

Long-term consequences of the delay between virologic failure of highly active antiretroviral therapy and regimen modification

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Objectives: Current treatment guidelines recommend immediate modification of anti-retroviral therapy in HIV-infected individuals with incomplete viral suppression. These recommendations have not been tested in observational studies or large randomized trials. We evaluated the consequences of delayed modification following virologic failure.

Design/methods: We used prospective data from two clinical cohorts to estimate the effect of time until regimen modification following first regimen failure on all-cause mortality. The impact of regimen type was also assessed. As the effect of delayed switching can be confounded if patients with a poor prognosis modify therapy earlier than those with a good prognosis, we used a statistical methodology – marginal structural models – to control for time-dependent confounding.

Results: A total of 982 patients contributed 3414 person-years of follow-up following first regimen failure. Delay until treatment modification was associated with an elevated hazard of all-cause mortality among patients failing a reverse transcriptase inhibitor-based regimen (hazard ratio per additional 3 months delay = 1.23, 95% confidence interval: 1.08, 1.40), but appeared to have a small protective effect among patients failing a protease inhibitor-based regimen (hazard ratio per additional 3 months delay = 0.93, 95% confidence interval: 0.87, 0.99).

Conclusion: Delay in modification after failure of regimens that do not contain a protease inhibitor is associated with increased mortality. Protease inhibitor-based regimens are less dependent on early versus delayed switching strategies. Efforts should be made to minimize delay until treatment modification in resource-poor regions, where the majority of patients are starting reverse transcriptase inhibitor-based regimens and HIV RNA monitoring may not be available.

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Introduction

Current treatment guidelines recommend careful monitoring of plasma HIV RNA levels during anti-

retroviral treatment, with a goal of identifying virologic failure as early as possible and modifying therapy once failure is confirmed [1]. The rationale for this recommendation is two-fold. First, ongoing viral replication can

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confer additional damage to a patient's immune system, most notably resulting in declining of CD4+ T-lymphocyte counts. Second, ongoing viral replication in the presence of drug can favor the accumulation of additional resistance mutations, potentially compromising future drug options [2].

In practice, however, modification of a failing highly active antiretroviral therapy (HAART) regimen may be delayed as a result of delayed detection of failure, sporadic follow-up, and/or lack of access to alternative regimens. Access to HAART is being rapidly expanded in Africa and other resource poor settings where the burden of HIV disease is the greatest [3]. The laboratory capacity and healthcare infrastructure in many of these settings will not be able to support real-time monitoring of plasma HIV RNA levels, suggesting the potential for substantial delays between treatment failure and regimen modification [4–8]. Improved understanding of the long-term consequences of delayed treatment modification is urgently needed to inform this scale-up.

Although theoretical reasons suggest that delay until modification of a first-line failing regimen should increase mortality, long-term data substantiating this claim are lacking. In addition, there are reasons to think that the consequences of a delay until modification may differ if the failing regimen contains a protease inhibitor drug as compared with a regimen that contains a nonnucleoside reverse transcriptase inhibitor. Mutations conferring resistance to protease inhibitors (particularly ritonavir-boosted protease inhibitors) generally do not emerge rapidly during virologic failure, and when they do emerge do not inevitably result in cross-resistance to the entire drug class [9–14]. Also, protease inhibitor resistance mutations result in a greater reduction in viral fitness than do mutations conferring resistance to other drug classes [15,16]. Perhaps as a result, failing HAART regimens containing a protease inhibitor are often able to maintain stable CD4+ T-lymphocyte counts [17,18].

The most definitive manner in which to test the impact of early versus delayed switching on long-term outcomes is to randomize patients to one of these two strategies. Such a study is not feasible given current guidelines and the clear evidence that a delayed switch results in the sequential accumulation of drug-resistance mutations. In the absence of a definitive randomized study, prospectively collected observational data from well established clinical cohorts are needed. This approach, however, is problematic due to the presence of time-dependent confounding (confounding by indication). For example, disease progression over the course of nonsuppressive therapy, as reflected in CD4+ T-lymphocyte counts, can influence the decision when to modify failing therapy; thus, patients who delay modification may disproportionately be those who progress more slowly, contributing to the appearance of a spurious protective effect from

delayed switching. Standard statistical approaches are unable to control for such confounding because prognostic factors over the course of nonsuppressive therapy may themselves be influenced by past exposure to failing therapy [19].

Here, we used prospective cohort data to estimate the effect of delay until treatment modification following first and second virologic HAART failures on hazard of mortality and how this effect differed between common first-line therapeutic regimens. Immunologic failure was considered as a secondary outcome. We employed a statistical methodology – marginal structural models – that allows for control of time-dependent confounding [20]. The utility of this approach has been demonstrated in HIV-related and other applications [21–25].

