Comparison of Abacavir/Lamivudine and Tenofovir/Emtricitabine Among Treatment-Naive HIV-Infected Patients Initiating Therapy

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Background: Controversy about the relative performance of abacavir (ABC)/lamivudine (3TC) and tenofovir (TDF)/emtricitabine (FTC) in initial combination antiretroviral therapy (cART) exists.

Methods: We compared the times to regimen failure (composite of virologic failure or switching/stopping nucleosides for any reason) according to nucleoside backbone in treatment-naive patients starting cART in a retrospective observational cohort study. Additional endpoints included virologic failure, switching/stopping nucleosides for nonvirologic reasons, and virologic suppression. Treatment-naive noninjection drug user individuals in the Canadian Observational Cohort initiating ABC/3TC-containing or TDF/FTC-containing cART with efavirenz, nevirapine, lopinavir/ritonavir, or atazanavir/-ritonavir with ≥6 months follow-up were included. Multivariable proportional hazards regression models accounting for competing risks were used to model outcomes.

Results: One thousand seven hundred sixty-four individuals (588 ABC/3TC, 1176 TDF/FTC) were included. Median (interquartile range) follow-up times were 34 (23–50) and 20 (13–30) months, respectively. Time to regimen failure was similar for ABC/3TC versus TDF/FTC [adjusted hazard ratio, (aHR) = 0.96, 95% CI = 0.80 to 1.17] after adjusting for baseline viral load (VL), sex, province, third antiretroviral agent, year of cART initiation, HLA-B*5701 test availability, and rate of VL testing. No differences were observed in time to virologic failure (aHR = 0.84, 95% CI = 0.58 to 1.20), switching/stopping nucleosides for nonvirologic reasons (aHR = 1.02, 95% CI = 0.81 to 1.28), or virologic suppression (aHR = 0.96, 95% CI = 0.83 to 1.10). There was no statistical interaction between backbone and baseline VL for any outcome. Results were similar when stratified by baseline VL ≤ 100,000 or > 100,000 copies per milliliter.

Conclusions: In our naive noninjection drug user HIV-infected patients starting cART, there was no difference in time to regimen failure, virologic failure, switching/stopping nucleosides, or virologic suppression with ABC/3TC versus TDF/FTC.

Key Words: abacavir, failure, nucleoside reverse transcriptase inhibitors, switch, tenofovir, virologic suppression

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INTRODUCTION

Selecting the optimal combination antiretroviral therapy (cART) regimen for treatment-naive HIV-infected patients is a complex process that must balance efficacy with safety and tolerability. Abacavir/lamivudine (ABC/3TC) and tenofovir/emtricitabine (TDF/FTC) remain the most commonly recommended nucleoside reverse transcriptase inhibitor (NRTI) backbones in current HIV treatment guidelines.[1–4]

Recent clinical trial data have raised concerns about their relative risks and benefits. In the ACTG 5202 trial, individuals with baseline HIV-1 plasma RNA above 100,000 copies per milliliter who were randomized to ABC/3TC experienced a significantly shorter time to virologic failure and to safety events than those on TDF/FTC, prompting the data safety

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Additional research team members are listed in the Appendix section.

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monitoring board to recommend premature discontinuation of further study of ABC/3TC in the high viral load (VL) stratum.[5] Yet differences in virologic efficacy were not observed in the low VL stratum (baseline HIV plasma RNA < 100,000 copies/mL),[6] consistent with the HEAT trial which similarly randomized treatment-naive individuals to one of these backbones with lopinavir/ritonavir and showed noninferiority.[7]

Differences may also exist regarding the relative safety and tolerability of these backbones. For instance, the abacavir hypersensitivity reaction (HSR) is a rare but potentially life-threatening reaction typically occurring within the first 6 weeks of abacavir therapy, and which, if suspected, represents an absolute indication for discontinuing that medication.[8] Presence of the major histocompatibility complex allele HLA-B*5701 is strongly associated with abacavir HSR with a negative predictive value of 100%, and genetic screening for this allele prior to initiation of abacavir-containing regimens dramatically decreases the incidence of HSR and is cost-effective.[9] Such testing is now recommended as part of the standard of care in resource-rich countries, but may not be routinely available in some settings.

Another safety concern is that the D:A:D study, a large observational database, and post hoc analyses from the SMART trial, a trial of treatment interruption, have described an increased risk of myocardial infarction associated with recent or current abacavir use. This signal has also been seen in other cohorts, but neither in randomized studies of abacavir nor in a recent FDA meta-analysis of randomized trials.[10–13]

On the basis of these findings, ABC/3TC has been repositioned as an "alternative" dual fixed-dose NRTI option for the treatment of naive HIV-infected patients in the United States Department of Health and Human Services HIV treatment guidelines and in the International AIDS Society-USA HIV treatment guidelines,[1,14] yet it continues as a "preferred" option in international and European guidelines.[2–4] Whether there are true differences in the efficacy, safety and tolerability of these backbones remains unclear. Any such differences may impact on the likelihood of switching or stopping therapy, and such regimen changes are important as they burden the patient and health care system by complicating patient care, requiring additional clinic visits, and potentially introducing new toxicities that may impact adherence.

