Impact of Recommendation Updates in Well-Controlled Patients on Nonrecommended Antiretroviral Therapies: The Swiss HIV Cohort Study

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Background: HIV treatment recommendations are updated as clinical trials are published. Whether recommendations drive clinicians to change antiretroviral therapy in well-controlled patients is unexplored.

Methods: We selected patients with undetectable viral loads (VLs) on nonrecommended regimens containing double-boosted protease inhibitors (DBPIs), triple-nucleoside reverse transcriptase inhibitors (NRTIs), or didanosine (ddI) plus stavudine (d4T) at publication of the 2006 International AIDS Society recommendations. We compared demographic and clinical characteristics with those of control patients with undetectable VL not on these regimens and examined clinical outcome and reasons for treatment modification.

Results: At inclusion, 104 patients were in the DBPI group, 436 in the triple-NRTI group, and 19 in the ddI/d4T group. By 2010, 28 (29%), 204 (52%), and 1 (5%) patient were still on DBPIs, triple-NRTIs, and ddI plus d4T, respectively. 'Physician decision,' excluding toxicity/virological failure, drove 30% of treatment changes. Predictors of recommendation nonobservance included female sex [adjusted odds ratio (aOR) 2.69, 95% confidence interval (CI) 1 to 7.26; $P = 0.01$] for DPBIs, and undetectable VL (aOR 3.53, 95% CI 1.6 to 7.8; $P = 0.002$) and lack of cardiovascular events (aOR 2.93, 95% CI 1.23 to 6.97; $P = 0.02$) for triple-NRTIs. All patients on DBPIs with documented diabetes or a cardiovascular event changed treatment. Recommendation observance resulted in lower cholesterol values in the DBPI group ($P = 0.06$), and more patients having undetectable VL ($P = 0.02$) in the triple-NRTI group.

Conclusion: The physician's decision is the main factor driving change from nonrecommended to recommended regimens, whereas virological suppression is associated with not switching. Positive clinical outcomes observed postswitch underline the importance of observing recommendations, even in well-controlled patients.

Key Words: recommendations, HIV, double-boosted protease inhibitors, triple-nucleoside reverse transcriptase inhibitors, nonobservance

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INTRODUCTION

The introduction of safe and effective combination antiretroviral therapy (cART) has dramatically improved the course of HIV infection.[1] As new agents are developed and introduced into the existing armamentarium, it is a constant requirement of clinicians to remain up to date. Treatment recommendations, compiled by expert panels, are updated regularly as clinical trial data are published, to guide clinicians in their regimen choice.

Some cART combinations are discouraged owing to toxicity, drug interactions, or suboptimal efficacy. Double-boosted protease inhibitor (DBPI) regimens, for example, although previously used as part of salvage treatment in cases of multidrug resistance because of their high genetic barrier to resistance,[2,3] were subsequently shown to have more side effects than new generation single-boosted PIs such as tipranavir and darunavir.[4,5] The August 2006 International AIDS Society—USA (IAS-USA) recommendations proposed that DBPI

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combinations should be avoided accordingly.[6] Triple-nucleoside (or nucleotide) reverse transcriptase inhibitor (NRTI) regimens, whose advantages over nonnucleoside reverse transcriptase inhibitor– or PI-based regimens included minimal drug interactions, ease of use and sparing of PIs and nonnucleoside reverse transcriptase inhibitors for future availability, were prescribed as alternatives for initial therapy.[7] However, the 2004 IAS-USA recommendations discouraged triple-NRTI regimens because of inferior potency (inferior virological control). Finally, the 2004 IAS-USA recommendations discouraged the combination of didanosine (ddI) plus stavudine (d4T), given synergistic toxicity such as peripheral neuropathy, lipodystrophy, pancreatitis, and hyperlactatemia.[3,8]

Recommendations are also published by the European AIDS Clinical Society (EACS)[9–11] and the US Department of Health and Human Sciences (DHHS).[8,12] Considering the cART regimens above, the 2007 EACS guidelines recommend against DBPIs, whereas the DHHS does not mention this combination.[8,10] Triple-NRTIs were identified as inferior in both the 2003 EACS and the 2004 DHHS recommendations. Finally, the 2003 DHHS recommendations advise against the combination of ddI plus d4T.[8]

Not all clinicians observe treatment recommendations, with inappropriate cART reported in 5%–47% of treatment-naive patients.[13–16] Patients who are highly treatment experienced, or in whom there are concerns regarding adherence or drug interactions, may be faced with treatment options that are limited or not conforming to recommendations. Regional variation, ethnicity, sex, pretreatment CD4 count, and HIV viral load (VL) have been shown to play a part in guideline nonobservance.[13,14,16] Surprisingly, the influence of new recommendations on clinical practice is understudied. To our knowledge, although some studies have examined guideline observance concerning initial cART,[13–18] no study has analyzed the clinical impact of guideline updates in patients already well controlled on cART.