Methods

Study design and participants

Two prospective cohort studies contributed data for the analysis. The Johns Hopkins HIV Clinical Cohort (JHHCC) and University of North Carolina HIV Clinical Cohort (UNCHCC) are longitudinal observational studies of patients receiving primary HIV care in the Baltimore, MD area and through the UNC HIV Clinic, respectively. In both cohorts, after informed consent, information is collected in person by trained medical record technicians and electronically from a variety of sources.

To be eligible for this analysis, patients must have initiated their first HAART regimen while under observation and have subsequently experienced virologic failure. HAART was defined as any of the following: any regimen containing four or more antiretroviral drugs; any three-drug regimen, including drugs from two or more therapeutic drug classes; any regimen containing a ritonavir-boosted protease inhibitor; or a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen containing zidovudine/lamivudine/abacavir or zidovudine/lamivudine/tenofovir.

Virologic failure was defined as two consecutive HIV RNA levels above a time-dependent threshold; the second viral load had to occur after week 16. Between weeks 12 and 24, the threshold for failure was defined as 1000 copies RNA/ml, whereas after week 24 a threshold of 500 copies RNA/ml was used. HAART failures occurring between February 1996 and May 2006 were included.

The exposure of interest was time until modification of the failing regimen. Modification was defined as the initiation of a new HAART regimen containing either a new drug class or at least two drugs not used in the failing

regimen. Patients were censored if they interrupted rather than modified their original failing regimen.

The primary endpoints were time to either all-cause mortality or a composite of all-cause mortality and immunologic failure, in which immunologic failure was defined as either two consecutive CD4+ T-lymphocyte counts or two CD4 cell counts within any 12-week period below the pre-HAART CD4 cell count level (this latter endpoint has been used by our group in prior studies [18] and is discussed in the DHHS treatment guidelines [26]).

Statistical analyses

All eligible patients were included in the primary analysis. We also performed two sets of supplementary analyses, in which patients were excluded if they failed a protease inhibitor regimen that was not ritonavir-boosted, or had received antiretroviral therapy prior to initiating HAART. Analyses were also repeated among the subset of individuals who experienced a second episode of virologic failure, treating time of second failure as baseline.

The following laboratory measurements were treated as time-varying confounders: CD4+ T-lymphocyte count, nadir CD4 cell count, CD4%, plasma HIV RNA level, and peak HIV RNA level. Longitudinal data on past and current antiretroviral treatment were summarized, respectively, as the number of drugs in each class experienced in the past, and the number of drugs in each class and total number of classes in the current regimen. Calendar date was considered as an additional time-varying covariate. Baseline and demographic covariates included sex, age, race, injection drug use, men having sex with men, date of first HAART, and history of antiretroviral use pre-HAART. Analyses of UNCHCC also included CD8+ T-lymphocyte counts and CD8%, diagnosis of an AIDS-defining illness, and HIV diagnosis date, whereas JHHCC included date of first antiretroviral use. This same set of baseline and time-dependent covariates were examined as potential predictors of censoring, regimen modification, and treatment interruption.

Data were analyzed on a discrete monthly time scale, beginning at time of confirmed virologic failure. Values of time-varying covariates reflected the most recent measurement available on the last day of the month. All time-varying covariates were lagged by 1 month when controlling for confounding to ensure that confounder values preceded any treatment decision.

Marginal structural model analyses aimed to replicate the results of a trial in which patients experiencing HAART failure were assigned to remain on their failing therapy for a random duration before switching to a new HAART regimen [19,20,24]. Estimation was based on

inverse probability of treatment weighting. Under this approach, patients were assigned weights inversely proportional to their probability of having received their observed treatment histories given their covariates. A reweighted population was thus created, in which treatment groups were balanced with respect to covariate distributions, and a weighted Cox (or pooled logistic regression) model was fit. Inverse probability weights were used to control for confounding of the delay until modification, potential bias as a result of informative censoring and treatment interruption, and baseline differences between patients whose failing regimen did versus did not contain a protease inhibitor [20]. All weights were stabilized.

Models for the weights were fit using logistic regression, in which model selection was based on the deletion/substitution/addition (D/S/A) algorithm and five-fold cross validation [27], a flexible approach that allows for data-adaptive selection of nonlinear covariate effects, interactions between covariates, and variation over time. All models used in the weights were estimated separately for the two cohorts, allowing for heterogeneity in the way in which covariates were used to make treatment decisions, how the probability of censoring and interruption depended on covariates, and the distribution of covariates between patients failing protease inhibitor versus reverse transcriptase inhibitor regimens. Sensitivity analyses were performed using several alternative weight models.

