

FACTORS ASSOCIATED WITH VIROLOGIC FAILURE AND THEIR IMPACT ON TREATMENT OUTCOMES: AN ANALYSIS OF VIROLOGIC FAILURE IN ACTG 388

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ABSTRACT

Background: Despite the success of HAART regimens in antiretroviral naive study subjects, virologic failure (VF) is seen in 10% to 30% of subjects over 3 years of follow-up. Understanding factors that influence the risk of VF is important to improve virologic outcome in these subjects.

Methods: We analyzed baseline and on-treatment factors associated with VF in subjects receiving zidovudine and lamivudine plus either indinavir (IDV), efavirenz+indinavir (EFV+IDV) or nelfinavir+indinavir (NFV+IDV) in ACTG 388, a randomized phase III study with a median follow-up of 108 weeks. VF in the study was defined as confirmed plasma HIV RNA (VL) \geq baseline or 1.0 log above nadir, >200 copies/ml (c/ml) at wk 24 (early VF) or relapse (confirmed VL \geq 200 following confirmed VL<200) [late VF]. Factors in proportional hazards analyses were age, race, gender, baseline viral load and treatment regimen and as time-dependent covariates, patterns of viral load responses, recent toxicity, drug holds or permanent treatment discontinuation.

Results: Of 517 subjects randomized to ACTG 388, 172 had VF. In multivariate analyses, non-white subjects were at a higher risk of VF (p=0.015, hazard ratio (HR)=1.47) as were younger subjects (p=0.001, HR=1.36 for each 10 years). Compared to continuous therapy, treatment discontinuation gave a 4.2-fold increase in the risk of VF (p<0.0001); temporary drug holds of 1-2 and >2 weeks gave 4.2 and 9.3 fold increases respectively (p<0.0001). These factors explained some of the treatment difference observed between the NFV+IDV and IDV arms. Although many of the treatment interruptions were due to toxicity, VF was not associated with treatment interruptions with early and late failure. In late failure, never achieving VL \leq 50 c/ml and a most recent VL 51-200 c/ml were both associated with an increased risk of subsequent VF (p<0.0001, HR=5.6, p<0.0001, HR=5.4); there was no evidence that a history of intermittent viremia (VL \leq 50 c/ml with subsequent VL \geq 50 c/ml) was associated with an increased risk of VF (p=0.49).

Conclusions: Non-white and younger subjects were at a greater risk for VF. Therapy discontinuation and temporary interruption of therapy, even of short duration, were highly associated with VF overall and with both early and late failure. Failure to achieve VL \leq 50 c/ml and current VL between 51 and 200 c/ml were both associated with an increased risk of late VF. Recent toxicity was not a risk factor for VF.

BACKGROUND

Despite the general good success of antiretroviral regimens, virologic regimen failure is seen in between 10% and 30% of subjects over 3 years of follow-up. We wanted to examine factors related to failure and how these may relate to the initial treatment regimen.

ACTG 388 was a randomized Phase III clinical trial in subjects with advanced HIV Disease (\leq 200 CD4 cells/mm³ or HIV-1 RNA levels \geq 80,000 copies/ml in plasma at screening) (Fischl et al.). Subjects were naive to protease inhibitors, non-nucleoside reverse transcriptase inhibitors and lamivudine. The ACTG 388 primary analyses suggested that treatment with 3TC/ZDV+IDV+EFV offered a superior virologic response (characterized by a prolonged period of suppression) than treatment with 3TC/ZDV+IDV. In contrast, treatment with 3TC/ZDV+IDV+NFV resulted in an inferior virologic response (characterized by a lower probability of initial suppression) than treatment with 3TC/ZDV+IDV¹. Within a subgroup of subjects participating in a randomized adherence intervention study, poor adherence, female sex and younger age were independently associated with an increased risk of virologic failure².

The objective of these analyses was to further investigate risk factors associated with the risk of virologic failure.