We therefore undertook a retrospective analysis of our cohort of Canadian HIV-infected patients to compare the time to switching or stopping NRTI backbone for any reason among ART-naive adults starting ABC/3TC or TDF/FTC-containing regimens. In further analyses, we considered whether switches/stops were due to virologic failure or other reasons. Finally, because it is also unclear whether there are differences in the time to virologic suppression between these backbones, and because there may be theoretical benefits to rapidly achieving undetectable plasma HIV-1 RNA levels in select situations, we further evaluated the time to virologic suppression between backbones.

METHODS

Cohort Description

The Canadian Observational Cohort (CANOC) Collaboration is an observational study of antiretroviral-naive HIV-infected patients initiating cART after January 1, 2000. The collaboration is open to Canadian HIV treatment cohorts with at least 100 eligible patients and to date includes 8 cohorts from Ontario, Quebec, and British Columbia. Data from British Columbia are obtained through a population-based database of all HIV-infected individuals receiving cART in the province, whereas data from Ontario and Quebec come from clinic cohorts. Criteria for inclusion into CANOC are documented HIV infection, residence in Canada, age 18 years and older, initiation of a first antiretroviral regimen comprised of at least 3 individual agents, and at least 1 measurement of HIV-1 RNA and CD4 cell count within 6 months before initiating cART. Patient selection and data extraction are performed at data centres of the participating cohorts. Nonnominal data from each cohort on a predefined set of demographic, laboratory, and clinical variables are then pooled and analyzed at the Project Data Centre in Vancouver, British Columbia. VL was measured with the branched DNA assay in Ontario and Quebec and the Ultrasensitive Amplicor assay in British Columbia. This analysis covered January 1, 2000, to August 22, 2010. All participating cohorts received approval from their institutional ethics boards to contribute nonnominal patient-specific data.

Study Participant Eligibility Criteria

Participants were eligible for inclusion in this analysis if they were antiretroviral naive with baseline VL >50 copies per milliliter (within 6 months before the date of cART initiation), first started ABC/3TC-containing or TDF/FTC-containing cART after January 1, 2000, in combination with efavirenz, nevirapine, lopinavir/ritonavir, or atazanavir/ritonavir (because these were the agents most commonly used with these NRTIs during the study period), had no known history of injection drug use, and had initiated cART ≥6 months before the end of the study period (before February 27, 2009, for British Columbia, February 17, 2010, for Ontario, and September 15, 2009, for Quebec). ABC/3TC use could include both twice daily and fixed-dose once-daily formulations. TDF/FTC use was tenofovir DF 300 mg plus emtricitabine 200 mg once daily as a fixed-dose formulation tablet. Individuals using more than 3 antiretroviral agents, not counting low-dose ritonavir, were excluded. The dates NRTI formulations became available in Canada are June 1999 for abacavir, August 2005 for coformulated ABC/3TC, March 2004 for tenofovir, April 2006 for coformulated TDF/FTC, and October 2007 for coformulated TDF/FTC/EFV.

HLA Screening

Because HLA-B*5701 testing could be an important determinant of discontinuing abacavir, the availability of this testing was considered as a covariate in the analyses. HLA-B*5701 screening became available in March 2006 in Ontario and Quebec, and in October 2007 in British Columbia. This dichotomous variable was thus designated "yes" for participants starting therapy after these dates and "no" otherwise. The procedures for developing this testing service in Canada and for implementing quality control are detailed elsewhere.[15] Before the availability of this testing, the standard of care was to counsel patients about abacavir HSR and to monitor clinically for suggestive signs and symptoms. Individual patient-level data on HLA-B*5701 status was not available.

Statistical Analysis

Demographic and clinical characteristics were characterized using descriptive statistics and compared using χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Baseline CD4 count and VL were defined as the closest values within 180 days before starting therapy.

Multivariable competing risks proportional hazards regression models were used to model time to each outcome,[16] with use of ABC/3TC or TDF/FTC as the primary predictor variable. Other covariates included in the models were baseline VL (above or below 100,000 copies/mL), third antiretroviral agent, the interaction of NRTI backbone with baseline VL, province of Canada, calendar year of ART initiation, and availability of HLA-B*5701 testing (defined as initiation of cART after March 2006 for Ontario and Quebec participants and after October 2007 for British Columbia participants). Rate of VL monitoring (<3, 3–4, 4–6, or >6 measurements per year) was also included in the models because prior work has shown this to vary by province.[17] Age, sex, hepatitis C coinfection, history of AIDS-defining illness, and baseline CD4 count were also considered for inclusion in the multivariate model. Each analysis was repeated after stratifying by baseline VL (≤100,000 copies/mL or >100,000 copies/mL). Cumulative incidence function plots, the competing risk analogy to Kaplan–Meier curves, were used to display probabilities of achieving outcomes over time and were compared between subgroups using Gray test.[18] Cumulative incidence function plots are less than or equal to the inverse of Kaplan–Meier curves due to the consideration of the competing risks.