Following estimation of weights, the cohorts were pooled to yield effect estimates. In our primary analyses, we employed a weighted pooled logistic regression model that included time spent on failing therapy and elapsed time since failure as main terms. We also employed several flexible approaches to modeling the conditional hazard of mortality, including weighted data-adaptive regression using the D/S/A algorithm. Standard error estimates were based on nonparametric bootstrap sampling.

Results

A total of 608 patients in the JHHCC and 374 patients in the UNCHCC experienced at least one virologic failure while on HAART. Together, these 982 patients contributed a total of 3414 person-years of follow-up, with a median of 36.5 months per person [interquartile range (IQR): 12.0, 70.0]. Seven hundred and forty two (76%) of first HAART failures occurred among patients treated with at least one protease inhibitor drug; of these, 234 (32%) received a ritonavir-boosted protease inhibitor. The majority of the remaining patients (225/240, 94%) were on a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen; of these, 163 (72%) received efavirenz.

All 982 patients contributed to analyses until they were censored, (administratively or due to loss to follow-up), interrupted therapy, or died, whichever happened first. Modification of the failing regimen was observed in 567 patients (58%) following first HAART failure; the remaining patients interrupted treatment ($N=286$, 29%), died ($N=6$, 1%), or were censored ($N=123$, 13%) before modifying therapy. Patients for whom a treatment switch was observed waited a median of 8 months following failure before modifying therapy (IQR: 3, 19).

There were 93 deaths and 243 immunologic failures. The crude mortality rate was equivalent (2.7 deaths per 100 person-years) among patients who failed a protease inhibitor-based regimen and those who failed a reverse transcriptase inhibitor regimen. The crude immunologic failure rates were 7.8 failures per 100 person-years and 10.3 failures per 100 person-years for protease inhibitor-based and reverse transcriptase inhibitor-based regimens, respectively. Three hundred and fifty-five patients also experienced a second HAART failure. These patients were observed for a total of 1014 years of person time following second HAART failure (median 30 months of follow-up per person; IQR: 20, 55). A total of 36 deaths and 107 immunologic failures were observed following second HAART failure.

Compared with patients failing a reverse transcriptase inhibitor regimen, those patients whose failing regimen contained a protease inhibitor failed their first HAART regimen at an earlier calendar date ($P < 0.001$), were more likely to have used antiretroviral drugs prior to starting HAART ($P < 0.001$), were on regimens containing fewer NRTIs at time of failure ($P < 0.001$), and had lower nadir CD4+ T-lymphocyte counts and lower CD4 cell counts at time of failure (Table 1). Mean plasma HIV RNA level measured prior to regimen modification was 3.54 \log_{10} copies/ml among regimens that contained a protease inhibitor and 3.70 \log_{10} copies/ml among regimens that did not contain a protease inhibitor ($P = 0.14$).

Patients were more likely to modify treatment after their first failure of HAART if their most recent and nadir CD4+ T-lymphocyte counts were lower, and if their most recent HIV RNA level was higher (Table 2). In the JHHCC, patients were less likely to modify if they remained on regimens with more drugs, more drug classes, or with ritonavir boosting. In the UNCHCC, patients diagnosed with an AIDS-defining illness ever or within the last month were more likely to modify therapy. Similar associations were found following second HAART failures (data not shown).

Effect of time to modification on mortality and immunologic failure

Among patients with a first HAART failure on a reverse transcriptase inhibitor-based regimen, a 3-month delay

until treatment modification was associated with an elevated hazard of mortality and immunologic failure (hazard ratio = 1.23; 95% confidence interval (CI) 1.08, 1.40; $P = 0.002$ for death and hazard ratio = 1.21; 95% CI 1.07, 1.36; $P = 0.002$ for immunologic failure) (Table 3). In comparison, among patients failing a protease inhibitor-based first HAART regimen, a 3-month delay until treatment modification slightly reduced the hazard of mortality (hazard ratio = 0.93; 95% CI 0.87, 0.99; $P = 0.03$ for death and hazard ratio = 0.98; 95% CI 0.94, 1.03; $P = 0.45$ for immunologic failure); however, this weak association should be interpreted cautiously given the multiple comparisons performed. These findings were reasonably consistent across cohorts and following second HAART failures (Fig. 1).