METHODS

Primary endpoint: Time to virologic failure *Defined regardless of treatment status*

Secondary endpoints: Time to early virologic failure *Follow-up beyond study week 24 is censored failure*
 Time to late virologic failure *Includes only subjects with confirmed HIV-1 RNA<200 cp/ml by week 24 (relapse)*
Virologic failure definition: Confirmed plasma HIV-1 RNA \geq baseline or 1.0 log above nadir, >200 copies/ml (c/ml) at wk 24 (early VF) or relapse (confirmed VL \geq 200 following confirmed VL<200) >200cp/ml
Analysis methods: Cox proportional hazards model
Fixed covariates: Age, Race/ethnicity, Sex, Baseline HIV-1 RNA, ACTG 388 treatment arm
Time dependent covariates*: Recent treatment status: on drug, temporary hold in drug (<2 \geq 2 weeks in duration), off drug
 Recent toxicity: Any grade 3 or 4 sign, symptom or laboratory toxicity or targeted diagnosis

HIV-1 RNA response history**:
 HIV-1 RNA never <50 cp/ml, Most recent HIV-1 RNA 51-200 cp/ml, Previous intermittent viremia (\geq 50 cp/ml), HIV-1 RNA consistently <50cp/ml

* Time dependent covariates update each subject's covariate values at each observed event time. In defining recent treatment status and recent toxicity covariates, a subject's data during the period 7-28 days prior to the event time of interest was used. Since it was expected that a subject's risk of virologic failure would not be instantaneously impacted by a each of the time dependent factors considered, a subject's response/treatment/toxicity history in the 7 days prior to an event time was not considered in defining covariate values for a given event time.

** Examined only for analyses of late failure

STUDY POPULATION

Baseline characteristic		517
All subjects		
Prior nRTI therapy	Naive	468 (91%)
Sex	Male	96 (19%)
Age (years)	Mean	38
Race/Ethnicity	White non-Hispanic	248 (48%)
	Black non-Hispanic	167 (32%)
	Hispanic	88 (17%)
	Other	14 (3%)
ACTG 388 randomized treatment	3TC/ZDV+IDV	168 (32%)
	3TC/ZDV+IDV+EFV	173 (33%)
	3TC/ZDV+IDV+NFV	176 (34%)
HIV-1 RNA (log ₁₀ cp/ml) (cp/ml)	Mean (SD)	5.42 (0.60)
	<80,000	75 (15%)
	80,000-500,000	274 (53%)
	>500,000	167 (32%)
CD4 cell count (cells/mm ³)	0-50	186 (36%)
	51-200	358 (34%)
	>200	155 (30%)

Disposition

- Median follow-up: 108 weeks
- 127 subjects discontinued treatment prior to virologic failure
- Follow-up for HIV-1 RNA continued regardless of treatment status

Virologic failure endpoints		172
Total		
Rise above baseline	3	
1log10 cp/ml rise above nadir	32	
>200cp/ml at week 24	56	
Virologic relapse	81	

RESULTS

Univariate Analyses		All virologic failures			Early virologic failures			Late virologic failures (relapse)		
Covariate (reference group)		Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Sex (male)	Female	1.31	[0.90, 1.89]	0.16	1.65	[1.03, 2.64]	0.04	0.94	[0.51,1.73]	0.83
Age	Per 10 year decrease	1.33	[1.11, 1.59]	0.002	1.34	[1.05, 1.72]	0.019	1.31	[1.01, 1.70]	0.04
Race/Ethnicity (white non-Hispanic)	Non-white/Hispanic	1.46	[1.08, 1.98]	0.015	1.21	[0.80, 1.82]	0.36	1.83	[1.16, 2.89]	0.01
Baseline HIV-1 RNA	Per 1 log increase	0.91	[0.72, 1.15]	0.43	0.96	[0.69, 1.34]	0.81	0.86	[0.62, 1.20]	0.37
ACTG 388 randomized treatment (3TC/ZDV+IDV)	3TC/ZDV+IDV+EFV	0.65	[0.43, 0.99]	0.04	0.83	[0.48, 1.45]	0.52	0.48	[0.25, 0.90]	0.02
	3TC/ZDV+IDV+NFV	1.59	[1.12, 2.25]	<0.001	1.61	[0.99, 2.63]	0.05	1.58	[0.96, 2.60]	0.07
Recent Treatment status (continually on drug)	Hold in drug (1-2 weeks)	4.64	[2.33, 9.23]	<0.0001	2.96	[1.06, 8.23]	0.04	7.82	[3.12, 19.6]	<0.0001
	Hold in drug (>2 weeks)	11.4	[7.32, 17.8]	<0.0001	11.8	[6.87, 20.2]	<0.0001	11.4	[4.87, 26.9]	<0.0001
	Off drug	4.01	[2.70, 5.95]	<0.0001	4.65	[2.82, 7.69]	<0.0001	3.40	[1.78, 6.49]	0.0002
HIV-1 RNA response history (consistently <50 cp/ml)	Last HIV-1 RNA 51-200 cp/ml							5.4	[3.2, 9.0]	<0.0001
	Previous intermittent viremia				NOT ANALYZED			1.3	[0.6, 2.8]	0.49
	Never \leq 50 cp/ml							5.6	[2.5, 12.7]	<0.0001