In Switzerland, the first national treatment recommendations were published in July 2011.[19] Before this, most Swiss HIV physicians, and certainly those at Swiss HIV Cohort Study centers (SHCS; described below), referred to the IAS-USA recommendations (M.C., personal communication). We aimed to determine the impact of the August 2006 IAS-USA recommendations on the prescribing practices of Swiss clinicians by examining patients enrolled in the SHCS who were on nonrecommended regimens at that time.

METHODS

Study Design

We conducted a retrospective analysis from September 1, 2006, to December 31, 2010, using data recorded from patients enrolled in the SHCS. The SHCS is an ongoing, open, prospective observational cohort of HIV-infected patients followed at 7 centers in Switzerland, comprising outpatient clinics and their affiliated hospitals, and private practitioners.[20] Cohort patients undergo data collection (sociodemographic characteristics, comorbidities, cART regimen, treatment adherence, whether or not on lipid-lowering drugs and clinical course) and blood sampling (CD4 count, VL, and lipid values) at inclusion and approximately every 6 months. We used the SHCS database extract of May 31, 2011. Approval for this study was obtained from the local ethical committees of all participating centers.

The August 2006 IAS-USA recommendations were reviewed, and nonrecommended cART regimens were chosen for analysis: DBPI regimens, defined as those containing booster-dose ritonavir plus 2 other PIs (excluding tipranavir prescribed in the context of a clinical study)[2]; triple-NRTI regimens [particularly lamivudine (3TC) and zidovudine (AZT) with abacavir (ABC) or tenofovir (TDF)] and regimens containing ddI plus d4T. In the triple-NRTI group, a subanalysis was performed to compare reasons of switch before and after the 2008 Conference on Retroviruses and Opportunistic Infections, when the results of the D:A:D study, showing an association between ABC use and risk of myocardial infarction, were presented.[21]

Inclusion Criteria

Patients enrolled in the SHCS were included if they (1) were receiving cART containing DBPIs, triple-NRTIs, or ddI plus d4T and (2) had at least 2 consecutive undetectable HIV VLs (defined as <50 copies per milliliter) throughout a period of at least 12 weeks before September 1, 2006. SHCS patients on cART not containing DBPIs, triple-NRTIs, or ddI plus d4T, but having at least 2 consecutive undetectable VLs for ≥ 12 weeks before September 1, 2006, were taken as controls.

Definitions

The SHCS center location was recorded, and *source of follow-up* was classified as the SHCS center, other hospital, or private practitioner. For the sake of clarity, we use the term, *nonobservance* when referring to clinician nonadherence to treatment recommendations and the term, *nonadherence* when referring to patient nonadherence to the prescribed cART. *Drug adherence to cART* was recorded as the lowest adherence as reported by the patient during the period with an undetectable VL before September 1, 2006. We defined *suboptimal drug adherence* as the omission of at least 1 cART dose per month. *Framingham 10-year risk score* was calculated as previously described[22] and classified according to the 10-year risk of developing coronary heart disease (myocardial infarction, angina pectoris, heart failure, and/or coronary death) as low ($<10\%$), intermediate (10–20%), and high ($>20\%$) risk. Cardiovascular (CV) events included myocardial infarction, cerebral infarction, or hemorrhage, other cardiac events (coronary angioplasty/stenting, coronary artery bypass grafting), and other vascular events (deep vein thrombosis, pulmonary embolism, and vascular procedures such as carotid endarterectomy and phlebectomy).

The end of the nonrecommended cART was defined as a *switch* when involving a change of treatment to another regimen, or as a *discontinuation*, when cART was stopped for ≥ 4 weeks as previously described.[23] A switch to another regimen was defined as stopping the double PI association in the DBPI group and the triple-NRTI association in the triple-NRTI group and, in the ddI/d4T group, as stopping either of the 2 drugs.

Reasons for treatment switch or discontinuation were classified as *physician's decision*, *patient's wish/decision*, *abnormal fat distribution*, *toxicity* (of gastrointestinal tract, liver, pancreas, nervous system, kidneys, endocrine system, hematological toxicity, lactic acidosis, and other), *treatment failure* (virological, immunological, or clinical), *unknown*, and *other* (such as death, loss to follow-up or structured treatment interruption). *Physician's decision* encompassed treatment simplification or recommendation observance. These definitions correspond to the official classification used at the 6-monthly analyses of SHCS-enrolled patients.

Laboratory Values

The nearest CD4 count, VL (as performed by the Roche Amplicor HIV-1 Monitor Assay), and lipid values [total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride (TG)] obtained up to 6 months before September 1, 2006, were recorded as inclusion parameters. CD4 count and VL and lipid values obtained at 24 and 48 weeks after any treatment switch were analyzed as, respectively, 24- and 48-week outcomes. HIV RNA suppression (*undetectable VL*) was defined as a VL <50 copies per milliliter.