Secondary and sensitivity analyses

Supplementary analyses using alternative approaches to estimate the weights and excluding patients on protease inhibitor-based regimens that did not include ritonavir boosting did not substantively alter findings (data not shown). Following exclusion of patients with antiretroviral experience prior to initiating HAART, 187 failures on a protease inhibitor-based regimen and 127 failures on a reverse transcriptase inhibitor-based regimen were analyzed. Estimated hazard ratios associated with a 3-month delay in treatment modification among this subgroup were generally consistent with results of the primary analysis, though they no longer achieved statistical significance (among reverse transcriptase inhibitor-based failures: hazard ratio for death = 1.17, 95% CI 0.70, 1.93; hazard ratio for immunologic failure = 1.07, 95% CI: 0.85, 1.35; among protease inhibitor-based failures: hazard ratio for death = 0.93, 95% CI 0.69, 1.24; hazard ratio for immunologic failure = 0.95, 95% CI 0.85, 1.05). The relationship between delay until modification and hazard of mortality over time was further investigated using several alternative modeling approaches to allow for data-adaptive selection of interactions between terms and nonlinear contributions of delay until modification and elapsed time since failure (Fig. 2).

Discussion

Current antiretroviral treatment guidelines recommend modifying therapy as soon as virologic failure is confirmed, particularly following first and second HAART failure. This recommendation is based primarily on well accepted theoretical principles, but has not been rigorously addressed in either observational studies or large randomized clinical trials. Here, we applied a robust analytical technique that accounts for time-dependent confounding to two large prospective clinic-based cohorts and found that among patients failing a reverse transcriptase inhibitor-based regimen (the vast majority of

Table 1. Sample characteristics at time of first highly active antiretroviral therapy failure^a.

	UNC protease inhibitor ^b	UNC nonprotease inhibitor ^c	JHHCC protease inhibitor ^d	JHHCC nonprotease inhibitor ^e
Categorical covariates, <i>N</i> (%)				
Nonwhite race	182 (69%)	78 (71%)	374 (78%)	109 (84%)
ART use prior to HAART	186 (70%)	50 (45%)	369 (77%)	63 (48%)
Male	180 (68%)	77 (70%)	351 (73%)	81 (62%)
Man who has sex with men	84 (32%)	36 (33%)	145 (30%)	30 (23%)
Injection drug user	46 (17%)	13 (12%)	212 (44%)	62 (48%)
Prior AIDS diagnosis	104 (39%)	24 (22%)	NA	NA
NRTI drugs in failing regimen				
Zero or one	31 (12%)	0 (0%)	64 (13%)	1 (<1%)
Two	214 (81%)	92 (84%)	309 (65%)	81 (62%)
Three or more	19 (7%)	18 (16%)	105 (22%)	48 (37%)
Use of NNRTI drug in failing regimen	37 (14%)	105 (96%)	97 (20%)	120 (92%)
NRTI drugs prior to failing regimen				
Zero	53 (20%)	47 (43%)	70 (15%)	48 (37%)
One or two	99 (38%)	37 (33%)	194 (41%)	32 (25%)
Three or more	112 (42%)	26 (24%)	214 (45%)	50 (38%)
Continuous covariates, Median (IQR)				
Age (years)	39 (33, 46)	41 (33, 47)	40 (35, 45)	41 (35, 47)
Most recent CD4+ T-lymphocyte count (cells/ μ l)	260 (123, 402)	332 (216, 572)	189 (72, 346)	182 (76, 343)
Most recent CD8+ T-lymphocyte count (cells/ μ l)	911 (590, 1215)	970 (624, 1305)	NA	NA
Most recent CD4%	17 (9, 21)	19 (12, 26)	13 (6, 21)	15 (7, 22)
Most recent CD8%	54 (48, 64)	54 (45, 63)	NA	NA
Nadir CD4+ T-lymphocyte count (cells/ μ l)	96 (22, 214)	147 (47, 337)	60 (10, 167)	92 (21, 212)
Most recent plasma HIV RNA level (\log_{10} copies/ml)	4.1 (3.4, 4.8)	3.9 (3.0, 4.5)	4.3 (3.8, 5.1)	4.5 (3.9, 5.1)
Peak plasma HIV RNA level (\log_{10} copies/ml)	5.0 (4.4, 5.4)	4.9 (4.4, 5.4)	5.2 (4.8, 5.7)	5.4 (5.0, 5.8)
Date of first HAART failure	1/2000 (7/1998, 5/2002)	8/2002 (1/2001, 10/2003)	9/1998 (6/1997, 2/2000)	4/2001 (1/2000, 8/2002)
Date of first HAART use	10/1997 (11/1996, 6/1999)	12/1999 (9/1997, 6/2001)	4/1997 (8/1996, 3/1998)	9/1999 (2/1998, 10/2000)
Date of first ART use	NA	NA	10/1995 (10/1993, 4/1997)	11/1998 (1/1996, 7/2000)
HIV diagnosis date	9/1994 (11/1991, 6/1997)	7/1996 (6/1992, 3/2000)	NA	NA