Multivariate Analyses		All virologic failures			Early virologic failures			Late virologic failures (relapse)		
Covariate (reference group)		Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Sex (male)	Female	1.28	[0.87, 1.88]	0.21	1.58	[0.97, 2.57]	0.07	0.98	[0.52, 1.84]	0.94
Age	Per 10 year decrease	1.36	[1.13, 1.64]	0.001	1.40	[1.08, 1.82]	0.01	1.27	[0.98, 1.66]	0.07
Race/Ethnicity (white non-Hispanic)	Non-white/Hispanic	1.47	[1.08, 2.01]	0.015	1.11	[0.73, 1.69]	0.64	1.95	[1.22, 3.12]	0.005
ACTG 388 randomized treatment (3TC/ZDV+IDV)	3TC/ZDV+IDV+EFV	0.58	[0.38, 0.87]	0.01	0.74	[0.42, 1.30]	0.30	0.40	[0.21, 0.77]	0.006
	3TC/ZDV+IDV+NFV	1.40	[0.98, 2.01]	0.06	1.28	[0.77, 2.11]	0.34	1.57	[0.94, 2.63]	0.08
Recent Treatment status (continually on drug)	Hold in drug (1-2 weeks)	4.24	[2.13, 8.44]	<0.0001	2.67	[0.96, 7.41]	0.06	6.70	[2.66, 16.9]	<0.0001
	Hold in drug (>2 weeks)	9.34	[5.95, 14.7]	<0.0001	9.61	[5.53, 16.7]	<0.0001	12.7	[5.19, 31.0]	<0.0001
	Off drug	4.20	[2.80, 6.28]	<0.0001	4.65	[2.78, 7.77]	<0.0001	3.77	[1.95, 7.28]	<0.0001

SUMMARY

- Gender was not associated virologic failure overall (p=0.21) or late virologic failure (p=0.94), but there was a suggestion that woman had a higher rate of early failure (p=0.07).
- Younger subjects were at a greater risk for virologic failure (p<0.07).
- There was a greater risk of virologic failure amongst Non-white/Hispanic subjects; this was driven by an increased risk of relapse (p<0.005). No increased risk in early failure was seen (p=0.64).
- Baseline HIV-1 RNA and recent toxicity were not seen to be associated with virologic failure (p<0.37, p<0.55).
- Compared to being continually on drug
 - Temporary holds in drugs of short and long duration were associated with an increased risk of virologic failure;
 - Discontinuation of all drugs resulted in a 4-fold increase in the risk of virologic failure (p<0.0001);
 - There was no evidence of an interaction that would suggest a differential impact of treatment status according to randomized ACTG 388 treatment (results not shown);
- After a confirmed HIV-1 RNA response <200 cp/ml
 - Failure to achieve VL \leq 50 c/ml and current VL between 51 and 200 c/ml were each associated with an increased risk of virologic failure Relative to subjects with HIV-1 RNA consistently<50 cp/ml (p<0.0001);
 - There was no evidence that a history of intermittent viremia resulted in an increased risk of virologic failure (p=0.49).
- After adjusting for these covariates, the ACTG 388 randomized treatment effects previously reported¹ were sustained; compared to 3TC/ZDV+IDV
 - 3TC/ZDV+IDV+EFV showing a better response
 - 3TC/ZDV+IDV+NFV showing an inferior response.

IMPLICATIONS

- The results of this study,
- Highlight sub-populations that may benefit from specific strategies to help. Namely, younger patients, non-whites, and women.
 - Support other data that intermittent viremia (blips) are not important to continued virologic success.
 - Highlight that even short holds in drugs create a risk for subsequent virologic failure.

REFERENCES

¹ Fischl MA, Ribaudo HJ, Collier AC, Erice A, Giutiano M, Dehlinger M, Eron JI, Saag MS, Hammer SM, Vella S, Morse, GD and Feinberg FE. "A randomized trial comparing two different four-drug antiretroviral regimens with a three-drug regimen in persons with advanced HIV disease". *Journal of Infectious Diseases*, 2003;188:625-34.

² Collier A, Ribaudo H, Feinberg J, Mukherjee L, Fischl M, Chesney M. "Randomized Study of Telephone Calls to Improve Adherence to Antiretroviral Therapy", 7th conference on Retroviruses and Opportunistic Infections, Abstract 540-T.