Relationship Between Antiretroviral Prescribing Patterns and Treatment Guidelines in Treatment-Naive HIV-1–Infected US Veterans (1992–2004)

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Objective: To analyze temporal patterns of antiretroviral (ARV) prescribing practices relative to nationally defined guidelines in treatment-naive patients with HIV-1 infection.

Design: Retrospective cohort study.

Methods: We evaluated ARV prescribing patterns among ARV treatment-naive veterans who were receiving care within the US Department of Veterans Affairs (VA) from 1992 through 2004 in comparison to evolving adult HIV-1 treatment guidelines.

Results: A total of 15,934 patients initiated ARV treatment. Since 1999, >94% of patients initiated at least a 3-ARV medication combination, although the percentage of patients who initiated a guideline "preferred" or "alternative" regimen never rose to greater than 72% and was significantly associated with being black and with region of care. After 1999, 20% of patients started 4 or more active ARV agents in combination, which was significantly associated with lower baseline CD4 cell count, higher viral load, and receiving care in the western United States. The proportion of patients receiving guideline "not recommended" regimens (virologically undesirable or overlapping toxicities) was <1% after 1997. VA prescribing trends generally predated guideline recommendations by 6 to 12 months.

Conclusions: VA prescribing patterns for ARV initiation adhere to treatment guidelines that maximize safety. Guidelines designed to maximize efficacy were not followed as stringently. Evaluating clinical practice patterns against contemporary treatment guidelines can inform guideline development.

Key Words: antiretroviral, epidemiology, guidelines, HIV, patient safety, regional variation, veterans

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Evidence-based treatment guidelines are increasingly used to guide clinicians' medical care decisions in a variety of chronic diseases.[1] Expert panels, independent or convened by government agencies, develop and revise evidence-based guidelines. Evaluations of the quality of health care delivered and reimbursement decisions by payers are increasingly related to providers' adherence to published guidelines.

Rapid development of successful antiretroviral (ARV) therapies has dramatically changed the treatment of HIV infection. After 1996, when the use of combination ARV medications became standard, HIV infection was transformed from a rapidly progressive and nearly uniformly fatal condition to a treatable chronic infection.[2] The complexity of ARV treatment has reduced ARV adherence and increased drug–drug interactions and metabolic toxicities, however. Although many ARV combinations are widely recognized as standard treatment, other ARV combinations are discouraged because of excess toxicities, regimen complexity, or adverse drug interactions.[2] HIV expert panels have developed guidelines for initiation and appropriate use of ARVs in HIV-1 infection to account for this complexity of ARV management.[2–5]

The influence of the HIV treatment guidelines on clinical practice and outcomes is potentially important but understudied. In particular, better understanding of treatment

patterns contemporary with guidelines might show that evolving guidelines lead to changes in practice patterns or that guideline recommendations actually lag behind usage patterns. Several researchers have described ARV utilization patterns but have not specifically studied rates of adherence to HIV treatment guidelines.[6–17] We examined the relation between evolving treatment guidelines and initial ARV regimen choices.

METHODS

Reference Cohort

ARV data were analyzed using the US Department of Veterans Affairs (VA) immunologic case registry (ICR), which contains demographic and clinical data from VA clinical records.[18–22] Patients who received at least 1 annual service contact between January 1992 and December 2004 were included. ARV treatment-naive patients were defined as subjects who had not received an ARV prescription from the VA and whose date of first ARV prescription was at least 1 month after ICR entry. We excluded patients who had an HIV-1 viral load <500 copies/mL at any point 3 months before their first recorded treatment.

Patients were classified by age (based on their age on January 1 of the relevant year: 18–30, 31–40, 41–50, 51–60, 61–70, and ≥71 years). Patients were assigned to 1 of 6 predesignated VA race/ethnicity groups: non-Hispanic white, Hispanic, black, Pacific Islander/Asian, American Indian/Alaskan native, and other (patients with missing race/ethnicity information). Finally, patients were classified into 1 of 4 geographic regions in the United States (East, South, Midwest, and West) according to first ICR entry.

Antiretroviral Classifications

ARV medications were grouped into 3 classes: (1) nucleoside reverse transcriptase inhibitor (NRTI), (2) non nucleoside reverse transcriptase inhibitor (NNRTI), and (3) protease inhibitor (PI). ARV regimens were defined as (1) monotherapy, or treatment with a single NRTI, NNRTI, or PI; (2) combination NRTI therapy, consisting of 2 or more NRTIs used together with no other class of ARV; and (3) dual-class therapy, consisting of at least 2 NRTIs in conjunction with at least 1 PI or 1 NNRTI. Ritonavir (RTV) prescribed at ≥400 mg/d was considered an additional ARV agent.