IQR, interquartile range; JHHCC, Johns Hopkins HIV Clinical Cohort; UNCHCC, University of North Carolina HIV Clinical Cohort. ^aNRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy. ^bAmong 264 first HAART failures in the UNCHCC whose failing regimen contained a protease inhibitor drug. ^cAmong 110 first HAART failures in the UNCHCC whose failing regimen did not contain a protease inhibitor drug. ^dAmong 478 first HAART failures in the JHHCC whose failing regimen contained a protease inhibitor drug. ^eAmong 130 first HAART failures in the JHHCC whose failing regimen did not contain a protease inhibitor drug.

whom were receiving a NNRTI and two nucleoside analogues), delay until treatment modification following virologic failure increased the hazard of both long-term mortality and immunologic failure. There was no clear harm associated with a delayed modification after failure of a protease inhibitor-based regimen. These observations were stable when we limited our analysis to those who were treatment naive prior to their first HAART regimen and when we limited our analysis to those whose protease inhibitor regimen included ritonavir boosting.

Data-adaptive regression was used to explore how the hazard of mortality changed over time under various switch times. Following first HAART failure on a reverse transcriptase inhibitor regimen, the hazard of mortality increased sharply while the patient remained on his or her original failing therapy. The hazard of mortality plateaued

following regimen modification, but remained elevated for up to 4 years among patients who delayed switching. This finding is consistent with the two hypothesized mechanisms by which delayed modification increases mortality: ongoing viral replication contributes to immune depletion and increased mortality risk while patients remain on their nonsuppressive therapy; and delay of modification results in accumulation of additional resistance mutations, with long-term consequences for treatment options.

In contrast, we observed no harm from delaying modification of a regimen containing a protease inhibitor drug following first and second HAART failures. Data-adaptive regression supported a distinct pattern in the hazard of mortality over time in this group (as compared to patients failing a reverse transcriptase inhibitor

Table 2. Association of covariates with modification of first failing highly active antiretroviral therapy regimen^a.

Covariate	UNCHCC		JHHCC	
	Hazard ratio (95% CI)	<i>P</i>	Hazard ratio (95% CI)	<i>P</i>
Nonwhite race	0.86 (0.62, 1.20)	0.38	1.08 (0.83, 1.41)	0.58
ART use prior to HAART	1.23 (0.90, 1.70)	0.20	1.30 (1.02, 1.64)	0.03
Male	1.11 (0.76, 1.64)	0.59	1.01 (0.80, 1.28)	0.94
Man who has sex with men [^]	1.25 (0.92, 1.68)	0.15	1.13 (0.91, 1.40)	0.29
Injection drug user	0.75 (0.49, 1.17)	0.20	0.94 (0.76, 1.17)	0.59
Prior AIDS diagnosis	1.67 (1.20, 2.33)	<0.001	NA	NA
New diagnosis of AIDS-defining illness in past month [*]	7.03 (3.41, 14.50)	<0.001	NA	NA
NRTI drugs in failing regimen (per drug)	0.78 (0.58, 1.06)	0.11	0.74 (0.64, 0.87)	<0.001
Use of NNRTI drug in failing regimen	0.82 (0.57, 1.16)	0.26	0.53 (0.40, 0.71)	<0.001
Use of protease inhibitor drug in failing regimen [*]	1.28 (0.88, 1.85)	0.19	0.68 (0.54, 0.86)	0.001
Use of boosted protease inhibitor drug in failing regimen ^{**}	0.97 (0.67, 1.40)	0.86	0.68 (0.52, 0.90)	0.01
Number of classes in failing regimen (per class) ^{* #}	0.91 (0.50, 1.67)	0.76	0.35 (0.28, 0.44)	<0.001
NRTI drugs prior to failing regimen (per drug)	1.14 (1.01, 1.28)	0.03	1.06 (0.98, 1.13)	0.14
Age (per 5 years)	0.94 (0.88, 1.01)	0.11	0.97 (0.91, 1.03)	0.28
Most recent CD4+ T-lymphocyte count (per 100 cells/ μ l) ^{* #^}	0.75 (0.69, 0.81)	<0.001	0.85 (0.81, 0.90)	<0.001
Most recent CD8+ T-lymphocyte count (per 100 cells/ μ l)	0.97 (0.93, 1.01)	0.16	NA	NA
Most recent CD4% (per 10%)	0.58 (0.49, 0.69)	<0.001	0.74 (0.66, 0.84)	<0.001
Most recent CD8% (per 10%)	1.29 (1.11, 1.50)	<0.001	NA	NA
Nadir CD4+ T-lymphocyte count (per 100 cells/ μ l) [*]	0.63 (0.54, 0.73)	<0.001	0.89 (0.80, 0.98)	0.02
Most recent plasma HIV RNA level (per log ₁₀ copies/ml) [*]	1.93 (1.59, 2.33)	<0.001	1.58 (1.43, 1.74)	<0.001
Peak plasma HIV RNA level (per log ₁₀ copies/ml)	1.93 (1.49, 2.50)	<0.001	1.15 (0.98, 1.35)	0.09
Calendar date (per year) ^{#^}	0.92 (0.86, 0.99)	0.02	0.92 (0.87, 0.98)	0.01
Date of first HAART use (per year)	0.99 (0.90, 1.08)	0.83	0.93 (0.88, 0.99)	0.02
Date of first ART use (per year)	NA	NA	0.97 (0.93, 1.01)	0.11
HIV diagnosis date (per year)	0.98 (0.96, 1.01)	0.31	NA	NA

ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; JHHCC, Johns Hopkins HIV Clinical Cohort; NA, not available; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; UNCHCC, University of North Carolina HIV Clinical Cohort. ^aHazard ratios based on pooled logistic regression model; *P* values and 95% CIs based on nonparametric bootstrap. Covariates used in final models of treatment modification indicated with ^{*}. Covariates used in final models of censoring and treatment interruption indicated with [#], and [^], respectively. Final modification and censoring models also included indicators of laboratory measurements within past month. Final censoring models also included time spent on the failing regimen.

regimen). Following first HAART failure on a protease inhibitor regimen, the hazard of mortality increased over time, with very little short-term difference between patients who modified therapy immediately and those who delayed modification. To the extent that the hazard of mortality differed among patients with immediate versus delayed modification times, a protective effect of delayed modification emerged only several years following failure.

Several mechanisms may account for the lack of harm in delaying modification after failure of a protease inhibitor regimen. First, earlier work has shown that resistance emerges rapidly during failure of an NNRTI-based regimen but is uncommon after failure of most protease inhibitor-based regimens [9–14]. Second, during first and second HAART failure, cross-resistance among the protease inhibitors is less common than it is among the NNRTI class. Hence, patients who develop resistance to

Table 3. Estimated effect of delay until treatment modification following first and second highly active antiretroviral therapy failures on hazards of death and immunologic failure^a.

Outcome	Hazard ratio per additional 3 months on failing regimen (95% CI)		Hazard ratio per additional 3 months on failing regimen (95% CI)	
	Failing regimen contains protease inhibitor	<i>P</i>	Failing regimen does not contain protease inhibitor	<i>P</i>
Death	0.93 (0.87, 0.99)	First HAART failure	1.23 (1.08, 1.40)	0.002
		0.03		
Immunologic failure or death	0.98 (0.94, 1.03)	Second HAART failure	1.21 (1.07, 1.36)	0.002
		0.45		
Death	0.88 (0.77, 1.00)	0.06	1.12 (0.89, 1.41)	0.33
Immunologic failure or death	0.87 (0.75, 1.00)	0.05	1.21 (0.74, 1.99)	0.45

CI, confidence interval; HAART, highly active antiretroviral therapy. ^aEstimated using weighted pooled logistic regression, with weights used to control for confounding of time until treatment modification, baseline differences between patients failing a protease inhibitor versus reverse transcriptase inhibitor regimen, and potentially informative censoring/treatment interruption. 95% CIs and *P* values based on nonparametric bootstrap. Immunologic failure defined as two CD4+ T-lymphocyte counts, consecutively or within 12 weeks of each other, below last CD4+ T-lymphocyte count during month prior to HAART initiation.

