Selective Drug Taking During Combination Antiretroviral Therapy in an Unselected Clinic Population

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Objectives: Multidrug therapy is necessary to achieve sustained viral suppression. Discordant adherence to individual components of a multidrug regimen may lead to adverse outcomes.

Methods: Antiretroviral-naive patients initiating therapy from 1997 through 2002 were included. Adherence for each antiretroviral was determined using pharmacy refill data. Selective drug taking was defined as ≥5% difference in adherence between 2 components of an antiretroviral regimen lasting at least 60 days.

Results: A total of 322 of 415 patients (78%) met inclusion criteria. Selective drug taking occurred in 47 of 322 patients (15%) and on 51 of 438 regimens (12%). Factors associated with selective drug taking were lower baseline CD4 lymphocyte count (adjusted odds ratio [AOR]: 1.3, 95% CI: 1.1 to 1.6 per 100 cell/μL decrease); 3 times daily dosing schedule (AOR: 4.1, 95% CI: 1.1 to 15.5); and the presence of significant adverse drug events (AOR: 2.9, 95% CI: 1.3 to 6.4). Regimens containing a fixed-dose combination dosage form were less likely to have selective drug taking (AOR: 0.5, 95% CI: 0.2 to 0.99). Outcomes independently associated with selective drug taking included earlier progression to a new AIDS-defining illness or death (hazard ratio: 2.3, 95% CI: 1.2 to 4.5).

Conclusions: Selective drug taking was relatively common among patients taking combination antiretroviral therapy. The factor most closely associated with selective drug taking was the presence of an adverse drug event. Clinical outcomes appeared worse in patients with selective drug taking.

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Highly active antiretroviral therapy (HAART) effectively suppresses viral replication and improves outcomes in the treatment of HIV infection,[1] but a very high degree of adherence is required to obtain maximal benefit from antiretroviral therapy. Studies using different forms of adherence assessment have estimated that at least 95% adherence is required to have a high probability of achieving sustained complete viral suppression.[2,3] Most reports have documented median adherence levels of 50%–90%.[2,4,5]

To date, most adherence assessments have reported a single summary adherence statistic.[2,6] In clinical practice, however, it is not uncommon for patients to report missing doses of individual components of their regimen. The effects of this behavior are unknown but may lead to premature virologic failure, the development of antiretroviral resistance, and poor clinical outcomes. If selective nonadherence were common, the development and use of antiretroviral combination formulations containing the components of the most commonly used regimens would be supported. We evaluated the frequency, magnitude, associated factors, and outcomes of selective drug taking.

METHODS

Study Population

Denver Health is an integrated public healthcare system serving approximately 1300 HIV-infected individuals.[7] A comprehensive effort was made to identify antiretroviral-naive patients initiating therapy between January 1997 and December 2002. Patients were identified using the local database of the Adult and Adolescent Spectrum of Disease (ASD)[8] in conjunction with an administrative pharmacy refill database. At Denver Health, all HIV-infected patients are included in ASD; there is not a weighted sampling scheme to include women and people of color. It is known from previous work that approximately 90% of Denver Health patients use the Denver Health pharmacy system for prescription medications.[9] Patients were excluded if they initiated therapy at an outside facility, had no verifiable antiretroviral use, or did not have at least 1 multidrug regimen that lasted 60 days. Among included patients, individual regimens were excluded if

composed of a single dosage form or if the regimen duration was <60 days. Up to 3 regimens per person were analyzed. The Colorado Multiple Institutional Review Board approved the study.

Definitions

Patients were defined as having active psychiatric disease (International Classification of Diseases [ICD]-9 codes 295.X and 296.X) or active substance abuse (ICD-9 codes 304.X and 305.X) if these diagnoses were coded at least once from 6 months prior to 6 months after first regimen initiation. All regimen-specific variables were obtained through the pharmacy refill database. Duration of follow-up spanned from the dispense date for the first antiretroviral regimen until censoring, death, or March 2004, whichever occurred first. Follow-up was censored when an outside prescription source was identified or when a patient terminated care in the Denver Health system.

