Increased Virological Failure in Naive HIV-1–Infected Patients Taking Lamivudine Compared With Emtricitabine in Combination With Tenofovir and Efavirenz or Nevirapine in the Dutch Nationwide ATHENA Cohort

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(See the Editorial Commentary by Ford et al on pages 154–6.)

Background. Guidelines for treatment of human immunodeficiency virus type 1 (HIV-1) infection consider lamivudine and emtricitabine to be interchangeable components in first-line combination antiretroviral therapy (cART). The evidence for their clinical equivalence in cART is inconsistent. The primary aim of this study was to evaluate the virological responses to lamivudine and emtricitabine in recommended cART.

Methods. This was an observational study using data from the AIDS Therapy Evaluation in the Netherlands (ATHENA) nationwide HIV cohort. The virological responses to lamivudine and emtricitabine were compared by multivariable adjusted logistic regression and Cox proportional hazard models. Sensitivity analyses included propensity score–adjusted models.

Results. Therapy-naive HIV-1–infected patients without baseline resistance (N = 4740) initiated lamivudine or emtricitabine with efavirenz/tenofovir or nevirapine/tenofovir. The use of lamivudine was associated with more virological failure at week 48 compared to emtricitabine with efavirenz/tenofovir (10.8% vs 3.6%; adjusted odds ratio [AOR], 1.78; 95% confidence interval [CI], 1.11–2.84) and nevirapine/tenofovir (27% vs 11%; AOR, 2.09; 95% CI, 1.25–3.52) in on-treatment analysis. Propensity score–adjusted models and intent-to-treat sensitivity analyses gave comparable results. The adjusted hazard ratio of virological failure at week 240 using lamivudine instead of emtricitabine was 2.35 (95% CI, 1.61–3.42) with efavirenz and 2.01 (95% CI, 1.36–2.98) with nevirapine. The inclusion of lamivudine or emtricitabine in cART did not influence the time to virological suppression within 48 weeks or the probability of virological rebound after successful virological suppression.

Conclusions. The use of emtricitabine instead of lamivudine as part of cART was associated with better virological responses. These findings are relevant for settings with extensive use of lamivudine and for settings where generic lamivudine will be available.

Keywords. HIV-1; antiretroviral therapy; lamivudine; emtricitabine; virological failure.

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Treatment guidelines for human immunodeficiency virus type 1 (HIV-1) consider the nucleoside reverse transcriptase inhibitors (NRTIs) lamivudine and emtricitabine to be interchangeable components in recommended combination antiretroviral therapy (cART) [1–3]. Emtricitabine is frequently used as part of first-line cART with efavirenz and tenofovir in resource-rich settings, whereas lamivudine is more frequently combined with nevirapine and tenofovir in resource-limited settings. Major HIV-1 therapy–related cost savings are possible as generic lamivudine has become available in resource-rich settings [4]. However, the use of generic lamivudine instead of emtricitabine should be cautiously considered if these components do not have comparable effectiveness in clinical use.

The relative effectiveness of lamivudine vs emtricitabine in cART for HIV-1 infection is unclear. Comparisons by randomized trials have suggested lower virological responses in patients on lamivudine-containing NRTI backbone regimens, especially at higher baseline viral loads [5–11] with increased rates of acquired drug resistance [12–14]. Other randomized trials observed no difference in virological responses to lamivudine- vs emtricitabine-containing regimens [15–17]. The available evidence therefore remains inconclusive. The main reason for the presumed clinical equipoise is that not only lamivudine and emtricitabine but also the second NRTI differed in the treatment arms of most clinical trials. As such, the use of NRTI coformulations (with abacavir, zidovudine, or tenofovir) remains a confounder in determining the possible lower potency of lamivudine.

The aim of this study is to compare the virological responses to lamivudine and emtricitabine as part of first-line cART with efavirenz/tenofovir or nevirapine/tenofovir for HIV-1 in ART-naive patients without baseline resistance.

METHODS

Data Source and Regulatory Approval

HIV-infected individuals in the Netherlands are registered in the nationwide cohort maintained by the HIV Monitoring Foundation (Stichting HIV Monitoring), known as the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. ATHENA has collected data of individuals in HIV care since January 1996 from the 26 HIV treatment centers in the Netherlands [18]. HIV patients can opt out from the ATHENA cohort after being informed by their treating physicians on the purpose of data collection. The data collection in the ATHENA cohort is part of standard HIV care and no ethical approval of institutional review boards is needed. The study protocol was peer reviewed and is registered under Stichting HIV Monitoring number I13018 (available at: http://www.hiv-monitoring.nl/english/research/research-projects/).

Study Population

By 31 December 2012, 21 012 HIV-infected individuals were registered in the Netherlands; 20 676 (98.4%) patients consented to inclusion in the ATHENA cohort and subsequent structured prospective data collection [19]. Recorded data included demographics, comorbidities, initial cART, antiretroviral therapy (ART) switches, and clinical, immunological, and virological parameters. The reasons for switching ART were registered by the treating physicians and included, among other reasons, virological failure and toxicity. For this study, we identified HIV-infected adults from ATHENA who initiated lamivudine or emtricitabine in cART with either efavirenz/tenofovir or nevirapine/tenofovir between 1 January 2002 and 31 January 2012. ART-experienced patients and patients with baseline resistance (at least low level) according to the Stanford Database to any component of cART were identified and excluded from the analyses of outcomes.

