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Mortality among HIV+ Participants Randomized to Omit NRTIs vs. Add NRTIs in OPTIONS (ACTG A5241)

Karen T Tashima*[1], Laura Smeaton, Karin L Klingman[4], Adriana Andrade[6], Joseph J Eron[8], Carl J Fichtenbaum[5], Rajesh Gandhi[3], Victoria A Johnson[7], and Richard H Haubrich[9]

[1]The Miriam Hospital, Alpert Medical School of Brown University, Providence, RI, US~ [2]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, US~ [3]Massachusetts General Hospital, Boston, MA, US~ [4]HIV Research Branch RTP, DAIDS, NIAID, NIH, Bethesda, MD, US~ [5]Univ of Cincinnati, Cincinnati, OH, US~ [6]Johns Hopkins Univ, Baltimore, MD, US~ [7]Birmingham VA Medical Center and Univ of Alabama at Birmingham School of Medicine, Birmingham, AL, US~ [8]Univ of North Carolina at Chapel Hill, Chapel Hill NC, US~ and [9]Univ of California at San Diego, San Diego, CA, US

Karen T. Tashima, MD
ktashima@lifespan.org

ACTG AIDS CLINICAL TRIALS GROUP

Background/Methods

Background:

OPTIONS enrolled treatment-experienced participants with virologic failure who were randomized to a new regimen that omitted or included NRTIs. In the primary week 48 analysis, we found that omitting NRTIs was not inferior to adding NRTIs (CROI 2013, 153LB). In this analysis, we examined all-cause mortality.

Methods:

360 subjects who had PI, NNRTI and NRTI experience and/or viral resistance enrolled in OPTIONS. Personalized regimens with 3-4 ARVs (excluding NRTIs) having >2 active drugs, and NRTI combinations were selected; subjects were then randomized to add or omit NRTIs with the new regimen. All subjects were followed for 96 weeks for outcomes including mortality. Since mortality events were rare, multivariable models were not feasible and exact logistic regression models using one covariate were used to estimate exact odds ratios (eOR).

Vital status of subjects in OPTIONS

Screening—subjects continue NRTI containing regimens (N=516): 2 deaths **(IR = 4.15/100 p-y)**

Subsequent to leaving study (1 add'l death)

Randomization to Add or Omit NRTIs in addition to starting new regimens (N=360)

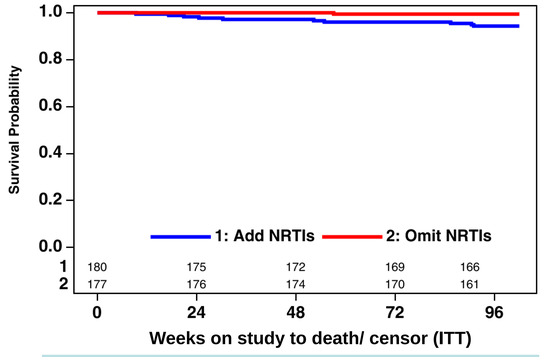
Never started study treatment(N=3): 1 death (Add NRTIs arm)

Add NRTIs (N=180 started study rx)	Omit NRTIs (N=177 started study rx)
10 deaths total	**1 death total**
6 died in year 1 4 died in year 2 **(IR = 3.1/100 p-y)**	0 died in year 1 1 died in year 2 **(IR = 0.31/100 p-y)**
N=168 left study alive 34 have subsequent* vital status info (20%)	N=171 left study alive 46 have subsequent* vital status info (27%)
2 post-study deaths **(IR= 3.6/100 p-y)**	3 post study deaths **(IR = 3.8/100 p-y)**

p-y = person-years
IR = incidence rate
(deaths per 100 p-y)

* Subsequent vital status collected from other network studies such as longitudinal cohort studies

Probability of survival by randomized arm



Cumulative probability of death (%)

Study week	Add NRTIs (95% CI)	Omit NRTIs (95% CI)
24	2.2 (0.8, 5.9)	0 (0, 0)
48	3.4 (1.5, 7.4)	0 (0, 0)
96	5.7 (3.1, 10.3)	0.6 (0.1, 4)

Modeling death by exact logistic regression

•Univariate analysis of selected baseline characteristics with mortality showed associations (relaxed significance level of 0.10 due to rare event) with CD4 cell count category and with choice of NRTIs (which were likely influenced by patient characteristics such as creatinine clearance).