Included regimens needed to be at least 60 days in duration (ie, the prescriptions needed to have been filled at least twice based on a typical 30-day supply per fill). Monotherapy and regimens using solely fixed-dose combination antiretroviral medications were excluded. Fixed-dose combination dosage forms available during this study included coformulated lamivudine/zidovudine, abacavir/lamivudine/zidovudine, and lopinavir/ritonavir. All medications initiated within 60 days of each other constituted a regimen. Regimens were considered modified if a single switch was made within an antiretroviral class. Tenofovir was categorized as a nucleoside analogue. Any other drug addition, deletion, or gap in refills lasting at least 180 days signified the termination of a regimen. The termination date was the date of dispensing of the last refill for a regimen, or the switch date if a new regimen was immediately started. A significant adverse drug event was any adverse event necessitating discontinuation of a medication. A lapse in care was defined as a concomitant gap in antiretroviral refills and clinical care of at least 180 days.

Adherence was determined based on pharmacy refill data and calculated by individual drug as doses obtained divided by doses prescribed. Regimen-specific adherence was calculated as the average adherence for medications included in that regimen over the entire duration of that regimen. Overall adherence for each patient was calculated as the duration-weighted average adherence of up to 3 regimens.

Selective drug taking was defined as a difference in adherence of at least 5% between any 2 individual components of a multidrug regimen during the course of a regimen. This difference in adherence was chosen based on the evidence that a decrement of 5% in overall adherence decreases the chance of achieving complete viral suppression.[2,3] Specific programming was developed to account for overlapping prescriptions, regimen modifications, and overlapping regimens to ensure that these factors did not contribute to the differences in adherence detected.

Data Abstraction

Medical records were reviewed to identify regimen initiation, modification, and termination dates. The reasons for regimen modifications and terminations were recorded. Most prescriptions are dispensed in 30-day supplies. To ensure that patients were receiving medicines through our pharmacy, we specifically reviewed the medical records corresponding to the dates of any gaps in refills lasting at least 30 days to look for evidence of outside pharmacy use. In addition, we reviewed all phone encounters, another common way to identify use of an outside pharmacy.

The Denver Health administrative databases were used to identify psychiatric comorbidity or presence of active substance abuse. Because antiretroviral resistance testing was not commonly obtained throughout the years included in the study, we could not evaluate the possible association between selective drug taking and the development of antiretroviral resistance. Both administrative and chart review data were abstracted to find evidence of any opportunistic infection or new AIDS-defining conditions.

Data Analysis

We validated the use of pharmacy refill data as a meaningful measure of adherence by evaluating the association between adherence to therapy during the first 6 months of treatment and the proportion of patients achieving an HIV RNA level <400 copies/mL 6 months after starting therapy. We evaluated possible risk factors for selective drug taking in 2 ways. First, we compared patients with selective drug taking with those without selective drug taking, and developed a multivariate model including all factors with a significance level of $P < 0.20$ in univariate analysis. We then compared regimens in which selective drug taking occurred with regimens in which there was no selective drug taking. Univariate and multivariate nonlinear mixed models were developed to account for repeated measures (ie, regimens) in the same individual.

Median overall adherence levels in patients with or without selective drug taking were compared using the Wilcoxon rank sum test. We evaluated the association of selective drug taking on the first regimen with time to first regimen termination using Kaplan-Meier analysis with the log-rank test. A Cox proportional hazards regression model was used to adjust for the effects of first regimen adherence on the time to first regimen termination.