Study Outcomes

We used a clinical approach to evaluate 5 outcomes. First, virological failure at week 48 after cART initiation was analyzed. Any HIV RNA ≥400 copies/mL within the 48 ± 10-week window defined virological failure. Patients without any HIV RNA in this window were not included in the analysis of this outcome. In addition, all cART discontinuations for registered virological failures or for deaths while the last HIV RNA level was ≥400 copies/mL prior to 48 ± 10 weeks were considered virological failures. HIV RNA copies/mL ≥400 was considered a "viral blip" if preceded and followed by HIV RNA <400 copies/mL. Patients without any HIV RNA levels recorded after cART initiation were considered lost to follow-up. The second outcome was virological suppression and was defined by the time from cART initiation to the first of 2 consecutive HIV RNA levels <400 copies/mL within 48 ± 10 weeks. Third, we analyzed the time to registered virological failure within 240 weeks after the initiation of cART. The time to virological failure was defined by the time from cART initiation to cART switches for registered virological failure or death while HIV RNA was ≥400 copies/mL. Fourth, the time from cART initiation to virological failure within 240 weeks was evaluated after achieving HIV RNA <400 copies/mL first on initial cART. These virological failures after an HIV RNA level <400 copies/mL were defined as rebounds. Last, the HIV-1 reverse transcriptase sequences at cART initiation and failure were evaluated and compared regarding mutations that resulted in at least low-level resistance according to the Stanford Resistance Database [20].

Data were collected on cART, previous ART, drug resistance, age at cART initiation, sex, region of origin, HIV-1 transmission route, hepatitis B /C virus coinfection (HBV/HCV), treatment hospital, last HIV RNA level (continuous until ≥100 000), and CD4 count prior to initiation of cART. The presence of HBV surface antigen, HCV RNA or, if unavailable, HCV antibody

defined HBV and HCV coinfection. Missing baseline HIV RNA (3.5% of total) and CD4 counts (3.9%) were imputed and estimated by age, sex, region of origin, transmission route, HCV, and cART initiation year.

Statistical Analysis

Data were described as means, medians, or numbers with percentages. Adjusted logistic regression models were used to estimate odds ratios (ORs) with 95% confidence intervals (95% CIs) on virological failure at week 48. These models included cART, HIV RNA, CD4 count, region of origin, and all covariates with $P < .1$ in unadjusted analysis of virological failure as fixed effects. The treatment hospitals were included as random covariate. The primary outcome was virological failure at week 48 by on-treatment (OT) analysis. In this analysis, patients with registered cART switches for other reasons than virological failure or loss to follow-up were not considered failures. The ratio of the patients with virological failure (numerator) and the OT population (denominator) defined the virological failure rates.

Three sensitivity analyses were used to evaluate virological failure at week 48. First, any HIV RNA >50 copies/mL instead of ≥400 copies/mL within 48 ± 10 weeks was defined as virological failure. Second, all patients lost to follow-up and all patients who switched cART for other reasons while HIV RNA was ≥400 copies/mL were considered virological failures in modified intent-to-treat (ITT) analyses. Third, propensity score–adjusted models were used to correct for selection bias [21]. The probability of initiating lamivudine or emtricitabine was calculated by all measured covariates in logistic regression models. The propensity scores were included as covariates and inverse weights with cART in logistic regression models to evaluate virological failure within 48 weeks.

Multivariable Cox regression models and Kaplan–Meier estimates were used for the analysis of (1) time to virological suppression within 48 weeks, (2) time to a cART switch for virological failure within 240 weeks, and (3) time to a rebound within 240 weeks. Hazard ratios (HRs) were adjusted for CD4 count and HIV RNA. Patients were censored at cART switches, last HIV RNA, or the end of the study period at week 48 after 31 January 2012. The analyses were done using SPSS software version 21.0 and GraphPad Prism version 5.0.

RESULTS

Cohort Characteristics

A total of 4836 HIV-1–infected patients initiated lamivudine- or emtricitabine-containing cART between 2002 and 2012. Baseline genotyping was available in 2267 patients and 39 patients (1.7%) had at least low-level resistance. Fifty-seven of 4836 patients (1.2%) were ART experienced. The characteristics of the 4740 naive HIV-1–infected patients are provided in Table 1. The patients initiated lamivudine/efavirenz/tenofovir (n = 535), emtricitabine/efavirenz/tenofovir (n = 3343), lamivudine/nevirapine/tenofovir (n = 193), or emtricitabine/nevirapine/tenofovir (n = 669). The mean age in the cohort was 40 years. Overall, patients on emtricitabine compared with lamivudine were more frequently men (88.0% vs 76.4%) having sex with men (69.2% vs 47.0%), from Western countries (70.0% vs 53.7%). The median cART initiation year was 2004 for lamivudine and 2009 for emtricitabine regimens. Patients on emtricitabine had higher median CD4 cell counts (260 vs 184 cells/μL) and lower median HIV RNA (82 173 vs 100 000 copies/mL) than those on lamivudine.

