Abacavir-Based Antiretroviral Therapy is Associated with a Long-Term Increase in Incidence of Cardiovascular Events in HIV Patients with Presumable Cardiovascular Disease

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Background

Human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) are considered a pandemic by the World Health Organization. In 2018, there were more than 37.9 million people world-wide living with HIV/AIDS. Multiple studies have been conducted over the last decade to investigate the increased incidence of major cardiovascular events (MACE) in patients on various anti-retroviral therapies (ART). One medication in particular, abacavir (ABC), is a nucleoside analog reverse transcriptase inhibitor (NRTI) with an unclear association with cardiovascular disease (CVD). Abacavir's controversial role in the increased rate of MACE, such as recurrent unstable angina, acute myocardial infarction (AMI), new-onset heart failure, need for percutaneous coronary intervention (PCI), coronary bypass artery grafting (CABG), and/or all-cause mortality, is of major concern. Considering the paucity of data regarding ABC-based ART use in HIV patients, as well as its relationship with CVD risk and MACE, we sought to specifically study the effect of ABC-based ART use on adverse cardiac events, cardiac readmissions, myocardial infarction, and all-cause mortality as a part of our Advanced Cardiac Admission Pathway program (ACAP).

Methods

Study Design: Prospective, observational, cohort study conducted over a 6 year duration. During this time, a total of 286 patients with HIV, hospitalized for acute coronary syndrome (ACS) between June, 2005 and April, 2008, who received standardized care under our Advanced Cardiac Admissions Pathway registry were identified for analysis. Patients were stratified into two study cohorts- those patients with acute coronary syndrome (ACS) treated with non-ABC-based ART and those patients with ACS treated with ABC-based ART. Composite endpoints of CVD readmission, MACE and all-cause mortality were assessed at 18, 36, 54 and 72 month intervals.

Inclusion Criteria: HIV-infected patients with ACS, admitted to St. Luke's-Roosevelt Hospital Center in New York between June, 2005 and April, 2008.

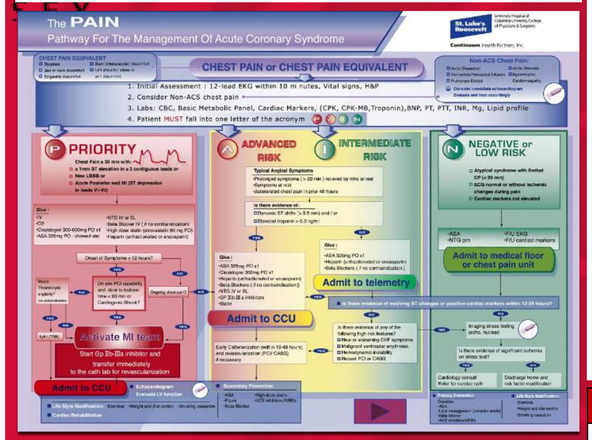
Patient Population: 377 patients identified with HIV according to the protocol for standardized care under the ACAP program.

Statistical Analysis: Statistical analysis was performed using a standard statistical software package (SPSS for Windows, version 17; SPSS; Chicago, IL). Cox proportional hazards regression and Kaplan-Meier curves were calculated for all-cause mortality in both groups.

Study Aim

The aim of this study is to evaluate the role of ABC-based ART on CVD in patients with HIV, and specifically, the effect of its use on MACE, including cardiac readmissions, AMI, and all-cause mortality. We further aimed to determine if the risk of MACE equalized following cardiac events in HIV-infected patients treated with an ABC-based ART compared to a non-ABC-based ART regimen.

The PAIN Pathway: Management of Acute Coronary Syndrome



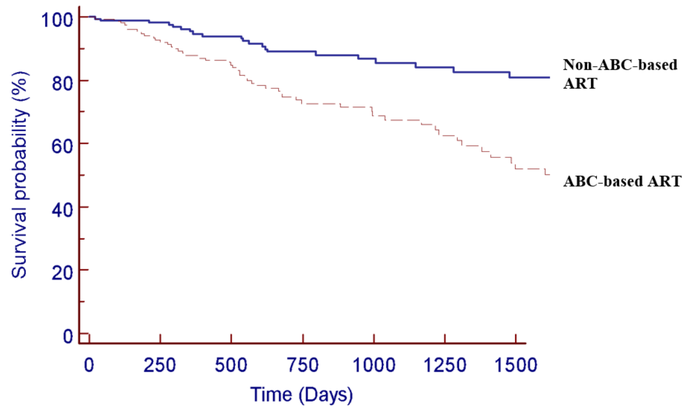
Advanced Cardiac Admission Program "ACAP"

The Advanced Cardiac Admissions Program, or ACAP for short, is an algorithm for instituting ACC/AHA guidelines in clinical practice. In 2004, various pathways were instituted at St. Luke's-Roosevelt Hospital Center in New York, NY. One such pathway, the Priority risk, Advanced risk, Intermediate risk, and Negative/Low risk pathway, or PAIN for short, is an algorithm for triaging and managing patients presenting with ACS. The goal of the algorithm is to approach ACS with a structured protocol from admission to discharge. All patients admitted via this pathway are registered in the ACAP system and agree to enroll in routine follow-up to ensure adherence to ACC/AHA guideline-directed medical therapy.