Virologic and CD4 lymphocyte outcomes were assessed based on whether selective drug taking occurred on the first regimen using an intent-to-treat approach. Using Kaplan-Meier analysis, we measured median time to virologic failure (defined as 2 consecutive viral load measurements >400 copies/mL, or a single value >10,000 copies/mL after initial suppression) and time to a CD4 lymphocyte increase of 100 cells/μL, respectively. For these analyses, censoring occurred if the specific outcome was not achieved during follow-up. Cox proportional hazards models were used to adjust for adherence during the first 6 months of therapy, baseline CD4 count, and baseline HIV viral load in these analyses.

We evaluated the association between selective drug taking and HIV disease progression (a new AIDS-defining illness by Centers for Disease Control definition or death) by calculating incidence rates of these outcomes.[10] Comparisons

of incidence rates were performed using the methods of Oleinick and Mantel.[11] A Cox proportional hazards regression model was used to adjust for baseline CD4 lymphocyte count and adherence during the first 6 months of therapy in these analyses. All analyses were performed using SAS statistical software version 8.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Of 415 patients who initiated antiretroviral therapy, 322 (78%) met the inclusion criteria. Patients were excluded for not having a single regimen meeting our inclusion criteria (n = 41), use of an outside pharmacy at initiation (n = 32), starting antiretroviral therapy while institutionalized (n = 10), or because antiretroviral use could not be verified (n = 10). Among patients included in the study, 90 individual regimens were excluded because of duration <60 days (n = 63), outside source of medications (n = 18), sole use of fixed-dose combination products (n = 8), or monotherapy (n = 1).

Similar to previous data from Denver Health,[9] we found that 42 of 415 patients (10%) used an outside pharmacy at some point during therapy. Thirty-two patients used it at first initiation and were excluded. Ten patients switched to an outside pharmacy during therapy and were censored at that time.

The cohort was primarily composed of men who had sex with men. White, Hispanic, and African American ethnicities were each well represented. Median baseline CD4 lymphocyte count was 158 cells/μL (interquartile range [IQR]: 44 to 283) and median baseline HIV viral load was 5.1-log copies/mL (IQR: 4.6 to 5.6). There were no significant differences between patients who were included in the study and those excluded (data not shown). Median follow-up of included patients was 2.5 years (IQR: 1.4 to 4.1).

These 322 patients received 438 individual regimens meeting our inclusion criteria. Nearly all regimens (426 of 438, 97%) contained at least 3 antiretrovirals. Forty-eight percent were protease inhibitor (PI) based, 38% were nonnucleoside reverse transcriptase inhibitor (NNRTI) based, and 10% contained both an NNRTI and a PI. Sixty-six regimens (15%) were modified. Adverse drug events were the cause of 96% of regimen modifications and 59 (31%) of 191 noncensored regimen terminations. The most common adverse events leading to modification or termination were gastrointestinal adverse effects (45%), anemia (16%), sleep disturbances and central nervous system adverse effects (10%), and metabolic adverse effects (10%).

Our adherence validation showed a strong relationship between adherence during the first 6 months of therapy and the likelihood of achieving an HIV RNA level <400 copies/mL at 6 months (Fig. 1). The overall median adherence level in our population was 89.5% (IQR: 75.9 to 97.3).

Selective Drug Taking

Selective drug taking occurred in 47 of 322 patients (15%) and in 51 of 438 regimens (12%). Four patients had selective drug taking during 2 regimens. In regimens with selective drug taking, the median difference in adherence between the least and most taken medication was 10.9% (IQR: 6.7 to 19.2).

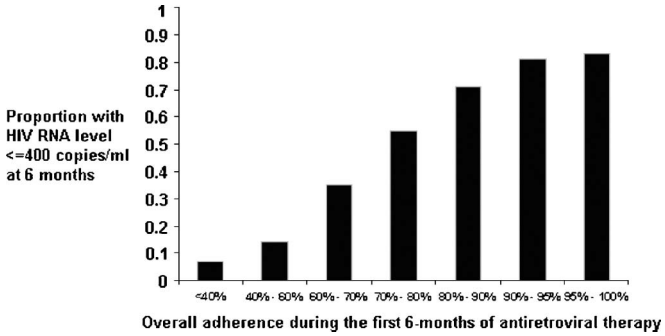

FIGURE 1. Association between overall adherence during the first 6 months of initial antiretroviral therapy and HIV viral suppression at 6 months.