Statistical Analyses

We compared patterns of ARV use in the VA with recommendations from published statements of National Institutes of Health (NIH) consensus conferences (1990 and 1993)[23,24] and from the International AIDS Society-USA (IAS-USA) Panel (1996 and 1997).[25,26] In 1998, the VA formally adopted the US Department of Health and Human Services (DHHS) guidelines, after which we compared patterns of ARV use in the VA with these guidelines. We computed the number of patients initiating ARV regimens according to categories specified in the guidelines: (1) "preferred," (2) "alternative," (3) "generally not recommended," and (4) "not recommended." We created a fifth category, "other," for regimens that did not fall into 1 of the 4 guideline-specified categories. For not-recommended regimens, we distinguished between those having overlapping toxicity and those having modest antiviral activity. For "other" regimens, we computed the frequency of different ARV components as well as the number and proportion of patients according to the number of agents in the regimen (1, 2, 3, or ≥4). We further calculated the number of agents in regimens, independent of the guideline classification.

Logistic regression was used (variables included age group, gender, race/ethnicity, US region, clinic size, academic affiliation, CD4 cell count, HIV-1 viral load within the 3 months preceding initiating therapy, and duration of care in VA) to determine why patients received a preferred or alternative regimen compared with "other" regimen as initial therapy. We carried out similar analyses using 3 versus 4 (or more) agents in combination as the dependent variable regardless of guideline status. Univariate and multivariate odds ratios (ORs) were calculated using the Intercooled STATA 8.0 for Windows 98/95 NT statistical software package (Stata Corporation, College Station, TX).

RESULTS

Guideline Development

Table 1 lists US guidelines on ARV treatment for HIV-1–infected ARV-naive adults. Initial NIH recommendations in 1990 and 1993 advocated use of zidovudine (ZDV) or didanosine (ddI) for patients with CD4 counts <500 cells/μL.[23,24] In 1996 and 1997, IAS-USA Panel guidelines recommended combination NRTI and dual-class therapy, respectively.[25,26] In 1998, the DHHS established a new format that contained 25 preferred, 10 alternative, and 4 not-recommended regimens.[2]

Until February 4, 2002, updates primarily reflected the availability of newly approved agents; recommendations concerning the isolated use of drugs with limited bioavailability without RTV; and greater emphasis on regimens with less toxicity, cross-resistance, or lower pill burden. Combinations on the preferred list peaked at 36 regimens in May 1999. The July 4, 2003, update contained several important changes: (1) reformatting the table displaying the preferred regimens, (2) reducing the list of preferred regimens to 5, and (3) distinguishing preferred NNRTI-based regimens from PI-based regimens. Updates in 2004 included substantially more alternative regimens.

Reference Cohort

During the study period, 57,210 unique patients were entered into the ICR. Patients were excluded if they were missing values for gender, date of first ICR data entry, or age (N = 397). Further excluded were patients older than 99 years or younger than 19 years (N = 19) and those whose date of AIDS diagnosis was recorded as before 1985 or after 2004 (N = 230). The final population included 56,564 living individuals, of whom 15,934 comprise the treatment-naive population from 1992 through 2004.

TABLE 1. Key Dates and Revisions to ARV Treatment Guidelines for Treatment-Naive HIV-1–Infected Adults

Number	Date Guideline Published	Key Features	No. Regimens			
			Preferred	Alternative	Generally Not Recommended	Not Recommended
1	3/3/1990	ZDV recommended	1	0	0	0
2	12/1/1993	ddI and ddC added as alternative NRTIs if intolerant to ZDV	1	2	0	0
3	7/10/1996	Dual NRTI with PI if available first recommended	4	13	0	0
4	6/25/1997	Dual NRTI + PI preferred recommendation, NNRTI offered as alternative	15	5	0	0
5	4/24/1998	5 choices of NRTI combinations 5 choices of PIs	25	10	10	2†
6	6/17/1998	SQV-HGC without RTV moved to not recommended	20	10	10	2†
7	12/1/1998	EFV added to preferred regimens	25	10	10	
8	5/5/1999	ddI/3TC added to preferred regimens Triple NRTI (ABC/ZDV/3TC) added as alternative regimen	36	11	10	2†
9	1/28/2000	EFV moved to top of preferred list of NNRTIs or PIs Reduced preferred NRTIs to 4 combinations (ddI or 3TC) + (ZDV or d4T)	16	14	10	2†
		Alternative NRTI combinations either (ddI + 3TC) or (ZDV + ddC)				2†
		ABC/ZDV/3TC dropped from alternative list, but ABC included in alternative list with ddI/3TC or ZDV/ddC				
		Reinforced that SQV-HGC only to be used as with RTV				2†
10	2/5/2001	Added LPV/r and IND/RTV to preferred regimens	24	14	2*	
11	4/23/2001	Detailed discussion of RTV used with P ("boosted PIs")	24	14	2*	2†
12	8/13/2001	Moved (ddI + 3TC) to preferred list	24	7	2*	
13	2/4/2002	No essential changes	30	7	3*	2†
		Mentioned limited data on TDF, so generally not recommended				
14	7/4/2003	Reformatted table (NNRTI- and PI-based preferred regimens)	5	16	0	2†‡
		Fewer preferred regimens				
		Added TDF as a preferred NRTI				
		Fewer regimens overall (ddC gone altogether, ddI now only recommended as alternative with EFV + 3TC)				
		Preferred NNRTI-based regimens are EFV/3TC combined with other NRTI (ZDV/TNF/d4T)				
		Preferred PI-based regimen are LPV/r + 3TC + (ZDV or d4T)				
		ABC/3TC/ddC dropped from alternative list				
		ABC/3TC + (ZDV or d4T) added to alternative list				
15	11/10/2003	FTC added as an alternative to 3TC in all regimens	5	30	0	2†‡
16	3/23/2004	fosA and fosA/r added as alternative PI-based regimens	5	56	0	2†‡
		ABC/3TC added as alternative 2-NRTI backbone				
		AMP/r and IDV (unboosted) removed as alternative PI-based regimen	6	87	0	2†‡
17	10/29/2004	d4T moved from preffered list to alternative list because of increasing reports of d4T-associated toxicities				
		TDF/3TC (or FTC) recommended as a 2-NRTI backbone for NNRTI- and PI-based regimens				
		FTC an option for part of a preferred or alternative 2-NRTI backbone				

