Acquired Drug-Resistance Mutations and Mortality among HIV Patients on First-line ART

Abstract # 589

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ABSTRACT

BACKGROUND: The potential long-term clinical risks of staying on failing nucleoside reverse-transcriptase inhibitor/non-nucleoside reverse-transcriptase inhibitor (NRTI/NNRTI)-based first-line antiretroviral treatment (ART) regimens and acquired drug-resistance mutations (DRMs) have not been well elucidated.

METHODOLOGY: The study population included adult HIV patients who were initially ART-naive and who started first-line regimens between 2003-2005 at two sentinel sites in China. ART regimens were either AZT/DDI/NVP or D4T/DDI/NVP, primarily. Given the national treatment program policy at that time, patients had no access to protease-inhibitor-based second-line regimens and remained on first-line despite virologic failure for prolonged periods. HIV RNA and CD4 testing were performed at pre-ART baseline and every 6 months (including after virologic failure). Patients with HIV RNA>1,000 copies/ml on ART had longitudinal genotyping to test for drug resistance. We estimated the effects of acquired DRMs on mortality, using marginal structural models to account for time-varying confounding.

RESULTS: Five hundred seventeen patients were included. With median 58 months follow-up, 404 (78%) patients had HIV RNA>1,000 copies/ml at least once, and 291 (56%) of the 517 had DRMs. At initial detection of DRMs, all patients but one had ≥1 NNRTI-class mutation and 63% had both NRTI- and NNRTI-mutations. Seventy six (15%) of the 517 patients died. Patients were more likely to develop DRMs if they had HIV RNA > 10,000 copies/ml at baseline (HR=1.42) or at the previous visit (HR=1.39), CD4 count < 350 cells/mm3 at the previous visit (HR=1.92), no education beyond elementary school (HR=1.35), used alcohol (HR=1.43), were farmers (HR=1.49), initiated ART in 2003 (HR=2.77) or 2004 (HR=1.79). The mortality hazards ratio for acquired DRMs was 2.49 (95% confidence interval: 1.38-4.51) after adjusting via inverse-probability-weights (IPW) for baseline (including age, gender, occupation, site, education level, marital status, alcohol use, calendar time of treatment initiation, level of initial adherence, baseline CD4 count and viral load) and time-varying confounders (modification of first-line ART regimens, CD4 count and HIV RNA at the previous visit). The hazard ratio increased over time since first detection of DRMs (see Figure 1).

CONCLUSIONS: We identified an elevated risk of mortality associated with acquired DRMs. The excess risk increased with time since first detection of DRMs.

BACKGROUND

•Staying on failing first-line antiretroviral treatment (ART) regimens leads to acquired drug-resistance mutations (DRMs) [1-2]
•The potential long-term clinical risks have not been well elucidated.

OBJECTIVES

• To assess the impact of acquired drug resistant mutations on long-term survival

• To assess the impact of duration of harboring acquired drug resistant mutations on long-term survival

METHODS

Study Population

- 517 adult HIV patients at two sentinel sites in China
- Initially ART-naive
- Started first-line regimens between 2003-2005
- Followed up to July 31, 2009, loss-to-follow-up or death, whichever occurred the earliest (median follow-up: 58 months)
- No access to protease-inhibitor-based second-line regimens at that time given the national treatment program policy
- ART regimens : AZT/DDI/NVP or D4T/DDI/NVP, primarily

Data Collection

- Demographic at baseline and self-reported adherence after ART initiation
- Blood sample collected every 6 months for
  - HIV RNA and CD4 testing: pre-ART baseline and every 6 months (including after virologic failure)
  - Genotypic drug resistance testing: conducted longitudinally when HIV1-RNA> 1,000 copies/ml

Statistical Considerations

Outcome measures
- Death at or after 6 months of treatment initiation

Exposure measures
- Occurrence of genotypic drug resistance mutations

Potential confounders that were controlled for
- Fixed: socio-demographic factors, calendar time of treatment initiation, earliest-measured adherence, baseline CD4 cell count and plasma HIV-1 RNA level
- Time-varying: CD4 cell count, plasma HIV-1 RNA levels and first-line ART modification

Analysis
- Cox proportional hazard marginal structural model to estimate the relative risk of mortality caused by drug-resistance mutations [3-4]

RESULTS

Patient Characteristics

TABLE 1. Demographic and clinical characteristics of 517 HIV+ patients at sites A and B at treatment initiation, 2003-2005

Characteristics	Site A N(%)	Site B N(%)	Total N(%)
Overall	245	273	517
Sex			
Male	105(43%)	112(41%)	217(42%)
Age, Median (range)	40(25-64)	38(25-64)	39(25-64)
Occupation			
Farmer	197(81%)	262(96%)	459(89%)
Mode of transmission route			
Blood donation	226(93%)	260(95%)	486(94%)
Alcohol consumption			
Yes	39(16%)	60(22%)	99(19%)
HIV RNA above 1000 copies/mL at baseline (among the 261 patients with baseline RNA data)	105(83%) N=126	79(59%) N=135	184(71%) N=261
CD4 count at baseline (cells/mm^3) (among the 262 patients with baseline CD4 data)	N=124	N=138	N=262
350 or above	14(11%)	56(41%)	70(28%)
200-349	37(30%)	45(33%)	82(31%)
100-199	41(33%)	23(17%)	64(24%)
0-99	32(26%)	14(10%)	46 (18%)
Initial ART regimen			
AZT/ddI/NVP	0(0%)	256(94%)	256(49%)
AZT/3TC/NVP	25(10%)	9(3%)	34(7%)
d4T/ddI/NVP	212(87%)	2(1%)	214(41%)
d4T/3TC/NVP	6(3%)	6(2%)	12(3%)
d4T/3TC/EFV	1(0.4%)	0(0%)	1(0.2%)
Calendar Year of ART Initiation			
March 2003 – December 2003	85(35%)	120(44%)	205(40%)
January 2004 – December 2004	115(47%)	86(31%)	201(39%)
January 2005 – December 2005	44(18%)	67(25%)	111(22%)