Statistical Analysis

The 3 nonrecommended cART regimens were analyzed separately. Patients in >1 treatment group were analyzed once in each group. Baseline characteristics of patients receiving each regimen were compared with that of the control group. Predictors of recommendation nonobservance were evaluated by comparing patients who continued nonrecommended regimens with those who switched/discontinued treatment at 2 different time points: 1 year (September 1, 2007) and 4 years (September 1, 2010) after the August 2006 IAS-USA recommendations. Predictors of receiving nonrecommended cART and of continuing outdated regimens were assessed using multivariable logistic regression analysis.

Drug adherence, lipid values, prescription of lipid-lowering agents, immunological, and virological outcomes at the time of treatment switch were compared with these parameters 24 and 48 weeks postregimen change for each patient using the Wilcoxon–Mann–Whitney test for continuous variables and the χ^2-test for categorical variables.

Finally, continuation on each of the 3 nonrecommended cART regimens over time was described using Kaplan–Meier survival analyses. Statistical analyses were performed using Stata software (StataCorp, College Station, TX, version 11.1).

RESULTS

Patients' Baseline Characteristics

On September 1, 2006, 104 patients were in the DBPI group, 436 in the triple-NRTI group, and 19 patients in the ddI/d4T group, with 3171 patient controls (Table 1). Of the patients on triple-NRTIs, 398/436 (91%) were on Trizivir (3TC ABC AZT), 22/436 (5%) were on 3TC AZT TDF, and the 16/436 (4%) were on other NRTI combinations. Of the 19 patients in the ddI/d4T group, 1 was additionally in the DBPI group, and 1 was in the triple-NRTI group.

Compared with controls, a higher proportion of patients in the DBPI group had advanced HIV infection (documented AIDS-defining illness) and was highly treatment experienced, 53% having had >8 treatment changes. Treatment adherence was lower, and total cholesterol and TG values were higher, despite the fact that these patients were more frequently on lipid-lowering treatment. Most patients were followed up in SHCS centers.

In the triple-NRTI group, fewer patients had advanced HIV infection. They were less treatment experienced, had higher Framingham risk scores but lower total cholesterol values compared with control patients. Most were followed up by private practitioners.

In the ddI/d4T group, more patients were followed up in peripheral hospitals compared with control patients. More than half had suboptimal treatment adherence (cART forgotten on ≥ 1 occasion per month).

Predictors of Nonobservance to the August 2006 IAS-USA Recommendations

Factors associated with recommendation nonobservance were examined at 1 and 4 years post-IAS-USA recommendation publication (September 1, 2007 and 2010, respectively), by comparing patients continued on nonrecommended cART to those who switched or discontinued such treatment (Fig. 1; see **Tables S1–S3**, **Supplemental Digital Content 1**, http://links.lww.com/AIE/A1).

By September 2007 and 2010, 75 (73%) and 28 (29%) patients, respectively, were still on DBPIs. After adjustment for relevant covariables, female patients and those with higher CD4 counts were more likely to continue on DBPIs until 2010. All the patients with a history of diabetes or a CV event discontinued DBPIs during the study period (Fig 1; see **Table S1, Supplemental Digital Content 1**, http://links.lww.com/QAI/A370).

For triple-NRTIs, 366 (86%) and 204 (52%) patients were still on this treatment by September 2007 and 2010, respectively. Patients with a history of a CV event were more likely to discontinue this regimen, whereas those with undetectable VLs were more likely to continue until 2010. Patients with fewer previous treatment changes were also more likely to continue up to 2007, but this characteristic was less relevant in 2010 (Fig. 1; see **Table S2**, **Supplemental Digital Content 2**, http://links.lww.com/QAI/A370).

For ddI plus d4T, 9 (47%) and 1 (5%) patients were still on this treatment by September 2007 and 2010, respectively. Patients continuing ddI plus d4T in September 2007 had higher lipid values (total cholesterol, low-density lipoprotein, and TG) than those who switched (Fig 1, see **Table S3**, **Supplemental Digital Content 3**, http://links.lww.com/QAI/A370).