The primary outcome was the time to regimen failure, defined as the composite of virologic failure, or switching or stopping ABC/3TC or TDF/FTC for any other reason. Because there are numerous definitions of virologic failure in the literature, we employed the definition used in the ACTG 5202 trial to facilitate comparison of our findings. Thus, failure was considered to have occurred if VL ≥1000 copies per milliliter at or after week 16 but before week 24, or VL ≥200 copies per milliliter at or after week 24.[5] Participants who did not experience virologic failure and who maintained their original regimen were censored at their last available VL measurement. Participants who switched or stopped the third drug were considered to have met a competing risk because such changes in antiretroviral therapy may impact on the outcome of interest. Addition of another antiretroviral agent was considered a switch.

In secondary analyses, we considered each component of the composite primary endpoint separately using survival models accounting for competing risks. First, we compared the time to virologic failure as defined above. Individuals who did not experience virologic failure and who maintained their original regimen were censored at their last available VL measurement. Individuals who switched/stopped therapy were considered to have met a competing risk.

Next, we compared the time to switching or stopping NRTI backbone for reasons other than virologic failure according to receipt of ABC/3TC or TDF/FTC. Individuals who experienced virologic failure or switched their third drug before switching or stopping their NRTI backbone were considered to have met a competing risk.

The final secondary analysis was the time to virologic suppression (defined as 2 consecutive VL <50 copies/mL at least 1 month apart) according to NRTI backbone. Participants who failed to suppress but continued on their prescribed regimen were censored at their last VL measurement, while those who switched/stopped their regimen were considered to have met a competing risk. The proportion of participants achieving VL <50 copies per milliliter at 24 weeks was calculated using an intention to treat, missing = failure approach. Because the duration of follow-up beyond 6 months for each patient was different, the proportion of patients achieving virologic suppression on each regimen at further time points and the median time to virologic suppression are not reported.

RESULTS

Study Population

In total, 1764 individuals (588 ABC/3TC, 1176 TDF/FTC) were included. Median (IQR) duration of follow-up was longer for the ABC/3TC group at 34 (23–50) versus 20 (13–30) months for the TDF/FTC group ($P < 0.001$). Demographic and clinical characteristics of the study population are summarized in Table 1. ABC/3TC users were more likely to have baseline VL above 100,000 copies per milliliter and initiated cART 2 years earlier than TDF/FTC users. There was more efavirenz (likely due to the fixed-dose combination tablet Atripla) and less atazanavir/ritonavir use in the TDF/FTC group, and TDF/FTC users were more likely to reside in British Columbia and less likely to reside in Ontario.

Time to Regimen Failure

In univariate analyses, the use of ABC/3TC relative to TDF/FTC was associated with an increased hazard of regimen failure [hazard ratio (HR) = 1.19, 95% CI = 1.01 to 1.39], as were female sex, residence in Ontario or Quebec, hepatitis C positivity, and boosted protease inhibitor (PI) use (Table 2). In the multivariate model, there was no difference in time to regimen failure associated with ABC/3TC use [adjusted hazard ratio (aHR) = 0.96, 95% CI = 0.80 to 1.17]. In this model, only female sex, residence in Ontario or Quebec, and boosted PI use were associated with a statistically significant increase in hazard. Importantly, no statistical interaction between NRTI and baseline VL was observed, and results were similar after stratifying by baseline HIV VL, with ABC/3TC having an aHR = 1.02 (95% CI = 0.78 to 1.32) relative to TDF/FTC for the low baseline VL stratum and aHR = 0.92 (95% CI = 0.69 to 1.22) for the high baseline VL stratum. The probabilities of regimen failure are shown according to initial nucleoside backbone and baseline VL (greater or less than 100,000 copies/mL) in Figure 1A, with no overall differences between the 4 groups (Gray test $P = 0.27$).

Time to Virologic Failure

No difference was seen in the time to virologic failure between NRTI backbones, with the HR = 1.11 (95% CI = 0.81 to 1.51) for ABC/3TC relative to TDF/FTC in univariate analysis and aHR = 0.84 (95% CI = 0.58 to 1.20) in multivariate analysis. No difference was seen in the time to virologic failure between NRTI backbones, with the HR=1.11 (95% CI=0.81 to 1.51) for ABC/3TC relative to TDF/FTC in univariate analysis and