Virological Responses

At week 48, 100 of 4740 patients (2.1%) were lost to follow-up and 831 (17.5%) discontinued cART prior to 48 ± 10 weeks for other reasons than virological failure, predominantly ART toxicity (Supplementary Data). Three hundred sixty-nine patients (7.8%) without HIV RNA recorded in the 48 ± 10-week window were equally distributed among the 4 groups ($P = .077$). The majority of these patients had HIV RNA <400 copies/mL (96.2%) or <50 copies/mL (80.5%) prior to this window. These patients were not included in the OT population, which consisted of 3440 patients.

By week 48, 38 of 352 patients (10.8%) on lamivudine/efavirenz/tenofovir had virological failure compared to 88 of 2437 patients (3.6%) on emtricitabine/efavirenz/tenofovir (OR, 3.23; 95% CI, 2.17–4.81; $P < .001$). Most patients (n = 91, 72.2%) met the definition of virological failure because of registered virological failure before the 48 ± 10-week window. Thirty-five patients were considered to have virological failure because they died with HIV RNA ≥400 copies/mL (n = 9; median baseline CD4 count, 90 cells/μL) or had HIV RNA ≥400 copies/mL in the 48 ± 10-week window (n = 26), including 24 patients on emtricitabine. Twenty-three of these 24 patients had HIV RNA <50 copies/mL with emtricitabine/efavirenz/tenofovir after this window. With nevirapine/tenofovir, 43 of 159 patients on lamivudine (27.0%) and 54 of 492 patients on emtricitabine (11.0%) had virological failure (OR, 3.00; 95% CI, 1.92–4.72; $P < .001$). Most patients were considered failures because of registered virological failure (n = 83 [85.6%]). Fourteen patients were considered failures because they died with HIV RNA ≥400 copies/mL (n = 7; median baseline CD4 count, 80 cells/μL) or had HIV RNA ≥400 copies/mL at 48 ± 10 weeks (n = 7), including 4 patients on emtricitabine. These 4 patients on emtricitabine achieved HIV RNA < 50 copies/mL on initial cART.

The multivariable adjusted ORs on virological failure for patients on lamivudine compared to emtricitabine were 1.78 (95% CI, 1.11–2.84; $P = .016$) with efavirenz/tenofovir and 2.09 (95% CI, 1.25–3.52; $P = .005$) with nevirapine/tenofovir (Table 2). These ORs were adjusted for CD4 count, HIV RNA, region of

Table 1. Baseline Characteristics of Therapy-Naive HIV-Infected Patients (N = 4740) in the ATHENA Cohort

	Efavirenz/Tenofovir					Nevirapine/Tenofovir				
	Lamivudine (n = 535)		Emtricitabine (n = 3343)			Lamivudine (n = 193)		Emtricitabine (n = 669)		
Characteristic	No.	(%)	No.	(%)	*P* Value	No.	(%)	No.	(%)	*P* Value
Male sex	412	(77.0)	2965	(88.7)	<.001	144	(74.6)	565	(84.5)	.002
Age, y, mean (SD)	39	(10)	41	(10)	.001	40	(10)	40	(10)	.906
Start year, median (IQR)	2005	(2004–2006)	2009	(2008–2010)	<.001	2004	(2003–2005)	2009	(2008–2010)	<.001
Documented HIV-1 wild-type	111	(20.8)	1732	(51.8)	<.001	54	(28.0)	321	(47.9)	<.001
Treatment hospital										
<500 patients	24	(4.5)	308	(9.2)		6	(3.1)	36	(5.4)	
500–2000 patients	216	(40.4)	1827	(54.7)		29	(15.0)	329	(49.2)	
>2000 patients	295	(55.1)	1208	(36.1)	<.001	158	(81.9)	304	(45.4)	<.001
Hepatitis B										
Positive	68	(12.7)	237	(7.1)		8	(4.1)	36	(5.4)	
Negative	445	(83.2)	2980	(89.1)		181	(93.8)	611	(91.3)	
Unknown	22	(4.1)	126	(3.8)	<.001	4	(2.1)	22	(3.3)	.527
Hepatitis C										
Positive	36	(6.7)	246	(7.4)		15	(7.8)	50	(7.5)	
Negative	458	(85.6)	2936	(87.8)		164	(85.0)	601	(89.8)	
Unknown	41	(7.7)	161	(4.8)	.021	14	(7.3)	18	(2.7)	.012
Transmission										
MSM	260	(48.6)	2316	(69.3)		82	(42.5)	460	(68.8)	
Heterosexual	212	(39.6)	822	(24.6)		82	(42.5)	164	(24.5)	
Intravenous drug use	16	(3.0)	32	(1.0)		11	(5.7)	13	(1.9)	
Other	6	(1.1)	22	(0.7)		2	(1.0)	5	(0.7)	
Unknown	41	(7.7)	151	(4.5)	<.001	16	(8.3)	27	(4.0)	<.001
Region of origin										
Western countries	278	(52.0)	2351	(70.3)		113	(58.5)	457	(68.3)	
Sub-Saharan Africa	116	(21.7)	337	(10.1)		36	(18.7)	63	(9.4)	
Asia	31	(5.8)	134	(4.0)		4	(2.1)	21	(3.1)	
Latin America	52	(9.7)	238	(7.1)		22	(11.4)	53	(7.9)	
Caribbean	30	(5.6)	130	(3.9)		7	(3.6)	38	(5.7)	
Other	28	(5.2)	153	(4.6)	<.001	11	(5.7)	37	(5.5)	.004
HIV RNA, copies/mL										
<1000	12	(2.2)	71	(2.1)		2	(1.0)	8	(1.2)	
1000–9999	34	(6.4)	310	(9.3)		13	(6.7)	89	(13.3)	
10 000–99 999	212	(39.6)	1414	(42.3)		86	(44.6)	312	(46.6)	
≥100 000	277	(51.8)	1548	(46.3)	.043	92	(47.7)	260	(38.9)	.037
CD4 count, cells/μL										
<100	149	(27.9)	441	(13.2)		45	(23.3)	71	(10.6)	
100–199	147	(27.5)	528	(15.8)		50	(25.9)	108	(16.1)	
200–349	208	(38.9)	1672	(50.0)		83	(43.0)	366	(54.7)	
≥350	31	(5.8)	702	(21.0)	<.001	15	(7.8)	124	(18.5)	<.001