Reason for Switching From Nonrecommended cART and Choice of New Regimen(s)

Discontinuation or switching from DBPIs to other regimens was driven mainly by the physician's decision,

TABLE 1. Characteristics of the 3 Nonrecommended Treatment Groups Compared With Controls

Baseline Characteristics	DBPIs (N = 104) N (%)	3-NRTIs (N = 436) N (%)	ddI–d4T (N = 19) N (%)	Control Group (N = 3171) N (%)	Factors Associated With DBPIs: Bivariate Analysis: OR (95% CI)	Factors Associated With DBPIs: Multivariable Analysis: OR (95% CI)	Factors Associated With Triple-NRTIs: Bivariate Analysis: OR (95% CI)	Factors Associated With Triple-NRTIs: Multivariable Analysis: OR (95% CI)	Factors Associated With ddI-d4T: Bivariate Analysis: OR (95% CI)	Factors Associated With ddI-d4T: Multivariable Analysis: OR (95% CI)
Age, yrs; mean (SD)	47 (8)	46 (11)	44 (11)	45 (10)	1.02 (1–1.04)*		1.01 (1–1.02)	1.02 (1–1.03)*	0.99 (0.94–1.03)	
Male sex	75 (72)	305 (70)	13 (68)	2186 (69)	1.17 (0.75–1.70)		1.05 (0.84–1.31)		0.98 (0.37–2.58)	
White	88 (85)	368 (84)	13 (68)	2647 (84)	1.09 (0.63–1.87)		1.07 (0.81–1.41)		0.43 (0.16–1.13)	
Mode of HIV acquisition										
Heterosexual	34 (33)	199 (46)	10 (53)	1371 (43)	*Ref.*		*Ref.*		*Ref.*	
MSM	45 (43)	174 (40)	4 (21)	1140 (36)	1.59 (1.01–2.5)*		1.05 (0.85–1.31)		0.48 (0.15–1.54)	
IDU	25 (24)	63 (14)	5 (26)	660 (21)	1.53 (0.9–2.58)		0.66 (0.49–0.89)*		1.04 (0.35–3.05)	
AIDS-defining illness	49 (47)	72 (17)	8 (42)	964 (30)	2.03 (1.37–3.01)*	1.68 (1.08–2.6)*	0.45 (0.35–0.59)*	0.54 (0.4–0.73)*	1.66 (0.67–4.14)	
No of past regimens; mean (SD)	9 (5)	3 (3)	5 (5)	5 (5)	1.16 (1.12–1.19)*		0.88 (0.85–0.91)*	0.85 (0.81–0.88)*	1.03 (0.94–1.12)	
0–2	3 (3)	250 (57)	7 (37)	1301 (41)	*Ref.*	*Ref.*	*Ref.*		*Ref.*	
3–5	17 (16)	135 (31)	6 (32)	833 (26)	8.85 (2.59–30.29)*	15.23 (3.48–66.69)*	0.84 (0.67–1.06)		1.34 (0.45–4)	
6–8	29 (28)	34 (8)	2 (11)	526 (17)	23.91 (7.25–78.83)*	38.54 (9.01–164.95)*	0.34 (0.23–0.49)*		0.71 (0.15–3.41)	
>8	55 (53)	17 (4)	4 (21)	511 (16)	46.68 (14.54–149.87)*	68.6 (16.45–286.11)*	0.17 (0.1–0.29)*		1.45 (0.42–4.99)	
Previous mono or dual therapy	91 (88)	98 (22)	7 (37)	1365 (43)	9.21 (5.13–16.54)*		0.38 (0.3–0.48)*		0.77 (0.3–1.96)	
SHCS center of follow-up										
No 1	34 (33)	100 (23)	6 (31)	1287 (41)	0.2 (0.13–0.31)*	0.2 (0.12–0.33)*	0.23 (0.17–0.3)*	0.25 (0.17–0.35)*	0.45 (0.13–1.6)	
No 2	3 (3)	15 (3)	0 (0)	307 (10)	0.07 (0.02–0.23)*	0.07 (0.02–0.22)*	0.140 (0.08–0.24)*	0.19 (0.1–0.35)*		
No 3	6 (6)	50 (11)	4 (21)	415 (13)	0.11 (0.05–0.25)*	0.09 (0.04–0.22)*	0.35 (0.24–0.49)*	0.57 (0.37–0.88)*	0.92 (0.23–3.71)	
No 4	7 (7)	116 (27)	3 (16)	437 (14)	0.12 (0.05–0.26)*	0.12 (0.05–0.28)*	0.76 (0.57–1.01)	1.2 (0.82–1.77)	0.66 (0.15–2.95)	
No 5	52 (50)	133 (31)	4 (21)	382 (12)	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*	
No 6	0 (0)	12 (3)	1 (5)	130 (4)			0.27 (0.14–0.5)*	0.46 (0.22–0.93)*	0.73 (0.08–6.63)	
No 7	2 (2)	10 (2)	1 (5)	206 (7)	0.07 (0.02–0.3)*	0.05 (0.01–0.21)*	0.14 (0.07–0.27)*	0.24 (0.12–0.49)*	0.46 (0.05–4.18)	
Source of follow-up										
SHCS Center	80 (80)	191 (45)	12 (67)	1980 (65)	*Ref.*	*Ref*	*Ref.*	*Ref.*	*Ref.*	*Ref.*
Other hospital	1 (1)	15 (4)	4 (22)	194 (6)	0.13 (0.02–0.92)	0.38 (0.05–2.99)	0.8 (0.46–1.38)	0.91 (0.5–1.64)	3.4 (1.09–10.65)*	3.95 (1.26–12.33)*
Private practitioner	20 (20)	220 (52)	2 (11)	890 (29)	0.56 (0.34–0.91)*	0.42 (0.25–0.72)*	2.56 (0.21–3.16)	1.71 (1.3–2.24)*	0.37 (0.83–1.66)	*Ref.*
Diabetes	7 (7)	19 (4)	0 (0)	127 (4)	1.73 (0.79–3.80)		1.09 (0.67–1.79)			
Cholesterol, mmole/L; mean (SD)	5.4 (1.4)	4.8 (1.1)	5.2 (1)	5.1 (1.2)	1.23 (1.02–1.44)*		0.76 (0.69–0.83)*	0.66 (0.59–0.74)*	1.11 (0.75–1.63)	
HDL, mmole/L; mean (SD)	1.4 (0.4)	1.2 (0.4)	1.6 (0.7)	1.4 (0.5)	0.89 (0.57–1.37)		0.35 (0.27–0.46)*		1.96 (0.89–4.32)	
LDL, mmole/L; mean (SD)	2.7 (1)	2.7 (0.9)	2.6 (1)	2.8 (1)	0.89 (0.73–1.1)		0.89 (0.78–0.99)*		0.83 (0.51–1.35)	
TG, mmole/L; mean (SD)	3.1 (2.2)	2 (1.8)	2.4 (1.4)	2.1 (1.7)	1.21 (1.12–1.29)*		0.96 (0.9–1.02)		1.08 (0.88–1.33)	