Table 1: Patient Demographics

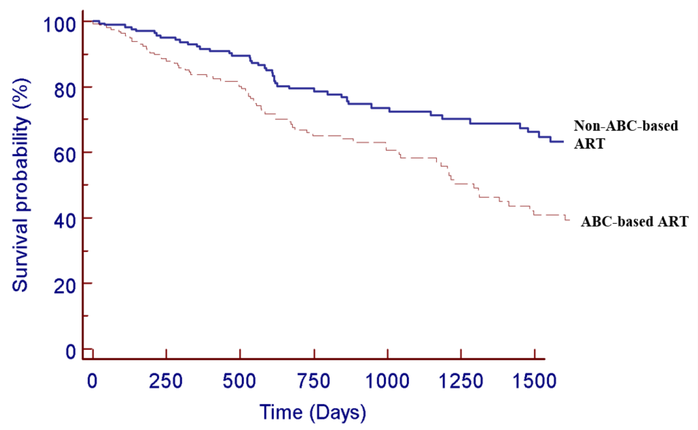
	All Patients	non-ABC-based ART	ABC-based ART	*p*
General Parameter:	**(n=377)**	**(n=205)**	**(n=172)**	
Age, yrs	53 ± 11	52 ± 11	55 ± 11	*0.496*
Sex, (% men)	282 (74)	150 (74)	132 (77)	*0.498*
Hypertension (%)	214 (56)	123 (60)	91 (53)	*0.200*
Diabetes Mellitus (%)	96 (25)	52 (25)	44 (25)	*0.943*
Hyperlipidemia (%)	127 (34)	74 (36)	53 (31)	*0.331*
Smoking (%)	165 (44)	104 (51)	61 (31)	*0.008*
Chronic Kidney Disease (%)	61 (16)	29 (14)	32 (19)	*0.961*
Cardiac History:				
Coronary Artery Disease (%)	32 (8)	14 (7)	18 (11)	*0.100*
CABG (%)	11 (3)	3 (1)	8 (5)	*0.127*
PCI (%)	43 (3)	20 (10)	23 (13)	*0.01*
Heart Failure (%)	65 (17)	36 (18)	29 (17)	*0.961*
LVEF	53 ± 13	53 ± 15	54 ± 12	*0.561*
Myocardial Infarction (%)	39 (10)	23 (11)	16 (9)	*0.66*

Figure 1: Kaplan-Meier for All-Cause Mortality



HIV Parameters:				
CD4 Count	436 ± 839	489 ± 1075	369 ± 338	*0.214*
Viral Load Count	24035 ± 70895	22608 ± 69141	26056 ± 73570	*0.459*
Cardiac Medication:				
Aspirin (%)	141 (37)	87 (42)	54 (31)	*0.001*
Beta Blocker (%)	106 (28)	68 (33)	38 (22)	*0.023*
Statins (%)	104 (28)	66 (32)	38 (22)	*0.03*
ACEi (%)	95 (25)	56 (27)	39 (23)	*0.36*
	All Patients	ARV without ABC	ARV with ABC	*p*
Cardiac Medication:				
CCB (%)	76 (20)	42 (21)	34 (20)	*0.005*
Clopidogrel (%)	30 (8)	17 (8)	13 (5)	*0.94*
All CV events, Cumulative Risk Factors, Death:				
All CV events (%)	151 (40)	67 (33)	84 (49)	*0.0002*
Cumulative Risk Factors	2.286 ± 1.63	2.361 ± 1.60	2.198 ± 1.66	*0.33*
Social Security Death Index (%)	88 (23)	32 (16)	56 (33)	*< 0.0001*

Figure 2: Kaplan-Meier for Composite Endpoint Mortality



Results

Patients who received an ABC-based ART regimen had a higher risk of MACE and all-cause mortality than patients on a non-ABC-based ART regimen (Figure 1, Figure 2). Risk of major adverse cardiovascular events was defined as admission for CHF exacerbation, non-fatal MI, non-fatal ischemic stroke, and all-cause mortality. This difference in survival between the ABC-based ART regimen group and non-ABC-based ART regimen group became apparent early in the study and escalated as the study progressed. By the six-year mark, the incidence of all-cause mortality according to the SSDI was significantly higher in the ABC-based ART group compared to the non-ABC-based ART group ($p<0.0001$) . Specifically, the ABC-based ART group had 33% all-cause mortality compared to 16% all-cause mortality in the non-ABC-based ART group. The ABC-based ART group also had a higher incidence of any CVD event compared to the non-ABC-based ART group. Specifically, the incidence of any CVD event in the non-ABC-based ART group and the ABC-based ART group were 33% and 49%, respectively (HR=2.288, $p< 0.0002$; 95% CI: 1.573-3.329). The difference in survival over the 72 months follow-up period between the two groups remained significant, even when composite endpoints were plotted using Kaplan-Meier survival analysis ($p<0.0001$) .

Table 2: Cox Hazards Ratios for Risk Associated with CVD events

Variable	Cox Hazards ratio	95% CI	*p*
Increased Age	1.0224	1.0067 – 1.0384	*0.0052*
Decreased Use of Beta Blockers	1.8148	1.2215 – 2.6963	*0.0033*
Decreased Use of Statins	0.6417	0.4127 – 0.9977	*0.0500*
Decreased LVEF	0.9728	0.9622 – 0.9835	*< 0.0001*
Abacavir-Based ART	2.2883	1.5730 – 3.3289	*< 0.0001*

Conclusion

The effect of abacavir on cardiovascular disease risk has been cause for debate over the past few decades. However, our study shows that treatment of HIV with ABC-based ART reveals an increased risk for cardiovascular disease-related mortality in both short-term and long-term usage. No conclusive mechanism has been found, with proposed mechanisms including increased cytokine production verus increased pro-thrombotic and pro-inflammatory activity triggered by ABC's purine-like structure and ability to trigger P2X7-nucleoside receptors. Given the demonstrated increased risk of CVD with ABC, further investigation into the underlying mechanism needs to be conducted.

References:
1. Prevention CfDCa. HIV Surveillance Report, 2018.
2. UNAIDS Data 2019, 2019.

Disclosures
No parties have any disclosures or conflicts of interest.