ABC, indicates abacavir; d4T, stavudine; EFV, efavirenz; fosA, fosamprenavir; FTC, emtricitabine; IND, indinavir; LPV, lopinavir; TNF, tenofovil; /r, ritonavir-boosted; RTV, ritonavir; SQV-HGC, saquinavir–hard-gel capsule; 3TC, lamivudine; TDF, tenofovir.

*Addition of hydroxurea with any ARVs.

†Includes 2 general classes of not recommended ARV regimens: toxicity based (ZDV/d4T, ddC/ddI, ddC/3TC, ddC/d4T) and those with modest activity (all monotherapies).

‡In 2003, 2 agent ARV combinations were classified as having modest activity and therefore not recommended.

Demographics and Clinical Outcomes

The number of unique treatment-naive patients was 1558 in 1992, increasing to a high of 2310 in 1996 and steadily declining to 651 through December 2004. More than 97% of patients were men. In 1992, 14% of treatment-naive patients were 51 years of age or older compared with 31% of patients in 2004. Individuals identified as white declined progressively from 1992 through 2004, whereas those identified as black and other increased. Finally, the number of patients receiving care in the South increased, whereas the number of patients receiving care in the East decreased.

Initial Combination Regimens and Guideline Recommendations

In 1992, 1255 patients (81.2%) initiated ZDV monotherapy, the preferred single-agent NRTI regimen at the time, whereas the remaining 290 patients (18.8%) received ddI or zalcitabine (ddC) monotherapy or a 2-agent NRTI regimen (Table 2). The proportion of patients receiving 2-agent combinations increased from 4.4% in 1992 to 53.6% in 1996.

The use of single-agent NRTI regimens for treatment initiation decreased to 2.3% of all initial ARV regimens prescribed in 1997 and has remained at <2%. The use of 2-agent NRTI combinations peaked in 1996, which is the only year that guidelines listed this combination as a preferred regimen. Approximately 80% of 2-agent combinations used in 1996 were from the preferred list.

Dual-class regimens consisting primarily of 3 or 4 agents were prescribed to 26% of patients in 1996, increasing to 64% in 1997. By 1999, the proportion receiving 3- or 4-agent combinations exceeded 94%. From 1997 onward, no more than 72% of patients initiated preferred or alternative dual-class regimens. Alternative regimens were used at a consistently lower rate than preferred regimens and were used in <1% of patients between 2000 and 2002. From 1998 onward, the use of "other" regimens not on the preferred or alternative list has ranged from 21% to 56%, with 15% to 24% of patients receiving 4 (or more) agents as an "other" initial regimen.

PI-based regimens have been recommended since 1997, although they were a frequently used alternative option in 1996 (N = 354). The percentage of patients receiving a preferred PI-based regimen has declined steadily since 1997 and was equivalent to 6.5% in 2004. NNRTI-based regimens were added to the preferred list in 1999 and have remained stable at between 29% and 36% since 2000.

Because the categories of not recommended and generally not recommended regimens were introduced in 1998, the use of these regimens has been consistently low (see Table 2). Before this, use of regimens that were subsequently recommended to be virologically undesirable or had overlapping toxicities varied between 8.3% (1993 and 1994) and 13% (1996). After 1998, no one received any of these

TABLE 2. Trends in Treatment-Naive Regimens According to Guidelines, 1992 Through 2004