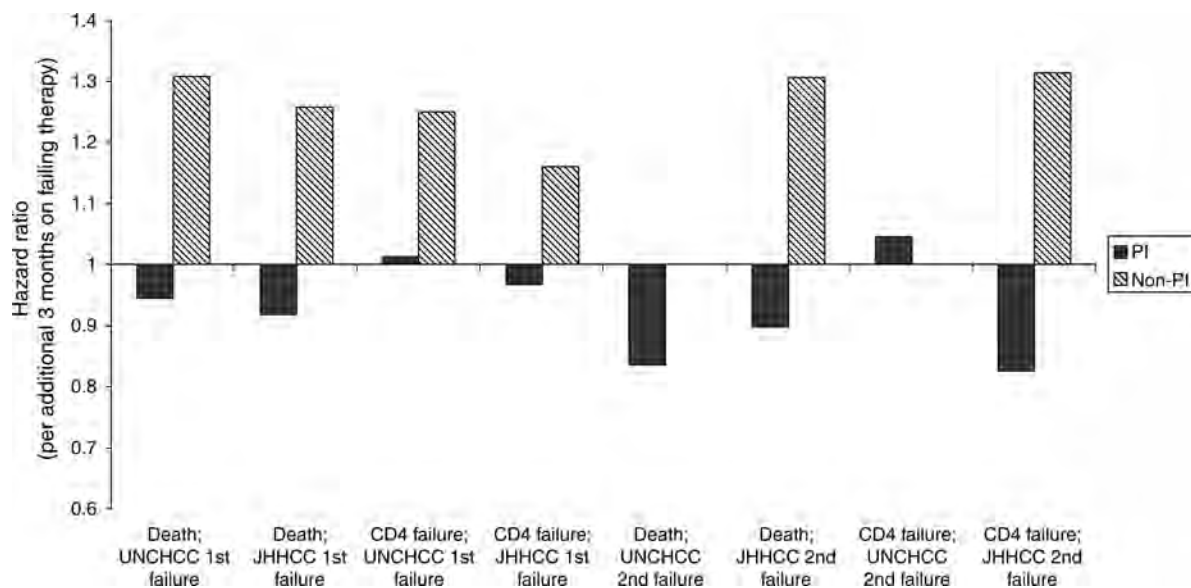


Fig. 1. Cohort-specific estimates of the hazard ratio associated with delay until treatment modification. Conditional hazard ratios estimated using weighted pooled logistic regression, with weights used to control for confounding of time until treatment modification, baseline differences between patients failing a protease inhibitor versus reverse transcriptase inhibitor regimen, and potentially informative censoring/treatment interruption. Hazard ratios for reverse transcriptase inhibitor regimens in the UNCHCC following 2nd HAART failure not reported because of small sample size ($N = 31$). PI: failing regimen contains protease inhibitor; Non-PI: failing regimen does not contain protease inhibitor; Death: outcome is all-cause mortality; CD4 failure: outcome is composite of all-cause mortality and immunologic failure; JHHCC 1st failure/JHHCC 2nd failure: among patients in JHHCC experiencing first and second HAART failures, respectively; UNCHCC 1st failure/UNCHCC 2nd failure: among patients in UNCHCC experiencing first and second HAART failures, respectively. HAART, highly active antiretroviral therapy; JHHCC, the Johns Hopkins HIV Clinical Cohort; PI, protease inhibitor; UNCHCC, University of North Carolina HIV Clinical Cohort.

the protease inhibitor component of their regimen may still be able to respond to other drugs in this class. A third and more speculative mechanism pertains to the virulence of protease inhibitor-resistant viruses. Failure of a protease inhibitor regimen has been associated with less rapid immunologic progression than failure of an NNRTI regimen [17,28]. This effect may be due both to reduced HIV RNA levels and to a reduced capacity of the protease inhibitor-resistant HIV variant to cause CD4+ T-cell decline *in vivo* [29,30]. Our observations suggesting differential long-term outcomes based on regimen type (NNRTI versus protease inhibitor) are supported by research showing that NNRTI resistance is a more consistent predictor of mortality than resistance to other therapeutic drug classes [25,31]. Collectively, these observations indicate that protease inhibitor-based regimens will be associated with lower rates of disease progression than NNRTI-based regimens in situations in which modification is delayed because virologic failure cannot be identified (due to lack of plasma HIV RNA monitoring) or because subsequent regimens are not available.

Given the observational nature of the data, unmeasured confounders may have biased results in an unpredictable direction. Importantly, however, both the JHHCC and UNCHCC included laboratory data collected at the

discretion of the clinician, providing access to important factors that affect treatment decisions. Additional bias could have resulted from misspecification of the models used to estimate the weights. In order to minimize this concern, we used flexible data-adaptive approaches in modeling the weights and performed sensitivity analyses considering alternative weight models. These additional analyses yielded consistent results, supporting the robustness of our findings.

Several factors should be taken into account when considering the extent to which our results can be generalized. First, detection of virologic failure, which determined time of eligibility for our sample, depended on the measurement of consecutive HIV RNA levels. Thus, virologic failure could be identified more rapidly among patients who had HIV RNA levels assessed more frequently. Similarly, detection of immunologic failure depended on the timing of CD4+ T-cell count measurements. In addition, a substantial proportion of our sample consisted of patients treated with nonboosted protease inhibitor regimens and of patients with exposure to antiretroviral drugs prior to initiating HAART, potentially limiting the applicability of our results to inform expanded access to HAART in treatment-naïve settings. To investigate the latter issue, we performed sensitivity analyses in which we excluded, in turn,