We evaluated the association between antiretroviral drug class and selective drug taking for the first regimen only. In the 271 first regimens, there were 827 individual medications that involved 672 dosage forms (fixed-dose combination preparations counted as one dosage form). Selective drug taking occurred on 25 first regimens and involved 32 individual dosage forms. Selective drug taking was most common with PIs (14/171 dosage forms = 8.2%), then NNRTIs (8/108 = 7.4%), and least common with NRTIs (10/393 = 2.5%). There was a significant difference in the frequency of selective drug taking by drug class for the comparison of PI vs. NRTI (P = 0.002) and for the comparison of NNRTI vs. NRTI (P = 0.02).

The demographic characteristics of patients with selective drug taking were similar to those of patients without selective drug taking (Table 1). However, patients with selective drug taking had lower baseline CD4 lymphocyte counts and more often had active psychiatric diagnoses. In a multivariate logistic regression, only baseline CD4 lymphocyte count remained significantly associated with the occurrence of selective drug taking. For every decrease of 100 cells/μL in baseline CD4 lymphocyte counts, the odds of selective drug taking increased by 1.3 (95% CI: 1.1 to 1.6).

Regimens that were modified were more likely to have selective drug taking; 25% of selective drug taking regimens were modified, whereas only 14% of nonselective drug taking regimens were modified (P = 0.03) (Table 2). Because modifications were almost always due to adverse events, we investigated the association of significant adverse events and selective drug taking. Among regimens with selective drug taking, 61% were associated with a significant adverse drug event on the current or prior regimen vs. 34% of nonselective drug taking regimens (P < 0.001).

Regimens with selective drug taking more often included a medication requiring 3 times daily dosing and less often contained at least one fixed-dose combination tablet (Table 2). There was an association between the regimen number and selective drug taking, occurring in 25 of 271 first regimens (9%), 21 of 112 second regimens (19%), and 5 of 55 third regimens (9%) (P = 0.007). In a multivariate logistic regression model, current or prior adverse drug event (OR: 2.9, 95% CI: 1.3 to 6.4), 3 times daily dosing frequency

TABLE 1. Comparison of Demographic and Clinical Characteristics of Patients With Versus Those Without Selective Drug Taking at Denver Health, Initiating First Antiretroviral Therapy From 1997–2002

	Bivariate Analysis			Multivariate Analysis
	Selective Drug Taking (n = 47)	No Selective Drug Taking (n = 275)	*P* Value	AOR (95% CI)
Age (years)*	37 (33–44)	37 (31–42)	0.49	
Gender				
Female	7 (15%)	30 (11%)	0.43	
Race				
White	18 (38%)	132 (48%)	0.56	
Black	11 (23%)	54 (20%)		
Hispanic	16 (34%)	86 (31%)		
HIV acquisition risk factor				
MSM	27 (57%)	150 (55%)	0.99	
IDU	4 (9%)	22 (8%)		
MSM/IDU	6 (13%)	38 (14%)		
Heterosexual	4 (9%)	22 (8%)		
Unknown	6 (13%)	43 (16%)		
Primary language				
English	31 (66%)	206 (75%)	0.55	
Spanish	3 (6%)	29 (11%)		
Missing	13 (28%)	40 (15%)		
Birth country				
US	40 (85%)	225 (82%)	0.69	
Mexico	4 (9%)	32 (12%)		
Other/missing	3 (6%)	18 (7%)		
Psychiatric comorbidity†	18 (38%)	67 (24%)	0.05	1.9 (0.9–3.7)
Active substance use‡	11 (23%)	89 (32%)	0.22	
Baseline CD4 lymphocyte count (cells/μL)*	71 (33–232)	167 (50–300)	0.03	1.3 (1.1–1.6) per 100 cells/μL decrease
Baseline log HIV-1 RNA (copies/mL)*	5.2 (4.9–5.6)	5.1 (4.6–5.6)	0.46	

*Median (IQR).
†Based on ICD-9 codes 295.X and 296.X.
‡Based on ICD-9 codes 304.X and 305.X.
MSM indicates men who have sex with men; IDU, intravenous drug user.