Virology and development of drug resistance mutations

•Viral Suppression (defined as RNA below 1,000 copies/ml): 63% at month 6, 43% at months 36 and 60
•404 patients with at least one HIV-RNA measurement above 1,000 copies/ml
•Among the 404, 291 had detected drug resistance mutations
•Median time from ART initiation to first detection of any drug-resistance mutation: 17 months (inter-quartile range: 11-36 months)
•Crude incidence of DRM: 2.5 per 100 person-years

Table 2. Drug-resistance mutation patterns among 291 drug resistant HIV+ patients at initial detection of their drug-resistance mutations.

	Initial detection (Total n=291)
NNRTI-class mutations	287 (99%)
NRTI- and NNRTI- classes mutations	183 (63%)
NRTI-class mutations only	3 (1%)
PI-class mutations	1 (0.3%)

Mortality

•Seventy-six deaths occurred at least 6 months after treatment initiation
•Crude mortality rate: 6.6 deaths per 100 person-years
•Median time to death: 36 months (inter-quartile range: 28-44 months)

Treatment modification and loss-to-follow-up

•Around a third switched from a ddI-containing regimen to a 3TC-containing NNRTI-based regimen when it became available, after a median duration of 36 months.
•A total of 49 (9%) were lost-to-follow-up

What were the predictors of drug resistance mutations?

Table 3. Baseline and time-varying characteristics associated with time to first detection of drug resistance mutations by multivariable analyses.

Variables that predicted drug-resistance mutations	Hazard Ratio (95%CI)	P-Values
Site B vs. A	2.03(1.45,2.84)	<0.0001
Occupation		
Farmer vs. other	1.49(0.92,2.43)	0.105
Education		
No more than elementary school	1.35(0.99,1.84)	0.061
Alcohol consumption		
Yes	1.43(1.02,2.02)	0.040
ART initiated in 2003	2.77(1.75,4.37)	<0.001
ART initiated in 2004	1.79(1.18, 2.69)	0.0057
Earliest self-reported adherence	1.17(0.75,1.83)	0.495
HIV RNA above 10,000 copies/mL at baseline	1.42(1.01,2.01)	0.0452
CD4 count below 350 cells/mm^3 at baseline	1.06(0.72, 1.55)	0.780
HIV RNA above 10,000 copies/mL at previous visit	1.39(1.02,1.89)	0.035
CD4 count below 350 cells/mm^3 at previous visit	1.92(1.37,2.68)	0.0001
Introduction of 3TC-containing regimen (time-varying)	1.00(0.62, 1.63)	0.999

Note. Multivariable analysis also included age, gender and marital status.

What was the effect of acquired drug-resistance mutations on mortality?

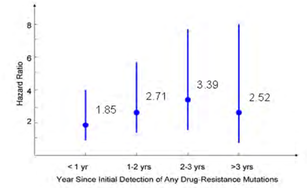
Table 4. Estimated effects of drug-resistance mutations on mortality

	Adjusted Hazard Ratio	95% Confidence Interval
Unadjusted analysis	5.96	(3.60,9.88)
IPW weighted analysis [a]	2.49	(1.38-4.51)
Standard Cox analysis without adjustment of time-varying variables [b]	3.42	(1.84-6.36)
Standard Cox analysis with adjustment of time-varying variables [c]	2.30	(1.19-4.43)

[a] Included age, gender, occupation, site, education level, marital status, alcohol use, calendar time of treatment initiation, level of initial adherence, baseline CD4 count and baseline viral load as fixed factors. Time-varying change of first-line ART regimen, CD4 count and viral load were accounted for by weighting.
[b] Included age, gender, occupation, site, education level, marital status, alcohol use, calendar time of treatment initiation, level of initial adherence as fixed factors. No adjustment for time-varying covariates.
[c] Included age, gender, occupation, site, education level, marital status, alcohol use, calendar time of treatment initiation, level of initial adherence, baseline CD4 count and baseline viral load as fixed factors. together with time-varying change of first-line ART regimen, CD4 count and viral load.

Whether the effect on mortality increased with longer duration of harboring drug-resistance mutations?

Figure 1. Estimated effect of time patients had any drug-resistance mutations on mortality based on IPW weighted analysis



CONCLUSIONS

•Acquired drug resistance mutations independently led to an elevated risk of mortality
•The excess risk increased with duration of harboring DRMs since first detection

REFERENCES

1. Cozzi-Lepri A, Phillips AN, Ruiz L, et al. Evolution of drug resistance in HIV-infected patients remaining on a virologically failing combination antiretroviral therapy regimen. AIDS 2007; 21:721-32.
2. Hosseinipour MC, van Oosterhout JJ, Weigel R, et al. The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy. AIDS 2009; 23:1127-34.
3. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 2000; 11:561-70.
4. Cole SR, Hernan MA, Robins JM, et al. Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. Am J Epidemiol 2003; 158:687-94.

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