TABLE 1. Baseline Characteristics of Study Participants

Variable	Total, (n = 1764)	ABC/3TC*, (n = 588)	TDF/FTC*, (n = 1176)	*P*
Age (yrs)		40 (34–46)	41 (34–48)	0.08
Sex				
Male	1572	507 (86.2)	1065 (90.6)	0.007
Female	192	81 (13.8)	111 (9.4)	
Province				
British Columbia	670	159 (27.0)	511 (43.5)	<0.001
Ontario	710	298 (50.7)	412 (35.0)	
Quebec	384	131 (22.3)	253 (21.5)	
Hepatitis C co-infection				
Yes	108	21 (3.6)	87 (7.4)	<0.001
No	1325	407 (69.2)	918 (78.1)	
Unknown	331	160 (27.2)	171 (14.5)	
Prior AIDS-defining illness	169	56 (9.5)	113 (9.6)	0.999
Baseline CD4 cell count (cells/mm^3)		217 (145–280)	230 (150–310)	0.007
Baseline HIV VL				
Below 100,000 copies/mL	1002	313 (53.2)	689 (58.6)	0.04
Above 100,000 copies/mL	762	275 (46.8)	487 (41.4)	
Third antiretroviral agent				
Atazanavir/ritonavir	525	227 (38.6)	298 (25.3)	<0.001
Efavirenz	774	183 (31.1)	591 (50.3)	
Lopinavir/ritonavir	352	130 (22.1)	222 (18.9)	
Nevirapine	113	48 (8.2)	65 (5.5)	
Class of 3rd antiretroviral				
NNRTI	887	231 (39.3)	656 (55.8)	<0.001
Boosted PI	877	357 (60.7)	520 (44.2)	
Calendar year of starting cART		2006 (2005–2007)	2008 (2007–2008)	<0.001
ART initiation after HLA test availability				
No	464	250 (42.5)	214 (18.2)	<0.001
Yes	1300	338 (57.5)	962 (81.8)	
Rate of VL testing (per year)				
Less than 3	230	81 (13.8)	149 (12.7)	0.007
3 to 4	402	160 (27.2)	242 (20.6)	
Greater than 4–6	692	218 (37.1)	474 (40.3)	
Greater than 6	440	129 (21.9)	311 (26.4)	

*Values are median (interquartile range) or frequency (percent).
NNRTI, nonnucleoside reverse transcriptase inhibitor.

aHR=0.84 (95% CI=0.58 to 1.20) in multivariate analysis (Table 3). Use of a boosted PI was associated with a higher hazard of virologic failure in both univariate and multivariate analyses. Again, there was no evidence of statistical interaction between NRTI and baseline VL, and results were similar after stratifying by baseline HIV VL (aHR = 0.96, 95% CI = 0.58 to 1.61 for low VL stratum and aHR = 0.81, 95% CI = 0.48 to 1.36 for high VL stratum). The probabilities of regimen failure are shown according to initial nucleoside backbone and baseline VL in Figure 1B, with no overall differences between the 4 groups (Gray test $P = 0.15$).

Time to Switching or Stopping NRTIs

The time to switching or stopping NRTIs was significantly different with use of ABC/3TC relative to TDF/FTC in univariate analyses, with a HR of 1.25 (95% CI = 1.04 to 1.50), but not multivariate analysis, with aHR = 1.02 (95% CI = 0.81 to 1.28) (Table 4). Variables associated with an increased hazard of switching/stopping NRTIs in both univariate and adjusted analyses included female sex, residence in Ontario or Quebec, and use of lopinavir/ritonavir. The probabilities of switching or stopping ABC/3TC or TDF/FTC is shown according to initial nucleoside backbone and baseline VL in Figure 1C. Stratified analyses showed similar times to this outcome for ABC/3TC versus TDF/FTC in the low VL (aHR = 1.04, 95% CI = 0.76 to 1.42) and high VL (aHR = 0.99, 95% CI = 0.71 to 1.38) groups. There was no evidence of statistical interaction between NRTI backbone and baseline VL.

Data regarding reasons for switching/stopping antiretrovirals were not available. To investigate whether NRTI switches/stops could be attributable to suspected abacavir HSR, we determined the timing of these events in post hoc analyses, because abacavir HSR typically occurs in the first 6 weeks of treatment. Among the 293 participants who stopped cART, median (IQR) follow-up at the time of the stop was 9 (6–23) months in the 126 ABC/3TC users and 6 (3–11) months in the 167 TDF/FTC users. However, among the 179 who switched