(OR: 4.1, 95% CI: 1.1 to 15.5), and inclusion of a fixed-dose combination dosage form (OR: 0.5, 95% CI: 0.2 to 0.99) retained significant associations with selective drug taking.

Association Between Selective Drug Taking and Outcomes

Patients with selective drug taking had lower median overall adherence levels, 78.7% (IQR: 64.8% to 89.3%) vs. 90.7% (IQR: 77.7% to 97.7%) for patients without selective drug taking ($P < 0.001$). In subsequent outcome analyses, adjusted models controlled for differences in overall adherence.

First regimen duration was significantly shorter in univariate analysis when selective drug taking was present (Fig. 2). The median time to first regimen termination with selective drug taking was 1.3 years vs. 2.7 years for regimens without selective drug taking ($P = 0.02$). There was a strong association between first regimen adherence and time to first regimen termination (data not shown). In a Cox proportional hazards model adjusted for first regimen adherence, the association between selective drug taking and time to initial regimen termination was no longer significant (hazards ratio: 1.5, 95% CI: 0.9 to 2.6).

In contrast to time to regimen termination, which includes reasons other than virologic failure, an assessment of time to first virologic failure showed no difference between patients with or without selective drug taking on the first regimen. In a Cox proportional hazards regression, adherence during the first 6 months of therapy was the only variable associated with time to virologic failure. For every 10% decrease in adherence, the hazard of first virologic failure increased by 26% (95% CI: 21% to 31%). CD4 lymphocyte changes were similar between patients with and without selective drug taking on the first regimen. The median time to achieve a CD4 lymphocyte increase of 100 cells/μL was 140 days vs. 162 days in patients with and without selective drug taking, respectively ($P = 0.82$).

Patients with selective drug taking on at least one regimen had higher rates of new AIDS-defining illnesses (8.6 vs. 3.6 per 100 person-years of follow-up [PY], $P = 0.008$), death (6.6 vs. 1.4 per 100 PY, $P < 0.001$), and the combined endpoint of new AIDS-defining illness or death

TABLE 2. Association Between Regimen-Specific Factors and Selective Drug Taking, Using a Nonlinear Mixed Model

	Selective Drug Taking (n = 51)	No Selective Drug Taking (n = 387)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Antiretroviral drugs in regimen, mean (SD)	3.2 (0.4)	3.1 (0.4)	1.7 (0.8 to 0.8)	2.2 (0.9 to 5.4)
Total regimen pills per day, mean (SD)	9.5 (4.8)	9.2 (4.0)	1.1 (0.8 to 1.7)	1.0 (0.6 to 1.5)
Dosing schedule 3 times daily, n (%)	8 (16%)	28 (7%)	3.0 (1.04 to 8.7)	4.1 (1.1 to 15.5)
Different dosing schedules, n (%)	20 (39%)	146 (38%)	1.1 (0.5 to 2.1)	0.6 (0.2 to 1.4)
Contained a fixed-dose combination tablet, n (%)	18 (35%)	210 (54%)	0.5 (0.3 to 1.03)	0.5 (0.2 to 0.99)
Modified regimen, n (%)	13 (25%)	53 (14%)	2.2 (1.01 to 4.8)	NA*
Significant adverse drug event, current or prior regimen, n (%)	31 (61%)	133 (34%)	2.0 (0.97 to 3.9)	2.9 (1.3 to 6.4)

*Modified regimens represent a subset of regimens with a significant adverse drug event on the current or prior regimen.