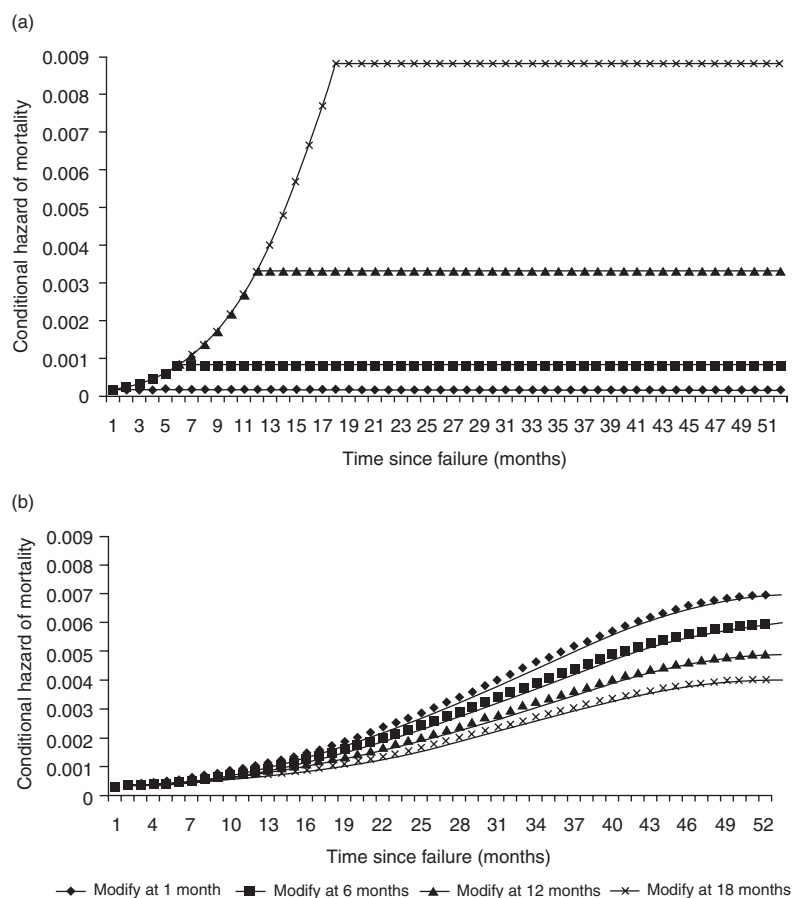


Fig. 2. Estimated hazard of mortality following first highly active antiretroviral therapy failure under various modification times.

Conditional hazard of mortality over time, plotted for a range of delay times until treatment modification. Estimates based on weighted pooled logistic regression, with weights used to control for confounding of time until treatment modification, baseline differences between patients failing a protease inhibitor versus reverse transcriptase inhibitor regimen, and potentially informative censoring/treatment interruption. The deletion/substitution/addition algorithm was used to model the conditional hazard of all-cause mortality as a function of time since failure occurred and months spent on failing regimen, making minimal parametric assumptions. (a) Among patients failing a protease inhibitor regimen. (b) Among patients failing a reverse transcriptase inhibitor regimen.

patients treated with nonboosted protease inhibitors and patients with antiretroviral experience prior to initiating HAART. Whereas the reduced sample sizes meant that the variability of our estimates increased such that the results were no longer significant, the reasonable consistency of the point estimates across these subpopulations suggests that the findings reported here are not solely the result of historical treatment patterns experienced by these observational cohorts.

Although we report here no clear harm to delaying a switch in therapy among protease inhibitor-treated patients, it should be emphasized that the optimal long-term clinical outcome was observed among those who were treated with reverse transcriptase inhibitor regimens (most of whom were on standard NNRTI/nucleoside analogue regimens) and who were managed aggressively during virologic failure. In other words, there was a hierarchy of efficacy in the context of first HAART failure: patients failing a reverse transcriptase

inhibitor regimen who modified immediately had the lowest mortality, followed by patients failing a protease inhibitor regimen at a range of switch times, and finally, patients failing a reverse transcriptase inhibitor regimen who delayed modification had the highest mortality.

In summary, our findings support the recommendation that treatment be modified immediately following first HAART failure. This is particularly true for individuals receiving a standard first HAART regimen containing nucleoside analogues and a NNRTI. Access to HAART is being expanded rapidly worldwide, and, at least in the short-term, first HAART regimens are likely to be NNRTI-based. Given the elevated risk of mortality that is associated with delayed treatment modification in patients receiving these regimens, our data support making viral load testing more available. Our data also suggest that the prolonged treatment benefits that have been repeatedly observed during virologic failure – all of

which have been based largely on protease inhibitor regimens – may not be realized in regions where access to these regimens is limited [17,18,32,33]. These considerations should be taken into account when planning HAART delivery systems, and within the context of resource constraints and the urgent need to scale-up therapy as rapidly as possible, efforts should be made to minimize delay until modification.

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