TABLE 2. Survival Analysis Model Results for Time to Regimen Failure

Variable	Unadjusted Hazard Ratio (95% CI)	*P*	Adjusted Hazard Ratio (95% CI)	*P*
Nucleoside backbone				
TDF/FTC	1.00	—	1.00	—
ABC/3TC	1.19 (1.01 to 1.39)	0.03	0.96 (0.80 to 1.17)	0.70
Baseline HIV VL				
Below 100,000 copies/mL	1.00	—	1.00	—
Above 100,000 copies/mL	1.03 (0.88 to 1.20)	0.71	1.04 (0.89 to 1.22)	0.64
Baseline CD4 count (per 100 cells/mm^3)	1.00 (0.94 to 1.07)	0.97	—	—
Age (per 10-year increment)	0.94 (0.87 to 1.02)	0.13	—	—
Sex				
Female	1.00	—	1.00	—
Male	0.57 (0.45 to 0.71)	<0.001	0.57 (0.45 to 0.72)	<0.001
Province				
British Columbia	1.00	—	1.00	—
Ontario	1.69 (1.41 to 2.02)	<0.001	1.96 (1.56 to 2.46)	<0.001
Quebec	1.79 (1.44 to 2.23)	<0.001	2.01 (1.56 to 2.60)	<0.001
Hepatitis C coinfection				
No	1.00	—	—	—
Yes	1.66 (1.26,2.18)	<0.001	—	—
Unknown	1.74 (1.45,2.08)	<0.001	—	—
Prior AIDS-defining illness	1.25 (0.99 to 1.59)	0.06	—	—
Third antiretroviral agent				
Efavirenz	1.00	—	1.00	—
Nevirapine	0.93 (0.64 to 1.35)	0.70	0.86 (0.59 to 1.26)	0.44
Atazanavir/ritonavir	1.33 (1.11 to 1.60)	0.003	1.33 (1.09 to 1.62)	0.004
Lopinavir/ritonavir	1.45 (1.19 to 1.78)	<0.001	1.46 (1.19 to 1.79)	<0.001
Calendar year (per year)	0.98 (0.94 to 1.02)	0.38	1.00 (0.93 to 1.08)	0.97
ART initiation after HLA test availability	1.17 (0.98 to 1.40)	0.08	0.90 (0.68 to 1.18)	0.43
Rate of VL testing (per year)				
Less than 3	1.00	—	1.00	—
3–4	0.91 (0.70 to 1.17)	0.46	0.91 (0.69 to 1.18)	0.47
Greater than 4–6	0.90 (0.71 to 1.14)	0.39	1.03 (0.80 to 1.33)	0.79
Greater than 6	1.16 (0.90 to 1.49)	0.24	1.41 (1.07 to 1.86)	0.02

NRTI backbones, median (IQR) follow-up times were 1 (0–7) month in the 76 ABC/3TC users and 3 (1–10) months in the 103 TDF/FTC users.

Because concerns about the cardiovascular risk profile of abacavir were first reported in February 2008[19] and could have prompted some to switch off this drug, we further determined the distribution of calendar dates at which participants switched or stopped ABC/3TC in post hoc analyses. The median (IQR) month of switching/stopping was May 2006 (March 2005, March 2008) for ABC/3TC and June 2008 (December 2007, March 2009) for TDF/FTC.

Because a switch in cART may occur in women who become pregnant without necessarily signifying a deficiency of regimen (eg. switching to zidovudine due to experience with this drug in pregnancy), we further determined the nature of regimen changes among females in post hoc analysis. Only 1 woman switched NRTIs onto a zidovudine-containing regimen after starting on TDF/FTC.

Time to Virologic Suppression

The probability of achieving VL <50 copies per milliliter at 24 weeks was 0.55 for ABC/3TC and 0.60 for TDF/FTC arm using an intention to treat, missing = failure approach. Among participants achieving virologic suppression, the median (IQR) time to virologic suppression was 4 (3–6) months for ABC/3TC and 4 (2–5) months for TDF/FTC.

The time to virologic suppression did not differ according to use of ABC/3TC relative to TDF/FTC in either the univariate (HR = 0.92, 95% CI = 0.83 to 1.03) or multivariate (aHR = 0.96, 95% CI = 0.83 to 1.10) models (full data not shown). There was no evidence of statistical interaction between nucleoside backbone and baseline VL in either univariate or multivariate analysis, and results were similar after stratifying for low baseline VL (aHR = 0.95, 95% CI = 0.79 to 1.14) and high baseline VL (aHR = 0.97, 95% CI = 0.79 to 1.20). The probabilities of virologic suppression are shown according to initial nucleoside backbone and baseline VL in Figure 1D, with a statistically significant increase in the time to suppression between groups driven by differences in baseline VL (Gray test $P < 0.001$).

DISCUSSION

In our cohort of 1764 treatment-naive HIV-infected non-injection drug user patients starting either ABC/3TC or TDF/FTC

