesized cDNA strand; this has been linked to the so-called thymidine-associated mutations (TAMs), which are typically selected by zidovudine (AZT) or stavudine (d4T).<sup>16</sup> When several resistance mutations are present at the RT, cross-resistance may halt the potential benefit of multiple drugs within the NA family. Multinucleoside resistance has been demonstrated for genotypes such as the Q151M complex, codon 67 inserts, more than three TAMs, K65 plus M184V, or L74V plus M184V.<sup>17</sup> Finally, resistance profiles have changed since the widespread use of TDF over the past 3 years, which has resulted in an increase in the rate of the K65R mutation.<sup>18–20</sup>

Herein, we assessed retrospectively the rate of virologic failure and drug resistance patterns in a relatively large group of HIV-infected individuals who received triple NA combinations as the sole HIV therapy at our institution.

## MATERIALS AND METHODS

A retrospective review of all HIV-1-infected individuals on antiretroviral therapy at our institution was carried out. Subjects who had received or were currently receiving triple NA combinations alone were identified. Several variables were recorded

in a case report form, which included age, gender, risk group, hepatitis B and C markers, antiretroviral treatment modality (drug-naive, simplification or rescue interventions), current and historical nadir CD4 counts, current and historical peak plasma HIV-RNA, treatment adherence, and side effects leading to drug discontinuation.

Patients followed routine visits every 3–4 months after a first assessment at week 4 following initiation of therapy. Medical records included information regarding physical examination, personal interview, and laboratory analyses.

Virologic failure was defined as a lack of achievement of plasma HIV-RNA below 50 copies/ml at week 16 following initiation of antiretroviral therapy or as viral rebound in subjects with prior undetectable viremia taking other regimens. Genotypic analyses were performed at the time of the first virologic failure using an automatic sequencer (Viroseq, Celerera/Abbott Diagnostics, Madrid, Spain). Resistance mutations were considered taking as reference the list recorded at the latest IAS-USA report.<sup>21</sup>

## Statistical analyses

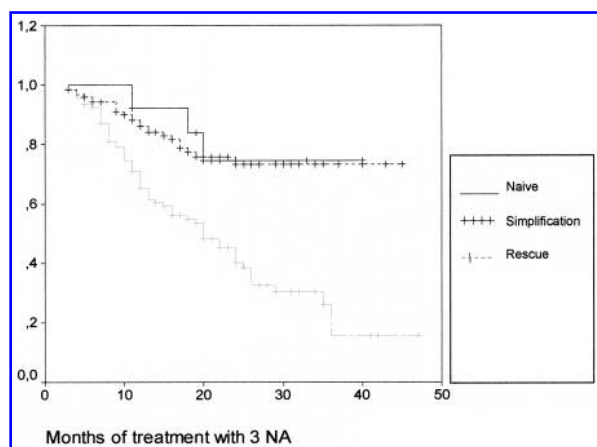
Data are described using percentages, means, and standard deviations. Association with virologic failure was assessed by univariate Cox-regression analysis. Those variables that were associated with virologic failure were included in the multivariate Cox regression analysis. Rates of failure were calculated using Kaplan–Meier tables. All results were analyzed using the SPSS version 11.0 software package (SPSS Corp., Chicago, IL), and statistical significance was assumed only for *p* values < 0.05.

## RESULTS

A total of 261 HIV-1-infected individuals were identified as receiving triple NA combinations as the sole antiretroviral therapy. A total of 2340 HIV-infected individuals were on regular follow-up at Hospital Carlos III, a reference center for HIV/AIDS located in Madrid, at the time the study was conducted. Their mean age was 39 years old; 52% had been intravenous drug users and 36% men who had sex with men. Seventy-two percent were native Spaniards, with the rest being immigrants from other regions, mainly from South America and sub-Saharan Africa. More than 80% of tested subjects carried

TABLE 2. NUMBER (PERCENTAGE OF PATIENTS EXPOSED TO EACH TRIPLE NUCLEOS(T)IDE ANALOGUE COMBINATION

Combination	No. (%)
ABC + 3TC + AZT	103 (39)
ABC + 3TC + D4T	25 (10)
DDI + D4T + ABC	25 (10)
TDF + ABC + DDI	19 (7)
TDF + DDI + 3TC	18 (7)
TDF + DDI + D4T	12 (5)
D4T + DDI + 3TC	11 (4)
Others	48 (18)
Total	261 (100)



**FIG. 1.** Probability of being without virologic failure based on using three nucleos(t)ide analogue combinations.

subtype B viruses. Coinfection with hepatitis B was present in around 5% of cases while coinfection with hepatitis C was recognized in nearly half of the whole cohort. A total of 1358 individuals were on antiretroviral therapy at the time the study was conducted. Regimens including NNRTi were taken by half of the treated population, while combinations based on PI were provided to nearly one-third of the patients. Overall, 79% of patients on antiretroviral therapy had undetectable plasma HIV-RNA at the time the study was conducted.

