SPILLOVER ADHERENCE EFFECTS OF FIXED-DOSE COMBINATION HIV THERAPY

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BACKGROUND

Highly-active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV) disease generally includes multiple agents from two or more drug classes. Fixed-dose combination products (FDCs) consisting of two or more agents in a single tablet may simplify HAART.

FDCs improve adherence compared with their separate components. However, specific evidence of a spillover adherence effect on remaining regimen components is lacking.

The objective of this study was to compare third-agent adherence between individuals receiving HAART containing an FDC of abacavir sulfate (ABC) 600 mg + lamivudine (3TC) 300 mg (Epzicom [GlaxoSmithKline]) and those taking any combination of two nucleoside reverse transcriptase inhibitors (NRTIs) as separate pills.

METHODS

Data and Patients

- Data were from the Integrated Health Care Information Services (IHCIS) Managed Care Benchmark Database, a national sample of 30 managed care health plans covering approximately 38 million lives from 1997-2005.
- Individuals ≥ 18 years of age with one or more pharmacy claims for Epzicom (FDC group) or two or more NRTIs as separate pills (NRTI Combo group) were included. Exclusion criteria included:
  - Receipt of both Epzicom and one or more of its components on the index date
  - < 6 months' continuous enrollment prior to the index date
  - < 60 days' continuous enrollment after the index date
  - Age < 18 years on the index date

Study Follow-Up

- The date of the first study drug claim was designated the index date.
- Follow-up was defined as the period ending with the earliest of the following:
  - Expiration of the days' supply for the last observed refill
  - Receipt of alternative study therapy
  - Failure to receive a third regimen component within 7 days of the index date
  - A gap of > 180 days in study therapy
  - End of health plan enrollment
  - End of the IHCIS database

Adherence Measure

- The primary outcome was treatment adherence to the third agent.
- Adherence was measured by the medication possession ratio (MPR) as

$$\frac{\sum \text{Days supply in observation period}}{\text{Days in observation period}}$$

Statistical Analysis

- Patient characteristics measured at the index date included age, gender, geographic region, insurance payer type, insurance product type, prior exposure to antiretroviral therapy, and eligibility for mental health benefits.
- Substance abuse and/or mental health diagnoses were measured in the 6 months prior to therapy initiation.

METHODS

Statistical Analysis

- Third-agent adherence was estimated using both continuous (Eq. 1) and dichotomous (Eq. 2) MPR measures,
  (1) $MPR = \beta_0 + \beta_1 FDC + \beta_2 X_i + \varepsilon$
  (2) $ADHERE = \beta_0 + \beta_1 FDC + \beta_2 X_i + \varepsilon$ where FDC = 1 for patients in the FDC group and 0 otherwise.
- Eq. 1 was estimated using ordinary least squares. Eq. 2 was estimated by logistic regression across four MPR thresholds (≥ 0.80, 0.85, 0.90, and 0.95).

RESULTS

Study Sample Characteristics (Table 1)

- 650 and 1,947 individuals were included in the FDC and NRTI Combo groups, respectively.
- Both overall regimen and third-agent adherence were higher for the FDC group.
- Median duration of follow-up for the FDC group was 272 days; for the NRTI Combo group, 338 days.

Regression Analyses (Table 2)

- With continuous MPR, FDC use provided a small, statistically insignificant, improvement in third-agent adherence (β = 0.0102; standard error = 0.0128).
- FDCs increased the odds of third-agent adherence for MPR thresholds above 0.90.