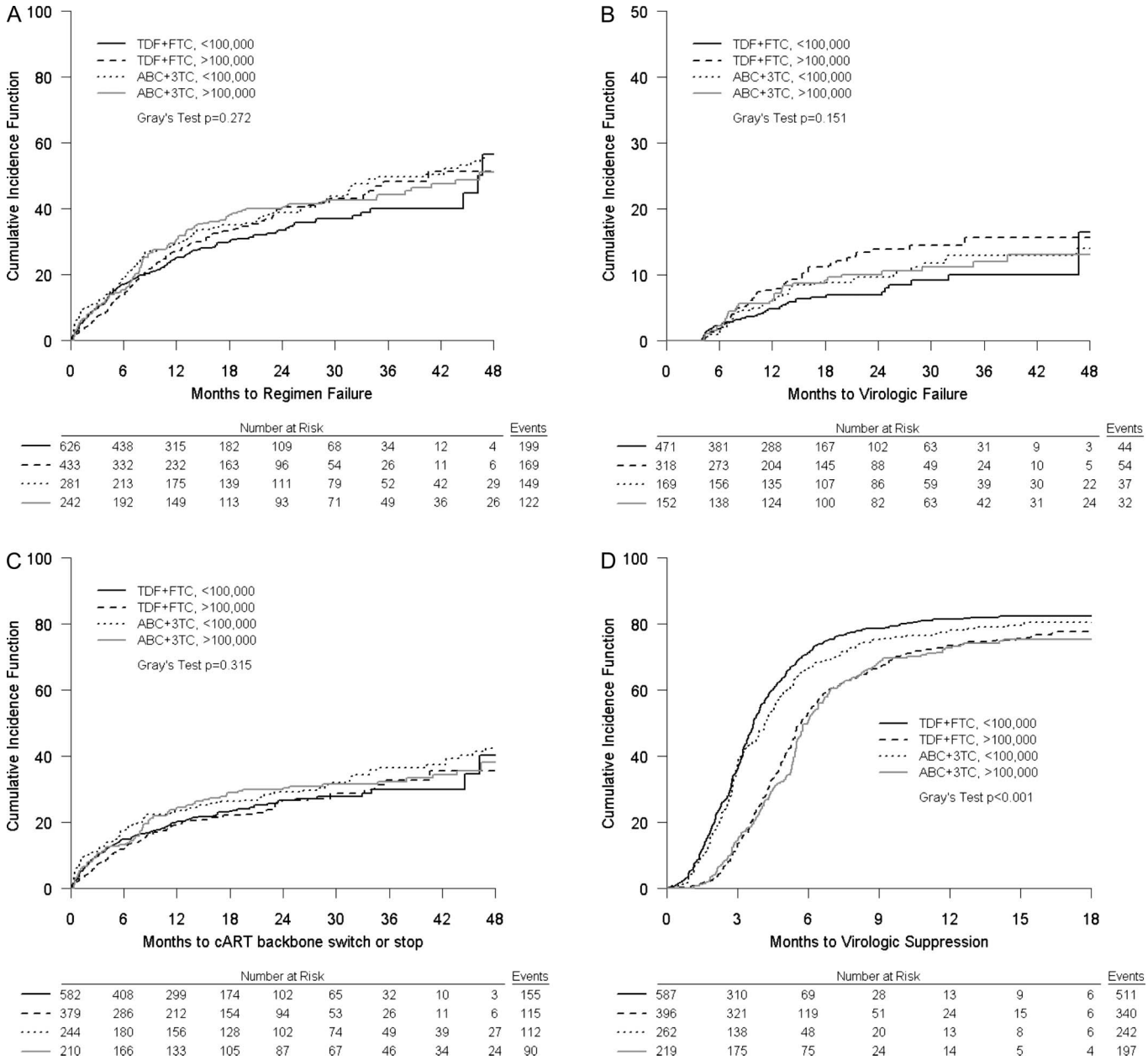

FIGURE 1. Time to regimen failure, virologic failure, switching/stopping NRTIs for reasons other than virologic failure and virologic suppression by initial nucleoside backbone and baseline VL. A, Shows the time to regimen failure, defined as the composite of virologic failure or switching/stopping NRTI backbone for other reasons, according to the initial NRTI backbone and baseline HIV VL. B, Shows the time to virologic failure by NRTI backbone and baseline HIV VL. C, Shows the time to switching/stopping NRTI backbone for reasons other than virologic failure by NRTI backbone and baseline HIV VL. D, Shows the time to virologic suppression (VL<50 copies/mL) according to NRTI backbone and baseline HIV VL.

in combination with efavirenz, nevirapine, atazanavir/ritonavir, or lopinavir/ritonavir, we detected no statistically significant differences in the time to regimen failure, virologic failure, switching or stopping antiretroviral agents for nonvirologic failure reasons, or virologic suppression according to NRTI backbone.

We found increased hazards of the primary composite outcome, regimen failure, with female sex, residence in Ontario and Quebec, and boosted PI use, mostly driven by increased hazards of switching/stopping NRTIs for nonvirologic reasons, but also driven by increased hazards of virologic failure with boosted PI use. These associations may be readily explained. In the GRACE trial, a study specifically designed to assess differences in the efficacy and tolerability of darunavir/ritonavir in treatment-experienced patients, higher rates of drug discontinuation for reasons other than virologic failure were observed in women than men;[20] similar sex differences have been observed in other studies and may relate to differences in adherence and the incidence of