(12.9 vs. 4.4 per 100 PY, $P < 0.001$) than patients without selective drug taking. Selective drug taking (Fig. 3), baseline CD4 lymphocyte count, and adherence during the first 6 months of therapy were independently associated with the risk of a new AIDS-defining illness or death in an adjusted Cox proportional hazards model. The adjusted hazard of HIV disease progression was 2.3 (95% CI: 1.2 to 4.5) among patients with selective drug taking. For every 100-cell/μL decrease in baseline CD4 lymphocyte count, the adjusted hazard of HIV disease progression was 1.5 (95% CI: 1.2 to 1.9). For every 10% decrease in overall adherence, the adjusted hazard of HIV disease progression was 1.2 (95% CI: 1.1 to 1.4). There was no association of HIV disease progression with the presence of a significant adverse event, the presence of a lapse in care, or baseline HIV viral load.

DISCUSSION

We describe the frequency, risk factors, and outcomes associated with selective drug taking (differential adherence to components of multidrug antiretroviral therapy). The adherence measure used (pharmacy refill data) has been shown in this and other studies to correlate well with virologic, immunologic, and clinical outcomes of antiretroviral therapy.[3,12,13] Selective drug taking was common, occurring in 15% of an unselected clinic population and on 12% of all regimens that had the potential for selective drug taking. Patient-specific factors associated with selective drug taking were lower baseline CD4 lymphocyte count and psychiatric comorbidity; regimen-specific factors were 3 times daily dosing, lack of a fixed-dose combination dosage form on that regimen, and the occurrence of significant adverse drug events. The presence of selective drug taking was associated with earlier regimen termination. It was also associated with an increased risk of a new AIDS-defining illness or death, even after adjusting for baseline CD4 lymphocyte count and overall adherence level.

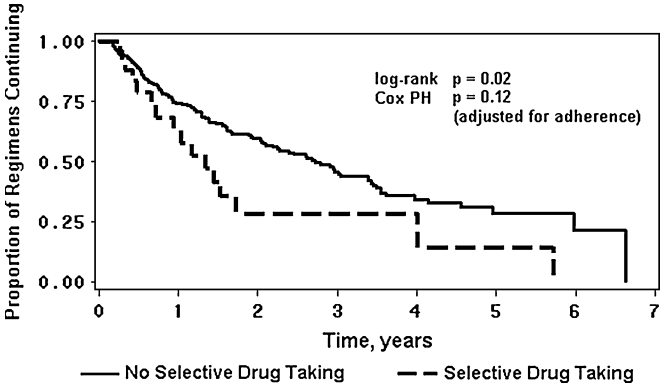

FIGURE 2. Kaplan-Meier analysis of time to first regimen termination in first regimens with vs. those without selective drug taking.

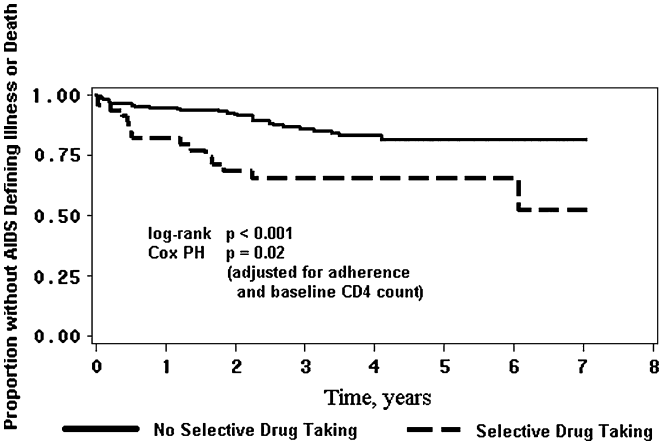

FIGURE 3. Kaplan-Meier analysis of time to new AIDS-defining illness or death among patients with vs. those without selective drug taking on at least one regimen.