(*continued on next page*)

TABLE 1. (*Continued*) Characteristics of the 3 Nonrecommended Treatment Groups Compared With Controls

Baseline Characteristics	DBPIs (N = 104) N (%)	3-NRTIs (N = 436) N (%)	ddI–d4T (N = 19) N (%)	Control Group (N = 3171) N (%)	Factors Associated With DBPIs		Factors Associated With Triple-NRTIs		Factors Associated With ddI-d4T	
					Bivariate Analysis: OR (95% CI)	Multivariable Analysis: OR (95% CI)	Bivariate Analysis: OR (95% CI)	Multivariable Analysis: OR (95% CI)	Bivariate Analysis: OR (95% CI)	Multivariable Analysis: OR (95% CI)
TG ≥ 2.26 mmole/L	55 (54)	107 (25)	9 (50)	966 (32)	2.6 (1.74–3.87)*	2.194 (1.42–3.39)*	0.73 (0.58–0.92)*		2.17 (0.86–5.49)	
Lipid-lowering drug	33 (32)	42 (10)	4 (21)	372 (12)	3.5 (2.28–5.36)*		0.8 (0.57–1.12)		2.01 (0.66–6.08)	
Intermediate-high CV risk	29 (29)	87 (26)	6 (33)	649 (23)	1.41 (0.9–2.19)	1.12 (0.66–1.91)	1.16 (0.9–1.5)	1.67 (1.19–2.34)*	1.7 (0.64–4.54)	
Previous CV event	3 (3)	18 (4)	0 (0)	117 (4)	0.78 (0.24–2.48)		1.12 (0.68–1.87)			
Suboptimal adherence†	27 (27)	78 (18)	9 (53)	585 (19)	1.54 (0.98–2.11)	1.6 (1–2.65)	0.95 (0.73–1.24)		4.74 (1.82–12.32)*	4.42 (1.69–11.57)*

*$P < 0.05$.
†Forgetting on ≥1 occasion per month.
HDL, high-density lipoprotein; IDU, injecting drug user; LDL, low-density lipoprotein; MSM, men who have sex with men.

including treatment simplification or recommendation observance (Tables 2 and 3). For triple-NRTIs, switching was mainly due to abnormal fat distribution. In the subanalysis of this group, concern of CV disease [odds ratio (OR) 4.64, 95% confidence interval (CI) 0.9 to 24.12, $P = 0.07$] and the physician's decision (OR 2.22, 95% CI 0.92 to 5.36, $P = 0.08$) were slightly more frequently reasons for switching or discontinuation after the D:A:D study,[21] than abnormal fat distribution. Switching from ddI plus d4T was driven mainly by the physician's decision. The alternative cART choices are shown in Table 3.