Data are presented as No. (%) unless otherwise specified. Comparisons were done using χ^2 test, independent *t* test, or Mann–Whitney *U* test.

Abbreviations: ATHENA, AIDS Therapy Evaluation in the Netherlands; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; SD, standard deviation.

origin, and all other covariates associated with virological failure in univariable analyses (Supplementary Data). Sensitivity analyses showed consistent virological failure rates if HIV RNA >50 copies/mL at the 48 ± 10-week window defined virological failure (OT), in analyses by ITT and in propensity score–adjusted models (Supplementary Data). Only 6 of 119 patients with an

Table 2. Multivariable Adjusted Logistic Regression Analysis on the Association Between Virological Failure and Combination Antiretroviral Therapy in Treatment-Naive HIV-Infected Patients in the ATHENA Cohort (On-Treatment Population: N = 3440)

	Efavirenz/Tenofovir (n = 2789)			Nevirapine/Tenofovir (n = 651)		
	Virological Failure			Virological Failure		
Characteristic	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value
cART						
Lamivudine	1.78	(1.11–2.84)	.016	2.09	(1.25–3.52)	.005
Emtricitabine[a]	1			1		
HIV RNA, copies/mL						
≥100 000	1.89	(1.24–2.89)	.003	2.35	(1.43–3.86)	.001
<100 000[a]	1			1		
CD4 count, cells/μL						
<100	3.45	(1.75–6.79)	<.001	9.33	(3.56–24.45)	<.001
100–199	1.46	(.72–2.97)	.300	2.56	(.98–6.70)	.055
200–349	0.69	(.35–1.35)	.276	1.42	(.58–3.49)	.440
≥350[a]	1			1		
Age, year increase	0.97	(.96–.99)	.013	. . .		

Abbreviations: ATHENA, AIDS Therapy Evaluation in the Netherlands; cART, combination antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

[a] Reference categories within covariates.

HIV RNA level >50 copies/mL but <400 copies/mL at 48 ± 10 weeks had subsequent registered virological failure. Compared to emtricitabine, the propensity score–adjusted OR (OT) for lamivudine with efavirenz/tenofovir on virological failure was 1.89 (95% CI, 1.20–2.97; $P = .006$). The OR on virological failure for lamivudine with nevirapine/tenofovir was 1.65 (95% CI, .99–2.77; $P = .057$). Similar results were obtained by weighed propensity score models.

The time to virological suppression within 48 weeks was not significantly influenced by including lamivudine or emtricitabine in cART (Figure 1*A*); adjusted HRs were 1.04 (95% CI, .93–1.15; $P = .498$) with efavirenz and 0.96 (95% CI, .79–1.17; $P = .680$) with nevirapine. The HRs for virological failure at <240 weeks were higher on lamivudine vs emtricitabine with efavirenz (2.35; 95% CI, 1.61–3.42) or nevirapine (2.01; 95% CI, 1.36–2.98; Figure 1*B*). However, if HIV RNA <400 copies/mL was achieved on initial cART, no significant differences were observed in rebounds between lamivudine and emtricitabine with efavirenz ($P = .090$) or nevirapine ($P = .255$; Figure 1*C*). The Kaplan–Meier estimate of the percentage of patients still on initial regimen after 240 weeks was 50%: an estimated 26% of patients had switched because of toxicity, 5% because of virological failure, and 19% for other reasons (Figure 2).