Year	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
No. Patients	1558	1275	1354	1608	2310	1743	1180	1002	805	861	781	806	651
Preferred regimens													
Single NRTI	1243	882	882	838	97								
Dual NRTI					977								
Dual-class regimens													
PI based						754	691	395	206	215	134	65	42
NNRTI based								212	230	249	202	240	235
Total, %	79.8%	69.2%	65.1%	52.1%	46.3%	43.3%	58.6%	60.6%	54.2%	53.9%	43.0%	37.8%	42.5%
Alternative													
Single NRTI		281	266	238	40								
Dual NRTI					140								
Triple NRTI								13	4	1	0	53	12
Dual-class regimens					354	37	105	93	1	1	0	89	100
Total, %		22.0%	19.6%	14.8%	23.1%	2.1%	8.9%	10.6%	0.6%	0.2%	0.0%	17.6%	17.2%
Generally not recommended							118	41	0	0	0		
Total, %							10.0%	4.1%	0.0%	0.0%	0.0%		
Not recommended													
Toxicity based							0	0	0	0	0	0	0
Modest activity							13	5	1	9	5	20	23
Total, %							1.1%	0.5%	0.1%	1.0%	0.6%	2.5%	3.5%
Other													
Single-agent regimen	245	0	61	130	349	40							
2-agent combination	68	110	138	350	121	585	17	12	22	22	16		
3-agent combination	2	2	7	46	140	130	57	34	169	185	238	115	88
4 (or more)-agent combination	0	0	0	6	97	197	178	197	172	179	186	224	151
Total, %	20.2%	8.8%	15.2%	33.1%	30.6%	54.6%	21.4%	24.3%	45.1%	44.8%	56.3%	42.1%	36.7%
Total single-agent regimen	1488	1163	1209	1206	481	40	13	5	1	9	5	9	10
	95.5%	91.2%	89.3%	75.0%	20.8%	2.3%	1.1%	0.5%	0.1%	1.0%	0.6%	1.1%	1.5%
Total 2-agent combinations	68	110	138	350	1238	585	131	51	22	22	16	10	13
	4.4%	8.6%	10.2%	21.8%	53.6%	33.6%	11.1%	5.1%	2.7%	2.6%	2.0%	1.2%	2.0%
Total 3-agent combinations	2	2	7	46	494	921	858	750	610	651	574	563	477
	0.1%	0.2%	0.5%	2.9%	21.4%	52.8%	72.7%	74.9%	75.8%	75.6%	73.5%	69.9%	73.3%
Total 4-plus agent combinations	0	0	0	6	97	197	178	196	172	179	186	224	151
	0.0%	0.0%	0.0%	0.4%	4.2%	11.3%	15.1%	19.6%	21.4%	20.8%	23.8%	27.8%	23.2%

combinations. The proportion of patients receiving regimens with modest activity has generally been <1% to 3%.

Use of 3-Agent ''Other'' Combinations

Table 3 summarizes the 3-agent "other" combinations from 1996 through 2004. The number of "other" regimens increased from 34 in 1999 to 238 in 2002. The decrease in "other" regimens in 2004 reflected, in part, the increase in alternative regimens, from 7 in 2002 to 87 in 2004.

In 1996 and 1997, triple NRTIs and saquinavir in combination with 2 NRTIs were the most common 3-agent "other" combinations. Efavirenz was part of the most commonly prescribed 3-agent "other" regimen 1 year before being included in a preferred regimen (1998). Nevirapine in combination with 2 NRTIs was widely used from 2000 through 2002. A triple-NRTI regimen consisting of abacavir, lamivudine, and ZDV was listed as an alternative regimen in 1999. From 2000 through 2002, this combination was omitted from the alternative list, becoming one of the most commonly prescribed 3-agent "other" regimens. In 1999, abacavir and tenofovir use began, steadily representing a greater proportion of "other" regimens from 2000 onward.

Factors Associated With Use of Preferred and/or Alternative Combinations Compared With ''Other'' Combinations

Table 4 shows the odds of using preferred or alternative combinations, compared with "other" combinations from 1996 through 2004. In univariate analyses, patients were significantly more likely to receive a preferred or alternative regimen if they were 61 to 70 years of age, were black, received care other than in the western US, had CD4 counts between 201 and 350 cells/μL (or data not recorded or not available), had an HIV-1 viral load between 20 and 50,000 copies/mL (or missing), or started treatment before 1999 (except for 1997). Adjustment for all factors simultaneously in multivariate logistic regression analysis revealed that factors associated with greater odds of receiving a preferred or alternative regimen still included being 61 to 70 years of age, being black, receiving care other than in the western US, having CD4 counts between 201 and 350 cells/μL (or data not recorded or not available), having an HIV-1 viral load between 20 and 50,000 copies/mL (or missing), or starting treatment before 1999 (except for 1997). A greater odds of receiving "other" regimens included clinic size >50 patients and receiving care in the western US.

Factors Associated With Use of 3-Agent Versus 4 (or more)-Agent Combinations

Age, gender, clinic size, and academic affiliation were not associated with greater use of 3-agent regimens (see Table 4). The odds of receiving 3 versus 4 or more agents were significantly greater in blacks, those starting treatment before 1999, and those with >7 months of follow-up preceding treatment. The odds of receiving 4 or more agents were higher in the western US, in those with CD4 counts <200 cells/μL, and in those with viral loads >50,000 copies/mL (univariate only).

Treatment Initiation Patterns Relative to Guideline Updates

Figure 1 displays the frequency of ARV regimen initiation relative to the timing of guideline recommendation announcements. In almost all cases, clinical practice patterns anticipated guideline recommendations by 6 to 12 months, particularly for regimens that were initially listed as preferred or alternative and later listed as alternative or not recommended (ie, monotherapies, unboosted PIs). Despite being listed as not generally recommended (for too little data available), tenofovir use increased significantly 15 months before being listed on the preferred list. For ARVs that were only listed as preferred, clinical utilization anticipated the guidelines for lopinavir and was simultaneously adopted for efavirenz-containing regimens.