Changes in Treatment Adherence, Lipid values, and Virological and Immunological Outcome at 24 and 48 Weeks After cART Switch

During the study period, 70 (71%) patients switched over from DBPIs to other regimens. Excluding patients not followed up 6 and 12 months later, patients who discontinued cART and patients resumed on a DBPI regimen, 50 and 41 patients were analyzed, respectively (Fig. 2, Table 4, see **Table S4, Supplemental Digital Content,** http://links.lww.com/QAI/A370). Postswitch, cholesterol values were lower ($P = 0.06$; Table 4; see **Table S4, Supplemental Digital Content**, http://links.lww.com/QAI/A370). Two additional patients started lipid-lowering treatment. However, the cholesterol values in these 2 patients increased with time.

Considering triple-NRTIs, 187 (48%) patients switched regimen (Fig. 2). Follow-up 6 and 12 months later occurred in 135 and 121 patients, respectively. Postswitch, all lipid values were higher ($P < 0.001$) despite the fact that 2 additional patients were receiving lipid-lowering agents. Fewer patients had detectable VLs ($P = 0.02$; Table 4; see **Table S4**, **Supplemental Digital Content 4**, http://links.lww.com/QAI/A370).

Eighteen out of 19 patients (95%) in the ddI/d4T group switched regimen (Fig. 2). Follow-up 6 and 12 months later occurred in 14 and 13 patients, respectively. No parameter was significantly different 6 or 12 months postswitch. Although there was a trend toward improved treatment adherence at 6 months ($P = 0.08$), by 12 months, this had returned to baseline ($P = 1$; Table 4; see **Table S4**, **Supplemental Digital Content 4**, http://links.lww.com/QAI/A370).

Finally, although concern of CV disease increased as a *reason* for switching patients on triple-NRTIs after the presentation of the D:A:D data at the 2008 CROI meeting, we observed no increase in treatment switches per se after this time point (Fig. 2).

DISCUSSION

In our study of patients on nonrecommended cART regimens, we observe that *physician's decision* (DBPIs; ddI plus d4T) and *concern over abnormal fat distribution* (triple-NRTIs) were the main factors driving treatment switches to recommendation-appropriate therapy. Conversely, patients with high CD4 counts (DBPIs) and suppressed VLs (triple-NRTIs) were more likely to continue on nonrecommended regimens.