Resistance-Associated Mutations

Acquired resistance to reverse transcriptase was evaluated in 267 of 4740 HIV-1–infected patients, including 234 patients with registered virological failure within 240 weeks and 33 patients with HIV RNA ≥400 copies/mL at week 48. At failure, patients on lamivudine regimens had a higher median HIV RNA level of 49 231 copies/mL compared with HIV RNA of 4230 copies/mL on emtricitabine regimens ($P < .001$). Sixty-four of 267 patients had HIV RNA <1000 copies/mL and their genotyping results, if available, were not used. Of these 64 patients, 57 patients (89.1%) were on emtricitabine-containing regimens. Of 203 patients with HIV RNA ≥1000 copies/mL at virological failure, the HIV-1 genotyping results were available for 123 patients. Baseline genotypes that did not show resistance were available in 88 of 123 patients, and these patients were used for analysis of acquired resistance. At least 1 low- or higher level resistance mutation was found in 80 of 88 (90.9%) patients, including 40 of 44 patients on lamivudine and 40 of 44 patients on emtricitabine (Table 3). The proportion of resistance against both NRTIs and NNRTIs was not different between lamivudine-containing (84.1%) and emtricitabine-containing (84.1%) regimens nor was the prevalence of the primary resistance mutations M184V/I and K65R.

DISCUSSION

This study compared the virological responses to lamivudine with emtricitabine as part of first-line cART with efavirenz/tenofovir or nevirapine/tenofovir. The use of lamivudine in both regimens was significantly associated with more virological

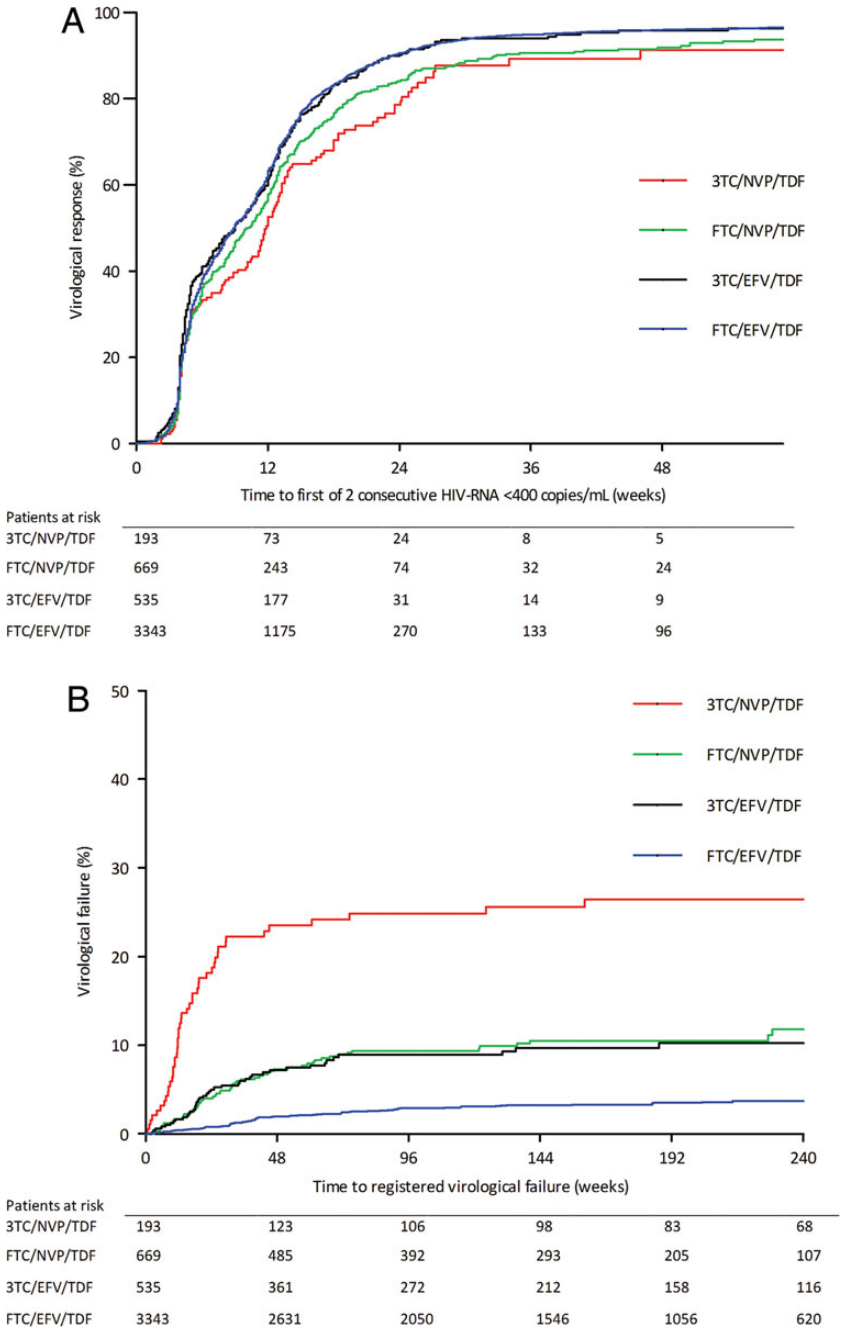
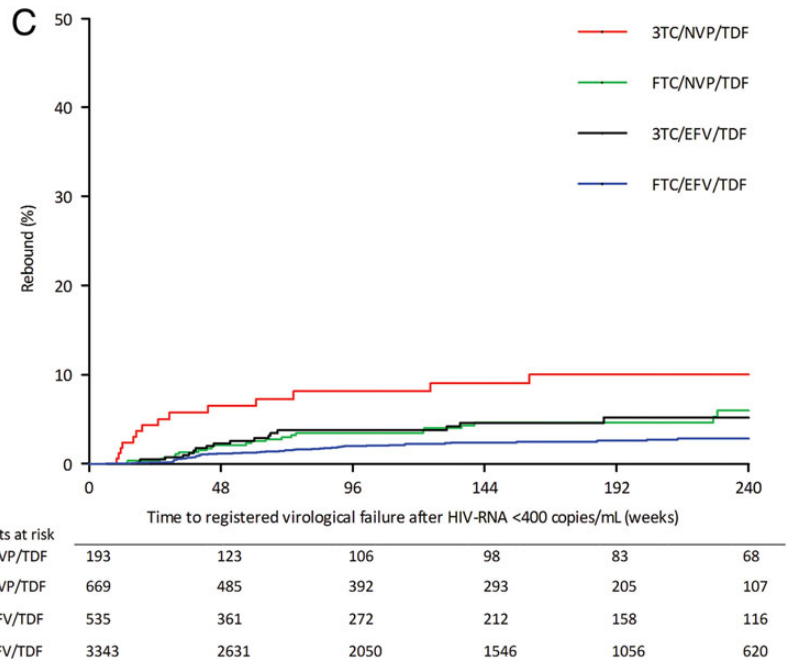