Table 1 summarizes the main characteristics of the study population of patients on triple NA therapy. Of note, only 13 (5%) were drug-naive, while 126 (48.3%) were on triple NA regimens following a simplification strategy after having <50 HIV-RNA copies/ml for longer than 6 months using other treatment regimens. Finally, 122 (46.7%) patients had initiated a triple NA regimen having detectable viremia under another treatment combination and therefore could be considered as rescue interventions. This latest group of patients mainly involved subjects with problems of drug compliance (i.e., drug addicts), side effects (i.e., lipid abnormalities or lipodystrophy), or drug interactions (i.e., methadone) while taking other antiretrovirals and/or subjects who did not wish to stay with drugs other than

NA. Of note, overall 133 (51%) patients had been exposed in the past to suboptimal mono or dual NA combinations. There was no significant difference when comparing patients who simplified and those who begun triple NA regimens having detectable viremia: 62/126 (49.2%) versus 71/122 (58.2%), respectively ( $p = 0.19$ ).

The most frequent triple NA regimens in use were AZT + 3TC + abacavir (ABC) (39.5%), d4T + 3TC + ABC (9.6%), d4T + ABC + didanosine (ddI) (9.6%), and TDF + ddI + ABC (7.5%) (Table 2). Considering each NA separately, ABC was the most prescribed ( $n = 199$ ; 76.2%), followed by 3TC ( $n = 193$ ; 73.9%) and AZT ( $n = 128$ ; 49%), while the less prescribed NA was TDF ( $n = 74$ ; 28.4%). None of these patients received zalcitabine or emtricitabine.

Ten (3.8%) patients were lost to follow-up and another 39 discontinued the triple NA regimen, due to either adverse effects ( $n = 23$ ; 8.8%) or voluntary decision ( $n = 16$ ; 6.1%).

Virologic failure occurred in more than one-third of the study population ( $n = 95$ ; 36.4%). The overall mean time to virologic failure was 11 months, ranging from 3 to 36 months. Global failure incidence was 1.9/100 patients/month of follow-up. According to the treatment modality, failure rates were 0.67/100 patients/month in drug-naive individuals, 0.55/100 patients/month in subjects on simplification, and 2.38/100 patients/month in patients failing another regimen ( $p < 0.05$  for rescue therapy compared to the other two groups). These results are reflected in Fig. 1.

In the univariate Cox regression analysis, failure was related to being on a rescue intervention and with prior exposure to suboptimal mono or dual NA therapies. According to each specific drug, failure was more often seen in patients receiving TDF and/or ddI, and less frequent in those receiving AZT, ABC, and 3TC (Table 3). No association could be found between virologic failure and any relevant demographic variable. Of note, no differences in the rate of virologic failure were found when comparing subjects belonging to different risk transmission categories (intravenous drug users versus homosexual men) or between individuals with chronic hepatitis B or C and the rest. Moreover, patients with high plasma HIV-RNA historical peaks (>100,000 copies/ml) or low CD4 counts ( $\leq 200$  cells/mm<sup>3</sup>) did not show an increased risk of virologic failure with respect to the rest in this study.

**TABLE 3.** FACTORS ASSOCIATED WITH VIROLOGIC FAILURE USING TRIPLE NUCLEOS(T)IDE ANALOGUE COMBINATIONS<sup>a</sup>

Variable	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Rescue vs. naive or simplification	3.07 (1.9–4.7)	<0.001	2.4 (1.6–4.2)	<0.001
CD4 count <200 cells/ $\mu$ l	1.6 (0.8–3.1)	0.15	—	—
Prior exposure to NRTI as mono or dual therapy	2.04 (1.2–3.3)	0.004	1.3 (0.8–2.2)	0.24
HIV-RNA > 100,000 copies/ml	1.08 (0.5–2.5)	0.8	—	—
Stavudine	1.01 (0.6–1.6)	0.94	—	—
Lamivudine	0.5 (0.3–0.7)	<0.001	1.3 (0.7–2.3)	0.38
Abacavir	0.5 (0.4–0.9)	<0.001	1.1 (0.6–2.3)	0.7
Zidovudine	0.4 (0.3–0.6)	<0.001	0.5 (0.3–0.8)	0.008
Didanosine	2.5 (1.7–3.8)	<0.001	1.4 (0.8–2.4)	0.27
Tenofovir	2.9 (1.9–4.4)	<0.001	2.04 (1.3–3.2)	0.002

HR: hazard rate ratio.

<sup>a</sup>Univariate and multivariate Cox regression analysis.