TABLE 3. Survival Analysis Model Results for Time to Virologic Failure

Variable	Unadjusted Hazard Ratio (95% CI)	*P*	Adjusted Hazard Ratio (95% CI)	*P*
Nucleoside backbone				
TDF/FTC	1.00	—	1.00	—
ABC/3TC	1.11 (0.81 to 1.51)	0.51	0.84 (0.58 to 1.20)	0.34
Baseline HIV VL				
Below 100,000 copies/mL	1.00	—	1.00	—
Above 100,000 copies/mL	1.32 (0.98 to 1.79)	0.07	1.24 (0.89 to 1.71)	0.20
Baseline CD4 count (per 100 cells/mm^3)	0.92 (0.79 to 1.07)	0.28	—	—
Age (per 10-year increment)	0.95 (0.82 to 1.12)	0.56	—	—
Sex				
Female	1.00	—	1.00	—
Male	0.95 (0.58 to 1.55)	0.84	0.88 (0.53 to 1.44)	0.60
Province				
British Columbia	1.00		1.00	
Ontario	1.13 (0.81 to 1.57)	0.48	1.40 (0.89 to 2.20)	0.14
Quebec	0.85 (0.54 to 1.32)	0.47	1.10 (0.64 to 1.91)	0.73
Hepatitis C coinfection				
No	1.00	—	—	—
Yes	2.10 (1.27 to 3.47)	0.004	—	—
Unknown	1.45 (1.01 to 2.10)	0.05	—	—
Prior AIDS-defining illness	0.98 (0.59 to 1.62)	0.92	—	—
Third antiretroviral agent				
Efavirenz	1.00	—	1.00	—
Nevirapine	1.34 (0.71 to 2.54)	0.37	1.36 (0.70 to 2.65)	0.36
Atazanavir/ritonavir	1.58 (1.10 to 2.28)	0.01	1.54 (1.04 to 2.26)	0.03
Lopinavir/ritonavir	1.63 (1.08 to 2.45)	0.02	1.55 (1.02 to 2.34)	0.04
Calendar year (per year)	0.93 (0.85 to 1.01)	0.10	0.91 (0.78 to 1.06)	0.23
ART initiation after HLA test availability	0.80 (0.59 to 1.09)	0.16	0.82 (0.47 to 1.43)	0.49
Rate of VL testing (per year)				
Less than 3	1.00	—	1.00	—
3–4	0.47 (0.28 to 0.79)	0.005	0.44 (0.26 to 0.75)	0.003
Greater than 4–6	0.60 (0.38 to 0.94)	0.03	0.59 (0.36 to 0.95)	0.03
Greater than 6	1.20 (0.77 to 1.87)	0.43	1.26 (0.76 to 2.08)	0.37

ARV, antiretroviral drug.

specific adverse events.[21,22] Higher rates of NRTI changes in Ontario and Quebec likely reflect differences in prescribing patterns, patient populations, and coverage of fixed-dose combination tablets by the various provincial drug reimbursement plans. The association between boosted PIs and poorer virologic efficacy likely reflect confounding by indication because these agents may have been more commonly used in challenging patients due to suspected greater potency and higher genetic barrier to resistance.

Data were not available on the reasons for switching/stopping therapy in this study but abacavir HSR is a rare but clinically important potential reason for changing NRTI therapy. Although patient-level data regarding HLA-B*5701 status were not available, the short median time to changing NRTIs of 1 month among those switching off ABC/3TC, compared with those switching off TDF/FTC and those stopping either backbone, suggests that suspicion of abacavir HSR drove some NRTI switches. Although initiation of cART after HLA testing became available was not significantly associated with NRTI switching/stopping, the majority of this cohort had access to HLA testing, and knowing patients' HLA-B*5701 status may boost clinician confidence in ruling out HSR and continuing therapy in the setting of otherwise suggestive symptoms. Importantly, the existence of publically funded drug insurance programs in Canada means that insurance problems represent relatively uncommon reasons for antiretroviral switches. Improved understanding of how toxicity, tolerability, treatment simplification, and other factors drive treatment discontinuation could guide future efforts to improve regimen durability.

Our findings of similar virologic efficacy according to NRTI backbone contrast with those of the ACTG 5202 trial which observed an increased risk of virologic failure among those receiving ABC/3TC with baseline HIV RNA levels over 100,000 copies per milliliter,[5,23] but are consistent with those of the HEAT trial in which fixed-dose formulations of ABC/3TC and TDF/FTC performed similarly in combination with lopinavir/ritonavir, regardless of baseline VL.[7] Two trials examining a switch to ABC/3TC-based or TDF/FTC-based regimens also showed them to have similar efficacy.[24,25]

TABLE 4. Survival Analysis Model Results for Time to Switching or Stopping NRTIs for Reasons Other Than Virologic Failure