Figure 1. Kaplan–Meier curves of the virological responses to lamivudine (3TC) or emtricitabine (FTC) with efavirenz (EFV)/tenofovir (TDF) (black and blue lines) or nevirapine (NVP)/TDF (red and green lines) in 4740 antiretroviral therapy (ART)–naive human immunodeficiency virus (HIV) type 1–infected patients from the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. Hazard ratios (HRs) are adjusted for baseline CD4 cell count and HIV RNA < or ≥100 000 copies/mL. *A*, Time to virological suppression, defined as the first of 2 consecutive HIV RNA levels <400 copies/mL within 48 weeks on initial combination ART (cART). The adjusted HR on virological suppression were not significantly different between 3TC and FTC with EFV/TDF (1.04; 95% confidence interval [CI], .93–1.15; $P = .498$) and NVP/TDF (0.96; 95% CI, .79–1.17; $P = .680$). *B*, The time to cART switches for registered virological failure in the ATHENA cohort within 240 weeks after initiating cART. The adjusted HR of cART switches for virological failure were significantly increased for patients on 3TC with EFV/TDF (2.35; 95% CI, 1.61–3.42; $P = .001$) and NVP/TDF (2.01; 95% CI, 1.36–2.98; $P < .001$).

failure within 48 and 240 weeks of cART. Patients on lamivudine-containing cART had higher HIV RNA levels at virological failure. However, the time to virological suppression and the probability of rebound after successful virological suppression were comparable regardless of including lamivudine or emtricitabine in initial cART.



Patients at risk						
3TC/NVP/TDF	193	123	106	98	83	68
FTC/NVP/TDF	669	485	392	293	205	107
3TC/EFV/TDF	535	361	272	212	158	116
FTC/EFV/TDF	3343	2631	2050	1546	1056	620

Figure 1 continued. *C*, Time to cART switches for registered virological failure in the ATHENA cohort following successful virological suppression to HIV RNA <400 copies/mL first on initial cART (rebounds). No significant differences in adjusted HR on rebounds within 240 weeks were observed between 3TC with EFV/TDF (1.60; 95% CI, .93–2.76; $P = .090$) and NVP/TDF (1.48; 95% CI, .75–2.90; $P = .255$) once HIV RNA was suppressed to <400 copies/mL first.