In the multivariate analysis (Table 3) virologic failure on triple NA combinations was independently associated with being on a rescue intervention (HR 2.4; 95% CI: 1.6–4.2) and treatment with TDF (HR 2.04; 95% CI: 1.3–3.2). In contrast, patients treated with AZT had a lower rate of virologic failure (HR 0.5; 95% CI: 0.3–0.8).

Genotypic results could be obtained from 61 (64.2%) out of 95 patients experiencing virologic failure. Low plasma HIV-RNA levels precluded obtaining results in the rest. The mutation most frequently found was M184V ( $n = 46$ ; 75.4%), followed by T215Y ( $n = 32$ ; 52.5%) and K65R ( $n = 9$ ; 14.8%). Interestingly, K65R was recognized along with M184V in all but one subject, and was selected in 9/41 patients failing with NA other than AZT but in 0/20 taking AZT-containing regimens ( $p = 0.005$ ). Of the nine patients who developed K65R, seven were taking TDF + ddI, one ddI + ABC, and another TDF + ABC.

Finally, a total of 37 (60.7%) patients had TAMs at failure. None of them carried K65R concomitantly ( $p < 0.001$ ). Moreover, K65R did not appear in nine patients known to carry viruses with TAMs.

## DISCUSSION

In this study we assessed the rate of virologic failure in HIV-infected patients who had received triple NA regimens as the sole HIV therapy at our institution. Failure was seen in more than one-third of patients after an average of 19 months of follow-up. It was significantly more frequent among subjects who underwent rescue interventions after failing under other regimens. Our results are in agreement with those from recent trials that have highlighted the limited potency of triple NA combinations.<sup>1–8</sup> Several reasons may account for this observation, including pharmacologic issues and/or a low genetic barrier for resistance.<sup>15</sup> For instance, the rapid selection of the K65R mutation has been claimed to be responsible for the high rate of failures seen in patients treated with TDF and 3TC along with ABC or ddI.<sup>18–20</sup>

In our study, patients treated with TDF-containing regimens experienced more frequently virologic failure than those receiving AZT-based combinations. This is somewhat surprising considering that the antiviral potency of TDF is much higher than that of AZT.<sup>15,22</sup> On the other hand, resistance pathways driving to selection of K65R and TAMs seemed to be divergent, as these mutations were not selected together. This finding is of clinical relevance, since these genotypes influence to a different extent the response to other NAs.<sup>15</sup> For instance, while K65R may reduce the susceptibility to TDF, ABC, and ddI, it does not seem to compromise the activity of other NAs.<sup>15</sup> In contrast, single TAMs mainly compromise the activity of thymidine analogues and multiple TAMs may be required to reduce significantly the activity of other NAs.<sup>23</sup>

In the clinical arena, the limited potency of triple NA combinations should be balanced with its convenience. These regimens often are taken once or twice daily, represent just two to four pills per day, tend to be free of drug interactions, and generally have no food restrictions. Moreover, most NA have a lower risk of liver toxicity, which is one of the main limitations of many NNRTI and/or PIs, particularly in patients with chronic

hepatitis C.<sup>24</sup> In countries such as Spain, where a large proportion of HIV-infected individuals had been intravenous drug users, triple NA regimens have become popular in recent years,<sup>14</sup> since most of these regimens favor treatment compliance, are free of drug interactions with methadone, and could be less hepatotoxic. In this context, our data should be interpreted cautiously. The rate of virologic failure using triple NA combinations was high on average, but it occurred particularly in patients who had previously failed other antiretroviral regimens, and therefore received triple NA combinations as rescue interventions. Although we did not find a negative impact of prior suboptimal NA exposure on the multivariate analysis, other authors have demonstrated it in the setting of simplification strategies.<sup>9,10</sup> Therefore, when possible, triple NA combinations should also be avoided in this context.

Regimens including AZT showed less virological failures than the rest and, conversely, combinations based on TDF showed higher rates of failure. However, most patients treated with AZT received the triple combination AZT–ABC–3TC (Trizivir) (103/128). In this context and due to the characteristics of our retrospective study, in which many diverse NRTI combinations were analyzed, it is difficult to ascertain to what extent the benefit of AZT was due to the drug itself or to the global effect of the combination. However, a recent large observational study has similarly found good performance for Trizivir in drug-naïve individuals as long as baseline plasma HIV-RNA was below 100,000 copies/ml.<sup>25</sup>

In our opinion, the higher rate of virological failure seen with triple NA combinations should not preclude its use in particular situations, such as in many former drug users with chronic hepatitis B or C currently taking methadone.<sup>14,24</sup> However, our data highlight that some triple NA combinations should be avoided as well as their use in patients with prior suboptimal NA exposure. Hopefully, these subsets of patients might benefit from the use of new protease inhibitors, such as atazanavir or fosamprenavir, which have a low pill burden, a higher safety liver profile, and do not interact significantly with methadone.<sup>26,27</sup>

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