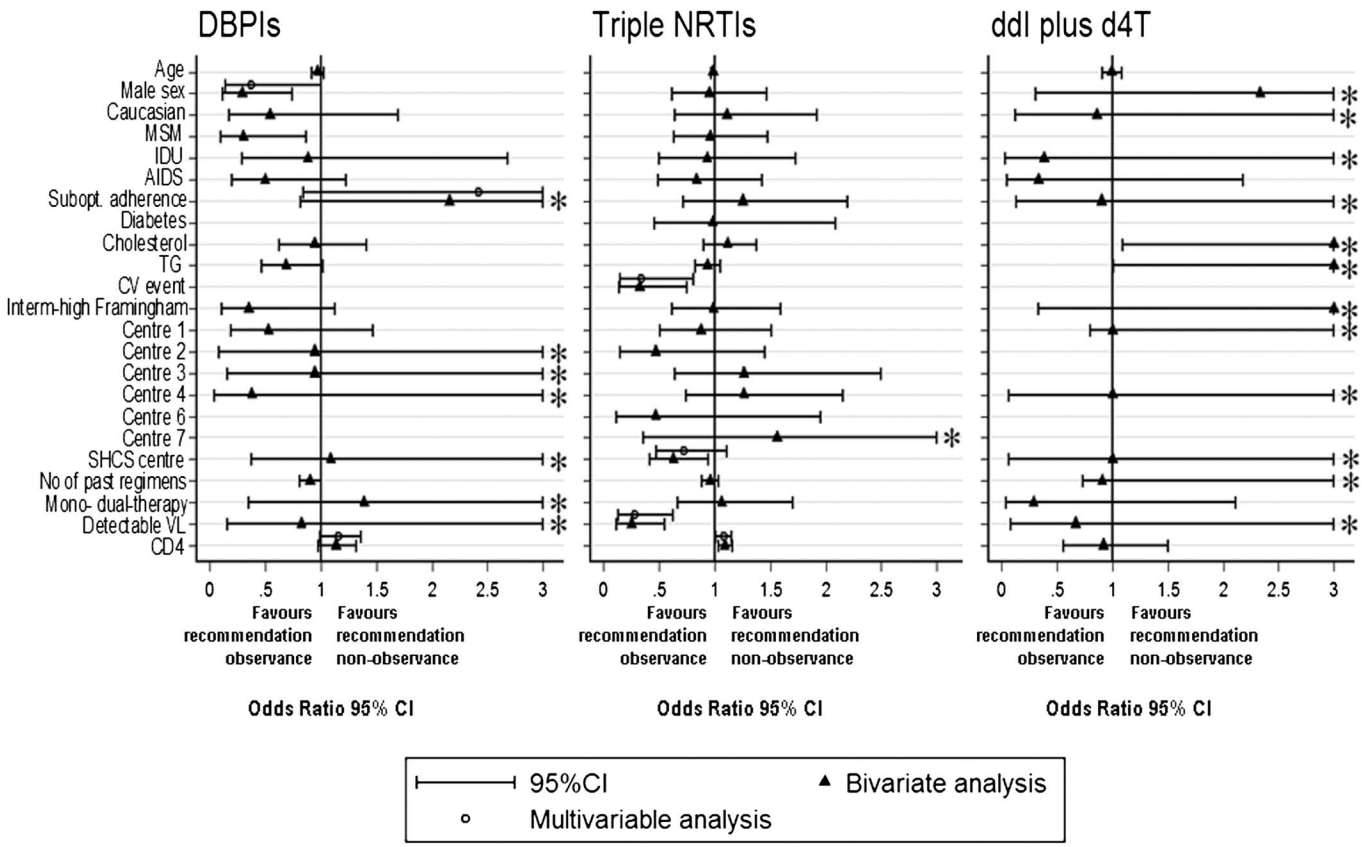

FIGURE 1. Predictors of nonobservance of the August 2006 IAS-USA recommendations in patients continued on cART containing DBPIs in 2010 (4 years after guideline publication), triple-NRTIs in 2010, or ddI plus d4T in 2007 (1 year after guideline publication) by comparing them with patients who switched over to another regimen or stopped cART. Undetectable VL: <50 copies per milliliter; suboptimal adherence: forgetting on ≥1 occasion per month. AIDS, history of AIDS defining illness; IDU, injecting drug user; MSM, men who have sex with men. *95% CI>3.

Patient characteristics differed between the treatment groups. The patients on DBPIs mostly had advanced HIV infection, were heavily treatment experienced, and were followed up in SHCS centers rather than in affiliated hospitals or private practitioners, characteristics related to the salvage therapy nature of this regimen. The slightly higher lipid (notably TG) values observed in this group are probably related to the PIs.[2,24] Patients on triple-NRTIs had less advanced HIV disease and were less treatment experienced, as expected for this regimen with a low genetic barrier to resistance. Most patients on ddI plus d4T had low treatment adherence suggesting that physicians were reluctant to change

TABLE 2. Reasons for Nonrecommended cART Switching or Discontinuation

	DBPIs Switch/Discontinuation: N = 70 (71%), N (%)	3NRTIs Switch/Discontinuation: N = 187 (48%), N (%)	ddI-d4T Switch/Discontinuation: N = 18 (95%), N (%)
Physician's decision	27 (39)	35 (19)	6 (33)
Patient's decision	12 (17)	21 (11)	1 (6)
Concern of CVD/dyslipidemia	10 (14)	10 (5)	2 (11)
Abnormal fat distribution	3 (4)	54 (29)	4 (22)
Other toxicity*	7 (10)	16 (9)	2 (11)
Treatment failure	2 (3)	13 (7)	1 (6)
Unknown	6 (9)	28 (15)	2 (11)
Other (death, lost to follow-up)	3 (4)	10 (5)	0 (0)

*Kidney, GI, liver, hematological, CNS.
CNS, central nervous system; CVD, cardiovascular disease; GI, gastrointestinal.

TABLE 3. Choice of New Regimen

	DBPIs Switch/Discontinuation: N = 70, N (%)	3NRTIs Switch/Discontinuation: N = 187, N (%)	ddI–d4T Switch/Discontinuation: N = 18, N (%)
NRTI and 1 boosted PI	15 (21.43)*	53 (28.34)	
NRTI and 1 NNRTI	0 (0)	84 (44.92)	
One PI and (NNRTI and/or FI and/or RAL)	35 (50)	0 (0)	
NNRTI and/or FI and/or RAL	6 (8.57)	18 (9.63)	
Other NRTIs plus other ARV class			13 (68.42)
NRTI-free regimen			2 (10.53)
Mono or dual-NRTI regimen			1 (5.26)
Stop treatment >30 d	14 (20)	32 (17.11)	2 (10.53)

*Lopinavir: 7/darunavir 6/tipranavir 2.
ARV, antiretroviral; FI, fusion inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; RAL, raltegravir.

treatment in this population or that patients did not want to change therapy. We observed some cART prescribing differences between the different center types, in keeping with the degree of HIV specialization. SHCS centers are centers of excellence in HIV care and treat more experienced or 'complicated' patients such as those on DBPIs; the majority (67%) of the patients on ddI plus d4T were also followed up at SHCS centers. Private practitioners are HIV community physicians who care for less ill patients such as those on triple-NRTIs. In addition to center differences, it is also possible that individual clinicians within a single center had cART preferences, although we did not examine this. A recent SHCS analysis reported large differences in prescription choices among clinicians treating cART-naive patients but no difference in patient outcome.[25]

The number of patients in each treatment group is very different, as is the slope of the survival analysis curve. Two years after the publication of recommendations advising against the use of ddI plus d4T and triple-NRTIs, we identified only 19 patients on ddI plus d4T and yet 436 on triple-NRTIs. Furthermore, at the end of the study period, 95%, 71%, and 48% of the patients in the ddI plus d4T, DBPI, and triple-NRTI groups, respectively, had switched over to another regimen. These differences could be related to different clinician perceptions regarding the toxicity of each regimen.