DISCUSSION

Professional group–derived treatment guidelines have been important vehicles for communication of scientific advancements, limitations, risks, and proper use of new therapies. Our study is the first comparing ARV utilization patterns with contemporary guideline recommendations in HIV-infected treatment-naive patients. That insurance was not a barrier for ARV access was of particular importance.

TABLE 3. Distribution of 3-Agent ''Other'' Combinations

	1996	1997	1998	1999	2000	2001	2002	2003	2004
Total other 3-drug regimens	140	130	57	34	169	185	238	115	88
Triple NRTIs*	116	34	5	1	32	81	116	15	7
Total, %	82.0%	26.2%	8.8%	2.9%	18.9%	43.8%	48.7%	13.0%	8.0%
NNRTI + 2 NRTIs*	3	4	28		102	63	53	4	3
Total, %	2.1%	3.1%	49.1%		60.4%	34.1%	22.3%	3.5%	3.4%
PI + 2 NRTIs*	20	82	4	2	13	7	1	12	13
Total, %	14.3%	63.1%	7.0%	5.9%	7.7%	3.8%	0.4%	10.4%	14.8%
Dual-PI or PI + NNRTI*	1	10	20	13	11	10	4	9	4
Total, %	0.7%	7.7%	35.1%	38.2%	6.5%	5.4%	1.7%	7.8%	4.5%
ABC- or TDF-containing				18	11	24	64	75	61
Total, %				52.9%	6.5%	13.0%	26.9%	65.2%	69.3%

*NRTIs do not include TDF or ABC.
ABC indicates abacavir; TDF, tenofovir.

TABLE 4. Factors Associated With Preferred/Alternative, ''Other,'' and 3- or 4 (or more)-Agent Regimens

	Preferred/Alternative (Compared with "Other")				3-Agent (Compared with 4-agent)			
			ORs				ORs	
Variable	Number/Total Number	%	Univariate	Multivariate	Number/Total Number	%	Univariate	Multivariate
Age (y)								
18–30	554/974	57%	Ref		531/647	82%	Ref	
31–40	2002/3401	59%	1.05	1.03	1871/2258	83%	1.02	1.04
41–50	2271/3850	59%	1.04	1.01	2249/2694	83%	1.05	1.16
51–60	840/1409	60%	1.02	1.04	921/1109	83%	1.03	1.28
61–70	260/414	63%	1.37*	1.36*	259/308	84%	1.12	1.41
71+	55/91	60%	1.09	1.16	65/76	86%	1.25	1.65
Gender								
Male	5843/9914	59%	Ref		5751/6923	83%	Ref	
Female	139/225	62%	1.18	1.20	145/169	86%	1.22	1.23
Race								
White	1712/3001	57%	Ref		1703/2127	80%	Ref	
Black	3269/5416	60%	1.13*	1.14*	3177/3741	85%	1.28†	1.32‡
Other	1001/1722	58%	1.04	1.09	1016/1224	83%	1.16	1.31*
US Region								
East	1874/3072	61%	Ref		1810/2120	85%	Ref	
South	2286/3780	60%	1.12	0.84	2315/2747	84%	0.92	1.02
Midwest	622/1040	60%	1.04	0.96	533/627	85%	0.97	0.98
West	1200/2247	53%	0.80†	0.66‡	1238/1598	77%	0.59†	0.68‡
CD4 count, cells/μL								
501+	602/1046	58%	Ref		608/703	86%	Ref	
351–500	801/318	61%	1.13	1.17	741/879	84%	0.85	0.86
201–350	1144/1871	61%	1.22*	1.28*	1117/1334	84%	0.82	0.83
101–200	748/1210	62%	1.12	1.21	747/905	83%	0.74*	0.74*
51–100	403/681	59%	1.13	1.2	413/508	81%	0.68*	0.68*
<51	607/985	62%	1.13	1.08	594/730	81%	0.67*	0.67‡
Missing	1696/3054	56%	0.95	1.57†	1694/2053	83%	0.74*	0.75
HIV-1 RNA viral load, copies/mL								
500–20,000	1034/1841	62%	Ref		1121/1337	86%	Ref	
20,001–50,000	672/1078	60%	1.21*	1.21*	742/861	81%	1.17	1.25
50,001–100,000	518/860	61%	1.16	1.17	587/729	80%	0.77*	0.85
100,001+	971/1600	58%	1.12	1.13	1071/1331	83%	0.76†	0.88
Missing	2522/4347	58%	0.99	0.82*	2074/2487	84%	0.94	1.06
CD4 percent								
0–6	713/1155	62%	Ref		713/878	81%	Ref	
7–15	1154/1883	61%	0.98	0.93	1139/1395	82%	1.00	0.91
16–21	744/1236	60%	0.93	0.91	733/876	84%	1.16	0.91
22+	1257/2086	60%	0.95	1.04	1230/1438	86%	1.36†	1.07
Missing	1922/3443	56%	0.77***	0.62‡	1869/2252	83%	1.10	1.07
CD8 count, cells/mL								
<436	623/1028	61%	Ref		615/726	85%	Ref	
436–701	804/1325	61%	0.95	0.97	809/964	84%	0.96	0.87
702–1086	898/1562	57%	0.88	0.92	899/1099	82%	0.83	0.73*
1087+	956/1572	61%	1.06	1.15	932/1113	84%	0.95	0.84
Missing	2705/4657	58%	0.91	1.17	2645/3195	83%	0.86	0.77
Year of first ARV regimen								
2004	389/651	60%	Ref		477/595	80%	Ref	
2003	447/806	55%	0.94	0.92	562/732	77%	0.83	0.85
2002	336/781	43%	0.48‡	0.48‡	574/712	81%	1.04	1.07
2001	466/861	54%	0.83	0.83	651/783	83%	1.21	1.25