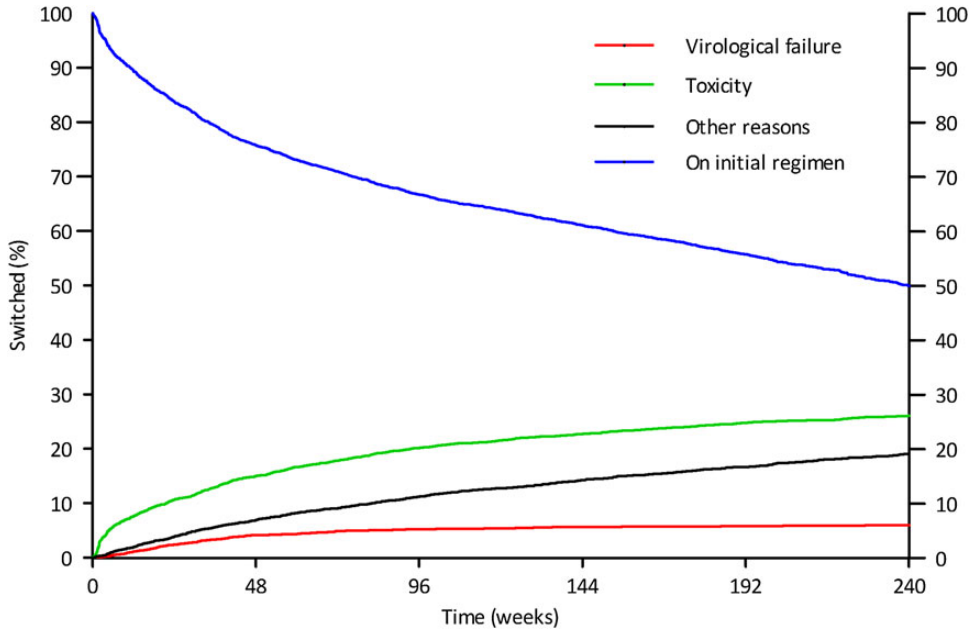


Figure 2. Kaplan–Meier estimates of the percentages of 4740 human immunodeficiency virus type 1–infected patients from the AIDS Therapy Evaluation in the Netherlands cohort who remained on initial lamivudine- or emtricitabine-containing regimens (blue line) and who switched combination antiretroviral therapy (cART) for any reason (red, green, and black lines) at week 240 after cART initiation.

Table 3. Acquired At Least Low Level Resistance According to Stanford HIV Resistance Database to Any Component of Combination Antiretroviral Therapy in Reverse Transcriptase of HIV-1–Infected Patients Experiencing Virological Failure With HIV RNA ≥1000 Copies/mL and Genotyped Baseline Wild-Type HIV-1 (n = 88)

	Efavirenz/Tenofovir				Nevirapine/Tenofovir				Overall			
	Lamivudine (n = 9)		Emtricitabine (n = 16)		Lamivudine (n = 35)		Emtricitabine (n = 28)		Lamivudine (n = 44)		Emtricitabine (n = 44)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
NRTI RAM												
K65R	2	(22.2)	3	(18.8)	13	(37.1)	10	(35.7)	15	(34.1)	13	(29.5)
K70E	0	(0)	0	(0)	0	(0)	1	(3.6)	0	(0)	1	(2.3)
Y115F	0	(0)	0	(0)	0	(0)	2	(7.1)	0	(0)	2	(4.5)
M184I/V	4	(44.4)	9	(56.2)	23	(65.7)	21	(75.0)	27	(61.4)	30	(68.2)
NNRTI RAM												
A98G	1	(11.1)	1	(6.2)	0	(0)	0	(0)	1	(2.3)	1	(2.3)
K101E	1	(11.1)	1	(6.2)	2	(5.7)	3	(10.7)	3	(6.8)	4	(9.1)
K103N	2	(22.2)	10	(62.5)	6	(17.1)	5	(17.9)	8	(18.2)	15	(34.1)
V106A/M	1	(11.1)	1	(6.2)	6	(17.2)	2	(7.1)	7	(15.9)	3	(6.8)
Y181C	0	(0)	0	(0)	20	(57.1)	20	(71.4)	20	(45.5)	20	(45.5)
Y188C/L	2	(22.2)	2	(12.5)	4	(11.4)	1	(3.6)	6	(13.6)	3	(6.8)
G190A/E/S	3	(33.3)	2	(12.5)	5	(14.3)	4	(14.3)	8	(18.2)	6	(13.6)
P225H	0	(0)	3	(18.8)	0	(0)	0	(0)	0	(0)	3	(6.8)
F227L	0	(0)	0	(0)	2	(5.7)	0	(0)	2	(4.5)	0	(0)
K238T	0	(0)	1	(6.2)	0	(0)	0	(0)	0	(0)	1	(2.3)
Y318F	0	(0)	0	(0)	1	(2.9)	0	(0)	1	(2.3)	0	(0)
Resistance patterns												
No RAM	2	(22.2)	2	(12.5)	2	(5.7)	2	(7.1)	4	(9.1)	4	(9.1)
≥1 NRTI/NNRTI RAM	7	(77.8)	14	(87.5)	33	(94.3)	26	(92.9)	40	(90.9)	40	(90.9)
≥1 NRTI and ≥1 NNRTI RAM	6	(66.7)	12	(75.0)	31	(88.6)	25	(89.3)	37	(84.1)	37	(84.1)

Data are presented as No. (%).

Abbreviations: NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation.