Table 1. Study Sample Characteristics

Characteristics	Treatment Group			
	FDC		NRTI Combo	
	n	%	n	%
Total study sample	650	100.0	1,947	100.0
Gender				
Male	550	84.6	1,597	82.0
Female	100	15.4	350	18.0
Age category				
18-34	96	14.8	329	16.9
35-44	278	42.8	920	47.3
45-54	205	31.5	534	27.4
55-64	62	9.5	142	7.3
≥ 65	9	1.4	22	1.1
Geographic region[a]				
Northeast	263	40.5	1,106	56.8
South	237	36.5	404	20.8
Midwest	62	9.5	114	5.9
West	69	10.6	82	4.2
Unknown	19	2.9	241	12.3
Insurance payer type				
Commercial	635	97.7	1,895	97.3
Medicaid	8	1.2	28	1.4
Medicare	7	1.1	24	1.3
Insurance product type[a]				
Health maintenance organization	231	35.5	699	35.9
Point of service plan	145	22.4	249	12.8
Preferred provider organization	266	40.9	915	47.0
Other	8	1.2	84	4.3
Year of study drug initiation				
1997	—	—	14	0.7
1998	—	—	13	0.7
1999	—	—	137	7.0
2000	—	—	185	9.5
2001	—	—	162	8.3
2002	—	—	248	12.7
2003	—	—	296	15.2
2004	119	18.31	547	28.1
2005	357	54.92	245	12.6
2006	174	26.77	100	5.2
MPR—regimen				
Mean (SD)[b]	0.88	0.170	0.82	0.20
Median (range)	0.96	0.26-1.00	0.86	0.08-1.00
MPR ≥ 0.80[b]	502	77.2	1,269	65.2
MPR ≥ 0.85[b]	459	70.6	1,126	57.8
MPR ≥ 0.90[b]	426	65.5	953	49.0
MPR ≥ 0.95[b]	355	54.6	766	39.3
MPR—third agent				
Mean (SD)[b]	0.92	0.168	0.85	0.245
Median (range)	1.0	0.03-1.0	0.98	0.005-1.0
MPR ≥ 0.80[b]	565	86.9	1,460	75.0
MPR ≥ 0.85[b]	542	79.1	1,250	64.2
MPR ≥ 0.90[b]	478	73.5	1,103	56.7
MPR ≥ 0.95[b]	242	37.2	522	26.8

SD = standard deviation.
[a] Indicates differences between groups at $P < 0.001$.
[b] $P < 0.0001$.

Table 2. Selected Odds Ratios for FDC Group Versus NRTI Combo Group by MRP Threshold

Selected Covariates	MPR Threshold			
	0.80	0.85	0.90	0.95
FDC vs. NRTI Combo	1.21 ($P = 0.25$)	1.27 ($P = 0.11$)	1.39 ($P = 0.02$)	1.48 ($P < 0.01$)
Third agent (vs. PI) = NRTI	20.59 ($P < 0.001$)	14.90 ($P < 0.001$)	10.55 ($P < 0.001$)	9.74 ($P < 0.001$)
= NNRTI	1.26 ($P = 0.03$)	1.20 ($P = 0.08$)	1.11 ($P = 0.29$)	1.12 ($P = 0.24$)
= EI	0.35 ($P = 0.19$)	0.51 ($P = 0.40$)	0.74 ($P = 0.70$)	0.62 ($P = 0.54$)
= Boosted PI	4.58 ($P < 0.001$)	4.25 ($P < 0.001$)	4.85 ($P < 0.001$)	5.44 ($P < 0.001$)
Switched third-agent class	1.35 ($P = 0.07$)	1.59 ($P < 0.01$)	1.71 ($P < 0.001$)	2.21 ($P < 0.001$)

EI = entry inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

- Contrary to some prior research, mental health diagnoses were associated with a higher likelihood of third-agent adherence.
- Gender, age, region, insurance payer and type, and year of initiation generally were not significant.

DISCUSSION

- To our knowledge, this is the first study to empirically quantify the spillover effect of FDCs in improving adherence to another regimen component *in addition to* the increase associated solely with the FDC component of the regimen.
- The standard for adherence in HIV remains high. This population of managed care enrollees was nearly 50% more likely to achieve 95% or better adherence to the third agent and nearly 40% more likely to meet the 90% adherence threshold.
- Mean regimen adherence in this population was relatively high (86.5%) and may have limited our ability to detect the influence of FDC use on third-agent adherence for lower MPR thresholds or for continuous MPR.
- Our results may be overestimated if individuals in the FDC group were more likely to adhere to a third agent than those in the NRTI Combo group. Conversely, if providers who are concerned about patient adherence tend to prescribe FDCs, the spillover effect may be underestimated.
- No gold standard for adherence measurement exists. Although our method may overestimate adherence, the bias would accrue to both groups.

CONCLUSIONS

- This study highlights an adherence advantage associated with FDC use that has not previously been identified: a spillover effect on a nonfixed regimen component.
- Although the spillover associated with other FDCs needs to be assessed, our work supports the use of NRTI FDCs as a means of encouraging adherence to an entire HAART regimen.
- Examinations of FDC adherence in patient populations with lower baseline levels of adherence and among FDCs consisting of more than two agents are needed to fully understand the spillover phenomenon.

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References and full study results available from Teresa L. Kauf (tkauf@ufl.edu).