(*continued on next page*)

TABLE 4. (*continued*) Factors Associated With Preferred/Alternative, ''Other,'' and 3- or 4 (or more)-Agent Regimens

Variable	Preferred/Alternative (Compared with "Other")				3-Agent (Compared with 4-agent)			
	Number/Total Number	%	ORs Univariate	ORs Multivariate	Number/Total Number	%	ORs Univariate	ORs Multivariate
2000	441/805	55%	0.85	0.87	610/734	83%	1.20	1.21
1999	713/1002	71%	1.56‡	1.61‡	749/895	84%	1.25	1.24
1998	796/1180	67%	1.37*	1.46‡	858/989	87%	1.60†	1.61†
1997	791/1743	45%	0.57‡	0.62‡	921/1073	86%	1.51†	1.50†
1996	1603/2310	69%	1.47‡	1.87‡	494/579	85%	1.48*	1.51*
Months of follow-up in ICR preceding first ARV regimen								
<2	1376/2274	61%	Ref		1497/1834	81%	Ref	
2–6	1291/2138	60%	0.97	0.98	1317/1626	86%	0.94	0.93
7–12	524/876	60%	0.97	0.97	483/563	86%	1.36*	1.34*
13–24	641/1098	58%	0.89	0.87	576/669	84%	1.38*	1.36*
25–36	453/785	58%	0.88	0.82*	364/432	82%	1.20	1.11
37–60	817/1365	60%	0.95	0.87	611/721	85%	1.22	1.14
61–84	495/900	55%	0.85	0.92	538/628	86%	1.33*	1.21
85+	385/703	55%	0.73†	0.82	510/619	82%	1.03	1.16
No. patients at treatment facility								
<10	19/24	79%	Ref		17/18	94%	Ref	
10–50	158/255	62%	0.42	0.39	162/183	89%	0.47	0.38
51–200	1033/1730	60%	0.39	0.33*	1013/1196	85%	0.32	0.25
>200	4460/7660	58%	0.36*	0.29*	4442/5397	82%	0.27	0.20
Missing	312/470	66%	0.47	0.39	262/298	88%	0.42	0.26
HIV staff on affiliated university faculty	4645/7903	59%	0.88*	0.98	4567/5501	83%	0.93	1.00

*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.
Ref indicates reference.

Therefore, we could explore other factors that may influence ARV prescribing patterns.

The correlation between prescribing patterns and guidelines was greatest for recommendations that inform physicians what not to do so as to avoid harm rather for than recommendations that inform physicians what to do so as to improve efficacy. This difference could reflect a number of factors, including a large and rapidly changing number, complexity and scope of recommendations, lag in available new evidence and publication of guidelines, varying interpretation of evidence between guideline committees and treating physicians, and local and regional considerations (eg, patient mix) that may affect treatment patterns.

We found systematic differences in ARV treatment among blacks compared with nonblacks. A number of previous studies reveal disparities in HIV care related to race.[11–13,15,16,27] Factors associated with non-HAART regimens in non-VA settings include active substance abuse,[7,28] inconsistent clinical follow-up,[9] and lack of insurance.[11,15] In the VA, blacks compared with nonblacks were more likely to receive preferred or alternative regimens and less likely to receive 4 (or more)-agent regimens, however. We know of no data (even in the guidelines) suggesting that blacks respond more or less effectively than nonblacks to 3-agent regimens. We also cannot ascertain the extent to which the choice was based on the regimen's convenience, tolerability, provider perceptions, or patient preferences. Recent provider survey data indicate that ARV treatment decision-making may be influenced by race or underlying HIV risk factors.[29] In addition, patient involvement in the treatment decision-making process is likely to influence initial choices as well.[30,31]

Patients receiving care in the western US were more likely to be prescribed "other" regimens and more than 3 agents in combination. Regional variation in clinical care has been a subject of intense study for decades.[32] Significant regional variation in clinical practice has been described for a variety of chronic diseases but has not been previously described in any detail for ARV use.[33] No consistent explanation can account for this phenomenon observed in the management of chronic non-HIV diseases. Although patient preferences and economic incentives (ie, payer mix, reimbursement rates, access to or limitations in care) may account for some of the variation, economic incentives are not an issue in the VA. Yet, the VA is subject to the same regional variation in chronic disease practice patterns even after accounting for risk adjustment.[34] Further analysis indicates that VA clinical practice mirrors local community practice and may simply reflect local provider opinions and patient preferences. Variation in ARV use is unlikely explained by differences in VA HIV provider experience or VA infrastructure differences compared with local community practice. Seventy-five percent of VA medical centers provide HIV care in subspecialty clinics, and the average VA HIV provider has more than 10 years of HIV clinical experience, having treated an average of 120 patients in the last 5 years.[35] Our findings highlight the need to understand the causes and implications of such variation better for the