Factor	Exact Odds Ratio Estimate	OR 95% Confidence Interval	P
Screening calculated creatinine clearance, mL/min (per 1 unit increase)	0.98	0.96, 1.00	.06
CD4 cell count, cells/mm^3 (< 100 versus at least 100 cells/mm3)	4.3	1.06, 18.39	.04
VACS Mortality Index (per 10 unit increase)	1.9	1.3, 2.8	.003

•Other baseline variables tested which were not significant include: age, IV drug use, hemoglobin years on ARVs, CD4 cell count, plasma HIV-1 RNA, history of AIDS, hepatitis B, HTN. Virologic failure during study was also not a significant association.

Baseline characteristics by randomized arm

Baseline Characteristics: Median (Q1, Q3) or %	Add NRTIs N=181	Omit NRTIs N=179
Age years	46 (41, 52)	46 (40, 51)
Male	75%	74%
Race: Black, non-Hispanic	44%	39%
Ethnicity: Hispanic	21%	26%
CD4 (cells/mm^3)	193 (104, 376)	212 (105, 348)
Plasma HIV RNA (log_{10} copies/mL)	4.2 (3.6, 4.7)	4.2 (3.6, 4.6)
Years on ARVs	11 (8, 14)	12 (9, 16)
R5-only tropism	49%	49%
Prior Enfuvirtide (ENF) or Integrase-inhibitor use	19%	18%
cPSS of study treatment regimen*	3 (3, 3)	3 (3, 3)

*Continuous phenotype susceptibility score

Details of deaths after randomization through week 96

Add NRTI Subjects	Number of weeks on study rx	Cause of death (and other medical conditions)	Prior regimen	Baseline CD4	Change in CD4 at visit prior to death	Study treatment	Lowest Viral load on study	Viral load prior to death
1	9	Heart failure (lymphoma)	ABC, d4T, 3TC, ATV	75	-69	ABC, 3TC, MVC, RAL, DRV/r	50	50
2	17	Listeria meningitis (HCV, hospital acquired pneumonia)	TDF, FTC, ATV/r	422	+78	ABC, 3TC, RAL, DRV/r, ETR	468	46102
3	21	Renal failure (drug reaction, autoimmune enteropathy)	TDF, 3TC, ATV/r	14	+60	ZDV, TDF, FTC, RAL, DRV/r, ETR	183	435
4	25	Sepsis (HCV, drug reaction, renal failure, liver failure)	TDF, FTC, ATV/r	584	+328	TDF, FTC, RAL, DRV/r, ETR	50	303
5	30	PML (liver disease)	ABC, TDF, 3TC, LPV/r	9	+103	TDF, FTC, RAL, DRV/r, ETR	707	707
6	52	Abdominal bleed (cirrhosis)	TDF, FTC, LPV/r	476	+14	ZDV, TDF, FTC, MVC, RAL, DRV/r	106	20509
7	55	Pneumonia (drug use)	TDF, 3TC, LPV/r	72	+272	TDF, FTC, ENF, RAL, DRV/r, ETR	50	50
8	86	Cardiac arrest (cardiac disease)	TDF, FTC, ATV/r	573	+266	TDF, FTC, MVC, RAL, DRV/r	50	80
9	91	Myocardial infarction (cardiac disease, drug use)	TDF, FTC, ATV/r	523	+176	ZDV, 3TC, MVC, RAL, ETR	50	50
10	91	Pneumocystis pneumonia	TDF, FTC, EFV, TPV/r	21	+225	TDF, FTC, ENF, RAL, DRV/r, ETR	50	50
Omit NRTI subject	57	Multisystem failure (assault, head trauma)	TDF, FTC, DRV/r, ENF	23	-112	RAL, DRV/r, ETR	6626	307162

Summary and discussion

- **Full multivariable assessment of mortality associations was difficult as there was only one event in the Omit NRTIs arm.**
- **Mortality rates during the screening period and post study follow-up were similar to the rate in the Add NRTIs arm during the study, but higher than for the Omit NRTIs arm.**
- **Mortality in OPTIONS was similar to that seen in cohort studies such as the HIV Outpatient Study where incidence rates ranged from 0.86 to 5.35 per 100 p-y.**
- **VACS mortality index (includes age, hemoglobin, creatinine clearance, CD4, HIV RNA, and HCV status) was useful in predicting mortality in this large randomized clinical trial.**

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