Despite the critical importance of multidrug therapy in a number of areas of medical therapeutics (eg, treatment of HIV, tuberculosis, diabetes, hypertension, cardiovascular disease), little information has been published on selective drug taking. A small study using electronic adherence monitoring of different components of combination antiretroviral therapy found that selective drug taking was more common among patients on 3 times daily dosing.[14] In an early study of adherence to multidrug tuberculosis treatment, 5 of 26 patients (19%) had apparent selective drug taking of isoniazid or para-aminosalicylic acid, based on urine testing.[15] Additional study of selective drug taking appears warranted.

Selective drug taking was common in our study; 1 of 7 patients (15%) met our criteria for selective drug taking on at least one regimen. Selective drug taking was more common during second regimens and correlated with adverse drug events on either the current or prior regimen. Adverse drug events have been a common cause of both modifications and terminations in several other published reports. In cohort studies of patients initiating combination antiretroviral therapy, 21%–29% of patients changed at least one drug during a median follow-up of 10–14 months.[16,17] There is also evidence that adverse drug events affect overall adherence in a detrimental way; in an adherence substudy of a trial of combination antiretroviral therapy, patients with adverse drug events were 12.8 times less likely to have self-reported adherence from 95% to 100%.[18] Our data demonstrate that adverse drug events are also associated with selective nonadherence.

A common finding in studies of adherence to treatment of diabetes, hypertension, asthma, and HIV infection is that adherence decreases with greater dosing frequency.[19–22] We found a similar association of a 3 times daily dosing schedule with selective drug taking when compared with once or twice daily regimens. We were unable to examine the question of whether decreasing dosing frequency from twice to once daily would show any further differences, because once daily regimens were not in wide use during our study.

Selective drug taking was associated with 2 clinically relevant outcomes: shorter first regimen duration and an increased risk of HIV disease progression (new AIDS-defining illness or death). Adverse events were one of the most common causes of regimen termination in this and other studies,[23] and they were also associated with selective drug taking. Therefore, it is not surprising that selective drug taking was associated with shorter regimen duration. HIV disease progression was associated with baseline CD4 cell count and overall adherence, as has been previously described.[24] Even after adjustment for these 2 key factors, selective drug taking was associated with an increased risk of HIV disease progression. Our retrospective study does not provide a clear explanation for this independent association, and the association between selective drug taking and HIV disease progression should be evaluated in other studies.

Our study has several limitations. First, there is no standard definition of selective drug taking. We used a definition of at least a 5% difference between the least- and most-taken component, and the association between selective drug taking and adverse treatment outcomes suggests that this was a reasonable definition. Second, this was a retrospective study, so assessment of adverse events included only those that led to a change in medication. Less severe adverse events may have affected adherence and selective drug taking, but we were unable to assess this. Third, we were unable to assess the effect of selective drug taking on the outcome with which it may be most closely related—the development of antiretroviral resistance. Fourth, the sample size of the cohort limited the power of subgroup comparisons. Finally, the use of ICD diagnosis codes to identify active substance abuse and psychiatric disorders may not accurately or completely define these groups.

There are several important implications of our research. Adverse drug events and psychiatric comorbidity have a significant impact on the management of HIV-infection in patients on HAART. Whether more intensive adverse event counseling and management or focused management of psychiatric comorbidity[25] would help decrease the clinical impact of these events is unknown. Our findings speak to the potential value of fixed-dose combination dosage forms in ensuring uniform adherence to medications on the same regimen. Increasing the use of these products may improve the outcomes of potent antiretroviral therapy. Finally, our findings may have implications for other disease processes requiring multidrug therapy. We hope our research encourages others to look at this potentially important phenomenon in different populations and with different adherence measures.

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