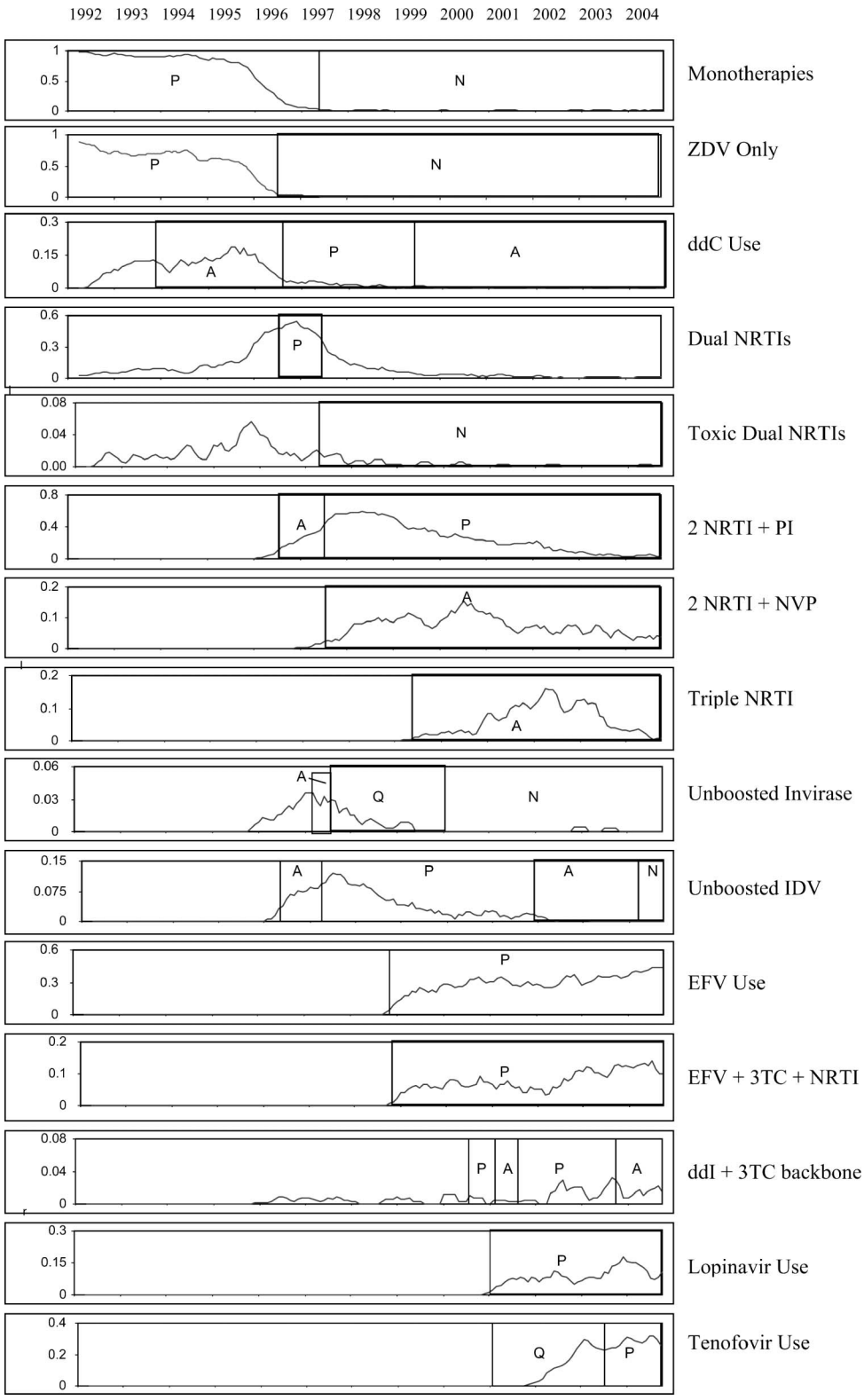

FIGURE 1. Initiation of ARV therapy relative to guideline development. Designated areas indicate guideline recommendation periods for the specific recommendation. A indicates alternative; N, not recommended; P, preferred; Q, generally not recommended. Line indicates number of prescriptions written during each quarter of the calendar year represented. Y-axis indicates percentage of patients receiving the ARV regimen. EFV indicates efavirenz; IDV, indinavir; NVP, nevirapine; unboosted, PI treatment without low-dose RTV; 3TC, lamivudine.

health of persons with HIV as well as the need to initiate targeted approaches to reduce unwarranted variation.