This study is the largest to date to directly compare lamivudine with emtricitabine in ART-naive patients and the first from a resource-rich setting. In vitro observations of lamivudine's lower efficacy against HIV-1 preceded a limited number of clinical studies on this subject to date [22–24]. The high virological failure rate we observed in patients on lamivudine/nevirapine/tenofovir is consistent with the results of 2 prematurely terminated prospective trials. In these studies, a 25%–30% virological failure rate was observed on this regimen, although only 59 patients were included in both studies combined [25, 26]. To our knowledge, only 3 studies compared lamivudine with emtricitabine as part of otherwise identical cART for ART-naive patients [27–29]. Their generalizibility to other HIV-1 populations, like ATHENA, remains questionable because these 3 studies were all conducted in sub-Saharan populations of resource-limited settings (South-Africa, Nigeria, Zambia). Only 2 were randomized clinical trials, of which 1 included stavudine, an NRTI that should no longer be used, in cART [27]. The other study was a prospective open-label randomized clinical trial on 332 predominantly female Zambians that did not show a significant difference in virological failure between lamivudine and emtricitabine with efavirenz/tenofovir. However, the power to detect a clinically significant difference in virological failure with the included number in this study is problematic [29]. The only randomized trial from a resource-rich setting that directly compared lamivudine with emtricitabine was done in already HIV RNA–suppressed patients [30]. All other randomized trials that included lamivudine or emtricitabine in the treatment arms for ART-naive patients had other NRTI variations as well [5–10, 15, 16]. Given the limitations of the trials that have directly compared lamivudine with emtricitabine, an adequately powered, double-blind randomized clinical trial is needed and should directly compare lamivudine with emtricitabine as part of currently recommended cART regimens. In certain resource-limited settings, this often still includes nevirapine.

Our study has several strengths. We used the data of an ongoing nationwide cohort with a well-established infrastructure and data collection. The diminished virological responses to

lamivudine in this large cohort were consistently found in all models and sensitivity analyses. Our study methods support the intended clinical relevance of the study. Virological failure was primarily analyzed by OT instead of ITT analysis because we considered an ITT analysis a method that is too conservative to evaluate drug effectiveness outside the context of a clinical trial. Nonetheless, the included sensitivity analysis by ITT showed comparable differences in virological failure. In our opinion, the use of HIV RNA ≥400 copies/mL instead of lower thresholds to evaluate virological failure improved the interpretation of the drugs' clinical effectiveness. Detectable HIV RNA 50–399 copies/mL could represent other situations (eg, temporary incompliance) rather than true virological failure. This is supported by the observation that the large majority of patients with HIV RNA 50–399 copies/mL at week 48 do not have virological failure in follow-up but resuppressed <50 copies/mL on initial regimens. Last, the decreased effectiveness with lamivudine appears to be independent of the NNRTI background regimens; all patients on efavirenz received once-daily cART regardless of lamivudine or emtricitabine.

Several limitations should also be noticed. First, we realize that treatment guidelines have changed during the study period, particularly on CD4 counts at cART initiation [31]. In the multivariable models, we adjusted for CD4 counts and other observed differences in patient characteristics. Second, the calendar year at the start of cART only minimally overlapped between the lamivudine and emtricitabine groups and as such could not be corrected for in the multivariable models. During the studied time frame, differences between treatment centers or between physicians may have influenced the results. Two factors make the influence of these potential confounders less likely: HIV care in the Netherlands is highly organized using internationally accepted guidelines, and the treatment centers have been accounted for in the models. Third, an observational study cannot correct for unmeasured confounders or balance known and unknown baseline differences. These factors can only be controlled for in a randomized trial. Furthermore, no data on medication adherence were available and adherence could have differed, as no single-tablet regimen exists that includes tenofovir and lamivudine. However, the large majority of patients in our cohort did not initiate emtricitabine with efavirenz/tenofovir as a single-tablet regimen but started Truvada with efavirenz. Therefore, the pill count differed by only 1 tablet (2 vs 3) in a once-daily regimen. As the observed virological responses were consistent on efavirenz and nevirapine, we do not consider adherence to be a major explanatory factor of our observations. Finally, resistance data were available in only 50% of patients at baseline and at the time of virological failure and should be interpreted cautiously with respect to selection bias for resistance testing at time of failure.

Our study could have important implications. The presumed clinical equivalence of lamivudine and emtricitabine in treatment guidelines could have a significant impact on HIV-1 care, as generic lamivudine has become available. The observed increased virological failure rate on recommended cART that includes generic lamivudine instead of emtricitabine could result in additional morbidity and costs. Whether these additional costs will exceed initial savings by using generic lamivudine is unknown. From a public health perspective, in particular in settings without routine HIV RNA monitoring, transmission of resistant HIV-1 may be another consequence. On the other hand, as we observed no difference in virological failure once HIV RNA was <400 copies/mL, a switch to lamivudine once patients are virologically suppressed on an emtricitabine-based regimen may be acceptable.

In conclusion, our findings add to the evidence that lamivudine and emtricitabine may not be interchangeable in recommended first-line cART. The use of emtricitabine was associated with better virological responses compared with lamivudine. As the potential implications are substantial, a randomized clinical trial is urgently needed.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. C. R., L. G., and B. J. A. R. designed the study. A. F. and M. S. collected and analyzed the genotypic resistance patterns. C. R., A. F., D. A. M. C. V., A. V., M. S., L. G., and B. J. A. R. analyzed and interpreted the data. C. R. and L. G. performed the statistical analysis. C. R. and B. J. A. R. wrote the first version of the manuscript. A. V., D. A. M. C. V., M. S., and L. G. critically revised the first version of the manuscript. C. R. and B. J. A. R. wrote the final version of the manuscript. The final version of the manuscript was reviewed and approved by all authors. We thank Charles A. B. Boucher for important intellectual input and Rosa Meijer for constructive statistical discussions.

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APPENDIX

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