Variable	Unadjusted Hazard Ratio (95% CI)	*P*	Adjusted Hazard Ratio (95% CI)	*P*
Nucleoside backbone				
TDF/FTC	1.00	—	1.00	—
ABC/3TC	1.25 (1.04 to 1.50)	0.02	1.02 (0.81 to 1.28)	0.87
Baseline HIV VL				
Below 100,000 copies/mL	1.00	—	1.00	—
Above 100,000 copies/mL	0.94 (0.78 to 1.12)	0.49	0.97 (0.80 to 1.16)	0.72
Baseline CD4 count (per 100 cells/mm^3)	1.03 (0.95 to 1.10)	0.47	—	—
Age (per 10-year increment)	0.95 (0.86 to 1.03)	0.22	—	—
Sex				
Female	1.00	—	1.00	—
Male	0.54 (0.42 to 0.69)	<0.001	0.58 (0.44 to 0.75)	<0.001
Province				
British Columbia	1.00	—	1.00	—
Ontario	1.90 (1.52 to 2.36)	<0.001	2.01 (1.54 to 2.61)	<0.001
Quebec	2.15 (1.67 to 2.77)	<0.001	2.23 (1.67 to 2.99)	<0.001
Hepatitis C co-infection				
No	1.00	—	—	—
Yes	1.35 (0.96 to 1.91)	0.08	—	—
Unknown	1.70 (1.38 to 2.09)	<0.001	—	—
Prior AIDS-defining illness	1.33 (1.02 to 1.75)	0.04	—	—
Third antiretroviral agent				
Efavirenz	1.00	—	1.00	—
Nevirapine	0.82 (0.52 to 1.29)	0.38	0.75 (0.47 to 1.20)	0.23
Atazanavir/ritonavir	1.19 (0.96 to 1.48)	0.11	1.22 (0.97 to 1.52)	0.09
Lopinavir/ritonavir	1.34 (1.06 to 1.68)	0.01	1.33 (1.05 to 1.68)	0.02
Calendar year (per year)	0.97 (0.92 to 1.02)	0.23	0.99 (0.91 to 1.07)	0.72
ART initiation after HLA test availability	1.23 (1.00 to 1.52)	0.05	1.00 (0.73 to 1.37)	0.98
Rate of VL testing (per year)				
Less than 3	1.00	—	1.00	—
3–4	1.17 (0.86 to 1.59)	0.33	1.20 (0.87 to 1.64)	0.26
Greater than 4–6	1.06 (0.79 to 1.42)	0.70	1.28 (0.94 to 1.73)	0.11
Greater than 6	1.06 (0.77 to 1.45)	0.71	1.36 (0.97 to 1.91)	0.08

The explanation for these discordant results is not clear. Possibilities include differences in the baseline characteristics of patients, including the distribution of baseline plasma HIV-1 RNA levels; 21% of ACTG 5202 patients had VL >500,000 copies/mL, and it is possible that differences in efficacy exist only at very high plasma VL. Actual levels of plasma HIV-1 RNA were not available for measurements above 100,000 copies per milliliter in our cohort. Importantly, however, we found no evidence of statistical interaction between NRTI backbone and baseline VL stratum in this study. Patients on both NRTI backbones experienced a longer time to virologic suppression with higher baseline VL in this cohort.

In addition, baseline genotyping was performed in 43% of participants in the ACTG study, but genotyping data were not electronically available in our cohort. Other differences include the antiretrovirals with which NRTIs were paired and the burden of comorbid conditions. Although HLA-B*5701 testing was available for the majority of our patients and only some ACTG 5202 participants, access to this test would not be expected to impact virologic efficacy, and rates of suspected HSR were similar between arms in the high VL stratum of the ACTG 5202 study.[5]

Our study has limitations that warrant consideration. First, because of the time period studied, the ABC/3TC arm included both once-daily and twice-daily dosing regimens, and many ABC/3TC patients initiated therapy before fixed-dose combination ABC/3TC tablets became available in Canada in December 2005. However, the impact of these dosing differences on the clinical outcomes examined here are unclear. Second, the limited follow-up time of our study precluded study of long-term drivers of regimen success. Third, as discussed above, patient-specific baseline genotyping and HLA-B*5701 data were not available. Finally, because of the observational nature of this analysis, assignment to receive ABC/3TC or TDF/FTC was not random and may have been driven by other variables that are themselves related to the outcomes of interest. However, we controlled for known potential confounders including baseline VL, accompanying antiretroviral agents, and demographic variables.

Our findings do not necessarily indicate a lack of difference in regimen safety or tolerability between these backbones because many such problems can be managed through non-pharmacologic and/or nonantiretroviral therapeutic strategies

without necessitating changes in cART. However, this retrospective analysis of 1764 treatment-naive noninjection drug user, HIV-infected adults in Canada did not identify differences in the hazard of regimen failure, virologic failure switching/stopping antiretrovirals for nonvirologic reasons, or virologic suppression according to use of ABC/3TC or TDF/FTC. These results support the use of either NRTI backbone in the initial therapy of ART-naive patients and would support continuing ABC/3TC as a "preferred" NRTI option.

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APPENDIX I: ADDITIONAL RESEARCH TEAM MEMBERS OF CANOC COLLABORATION

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