Whether patients may have received ARV prescriptions from outside the VA that were not recorded in the ICR is important to our study's validity. A recent representative survey of 573 veterans found that ARVs were obtained by veterans (primarily treatment experienced) outside the VA at a rate of <3.8%.[36] More than 80% of patients had greater than

2 months of follow-up in the ICR before ARV initiation. Extending follow-up to 3 months before treatment initiation did not change our findings (data not shown). Recent data from Gandhi and colleagues[37] indicate that 40% of HIV-positive veterans received care in the VA for an average of 3 years before their HIV diagnosis and entry into the ICR, emphasizing that a significant minority of veterans are already in care for years before diagnosis; therefore, ARV treatment initiation outside the VA would be unlikely. We cannot completely exclude the possibility that patients had prior ARV use and appeared in the ICR as ARV treatment naive. It is possible then, but unlikely, that ARV initiation choices in VA could have been affected or biased by ARV treatment history not recorded in the ICR.

A substantial number of the patients started treatment well below the CD4 cell count thresholds that were suggested by contemporary guidelines. Of those veterans initiating treatment between 1998 and 2000, when the guidelines suggested that treatment should be initiated when the CD4 count was <500 cells/μL, on average, 60% had a CD4 count <350 cells/μL and 40% had a CD4 count <200 cells/μL when treatment was initiated. Between 2001 and 2004, when the guidelines suggested that treatment should be initiated when the CD4 count was <200 cells/μL and should be offered when the CD4 count was <350 cells/μL, on average, 25% had a CD4 count <100 cells/μL and 15% had a CD4 count of <50 cells/μL at the time of treatment initiation. Our findings support evidence that this is a consequence of delayed identification of HIV infection rather than lack of adherence to treatment guidelines. A recent VA study found that 55% of patients who were recently diagnosed with HIV infection had CD4 counts <200 cells/μL.[37] This may correlate with key organizational, patient, or practitioner factors currently not recorded in the ICR such as hard-to-reach populations living in settings far from a VA facility[13] or comorbidities such as homelessness, mental illness, or substance abuse. As reported elsewhere, our data may help to identify strategies to narrow gaps related to disparities in care access, treatment, and outcome.[38,39]

The relatively high rate of "other" regimens suggests that research is warranted to assess how being assigned to different categories of ARV use—preferred, alternative, and 3- to 4-drug "other" combinations—is related to clinical outcomes. Some of the use of "other" combinations may be explained by revisions in guideline statements and preferred use of other agents, notably nevirapine, abacavir, and tenofovir. A recent study addressing this question in children initiating ARV treatment found that 22% were not placed on guideline-recommended regimens and that 15% were started on "other" ARV combinations.[40]

After 1997, approximately 20% of initial ARV regimens contained 4 or more active agents and were more likely to be prescribed to patients with lower CD4 cell counts and higher viral loads. This suggests that practitioners were augmenting regimens with additional agents in patients who were at particularly high risk for HIV complications or that patients were deemed less likely to respond to a recommended 3-agent regimen. Reports from at least 1 other large cohort indicate that a small percentage of patients (5%) were started on ARV regimens of 4 or more agents, although the reasons for such decisions were not given.[41] Several small studies comparing treatment initiation with 3 versus 4 or more ARV drugs in ARV-naive patients suggest equivalent virologic outcomes. Nevertheless, there is a suggestion that more ARV drugs may accelerate the timing and percentage of those achieving an undetectable viral load.[42–44]

Our study suggests that providers anticipated many guideline recommendations well before their publication. This may be explained, in part, by the lengthy process required for expert panel review or the fact that firm recommendations cannot be made until there are adequate data on potential efficacy or toxicities of specific regimens. Some guideline panel recommendations and updates are published in peer-reviewed journals, further lengthening the time to publication and availability to providers. The DHHS guidelines were originally published in 1998, however, with 1 update appearing in a peer review publication in 2002.[45,46] DHHS updates have consistently been updated electronically and are therefore available to VA practitioners via the Internet when released. As guidelines became released more often than annually and by the DHHS, the time between mean uptake/decrease and official guideline recommendations has narrowed.

Our study also suggests that adherence to safety recommendation guidelines is closely followed and serves as an important benchmark. Conversely, lower practitioner use of ARV effectiveness guidelines (possibly because of the rapidly changing nature and complexity of suggestions) suggests that simplification of guidelines should be studied to increase potential adherence.

There are numerous examples of departure from clinical practice guidelines,[47] including examples in HIV primary care. For example, current US Public Health Service (USPHS) guidelines recommend tuberculin skin testing (TST) for all newly diagnosed HIV-infected patients. A recent study in US clinics found that just more than half of the newly diagnosed patients had received TST. Patient demographics had little effect on adherence to guidelines. Factors associated with higher TST guideline adherence included underlying risk factors for tuberculosis, increased clinic visits, use of other prophylactic medications for HIV care, and a written policy for TST in the clinic.[48] Whether HIV treatment decisions based on adherence or nonadherence to guideline recommendations result in significant clinical outcome differences requires study. Improved understanding of the relation of providers' prescribing behavior to ARV treatment guidelines may help to identify ways to improve development and timely communication of future treatment guidelines.

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