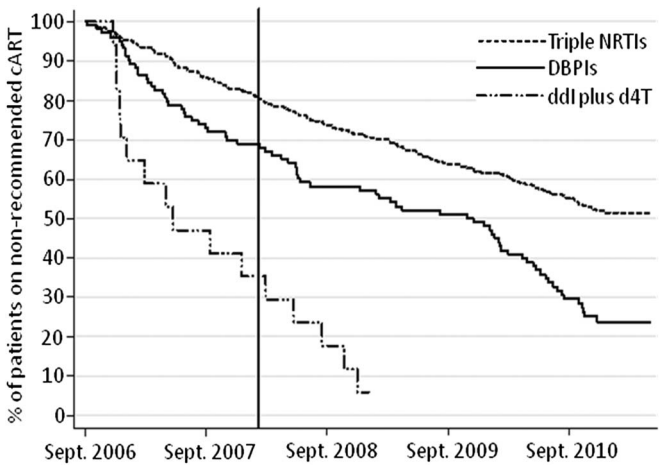

FIGURE 2. Longitudinal analysis of the 3 nonrecommended cART groups. The bold vertical line between September 2007 and September 2008 illustrates when the 2008 CROI meeting took place (presentation of data showing an association between ABC use and risk of myocardial infarction).

Predictors of continued nonrecommended cART prescription also differed according to treatment group: Predictors of continued DBPI prescription were female sex and, as a trend, higher CD4 counts; predictors of continued triple-NRTI prescription were undetectable VL, fewer previous treatment changes, and lack of CV events; patients who continued ddI plus d4T had higher lipid values. The differences observed between the 3 cART groups are understandable given the diverse characteristics of each. As no published study has examined if and how cART regimens are altered in response to updated recommendations, we can only compare our results with those of studies examining the choice of initial cART prescriptions in treatment-naïve patients. A gender association was described in a recent SHCS publication by Wandeler et al,[16] in which patients receiving an initial regimen in violation of the IAS-USA recommendations between 1998 and 2007 were more frequently female. This gender-based difference has already been described for prescription of specific types of cART[26,27] and could be related to the socioeconomic status that is correlated with gender among HIV-positive patients. The association between recommendation nonobservance and high CD4 count has also been reported by Wandeler et al (4189 patients), and in a smaller US cohort of HIV-infected women (217 patients).[13,16] For patients who are undetectable on triple NRTIs, the association between recommendation nonobservance and high CD4 count may be due to a perceived level of security on the part of the prescribing clinician. The clinician may be faced with the risks of continuing with a regimen that seems to work against the risk of starting a new recommended regimen that could precipitate problems with adherence and other adverse effects. We should mention also that, in Switzerland, the first

TABLE 4. Drug Adherence, Virological and Immunological Outcome, and Lipid Values Before and up to 48 Weeks After any Treatment Switch

	Under DBPIs: N = 41,* N (%)	48 Weeks After Switch: N = 41, N (%)	*P* Bivariate	Under Triple-NRTIs: N = 121,† N (%)	48 Weeks After Switch: N = 121, N (%)	*P* Bivariate	Under ddI-d4T: N = 13,‡ N (%)	48 Weeks After Switch: N = 13, N (%)	*P* Bivariate
Detectable HIV VL§	3 (8)	3 (8)	1	15 (13)	6 (5)	0.02	3 (23)	1 (8)	0.32
CD4 cell count; cell/mm^3, mean (SD)	549 (317)	530 (270)	0.85	668 (31)	706 (31)	0.06	582 (171)	607 (180)	0.58
Suboptimal adherence‖	6 (15)	5 (13)	0.71	13 (12)	14 (13)	0.81	4 (31)	4 (31)	1
Cholesterol total, mmole/L; mean (SD)	5.4 (1.2)	5.2 (2.2)	0.06	4.7 (0.1)	5.5 (0.1)	<0.001	4.9 (0.9)	4.9 (1.1)	0.27
HDL cholesterol, mmole/L; mean (SD)	1.3 (0.5)	1.2 (0.4)	0.14	1.2 (0.03)	1.3 (0.03)	<0.001	1.6 (0.8)	1.6 (0.7)	0.66
LDL cholesterol, mmole/L; mean (SD)	2.8 (0.9)	2.7 (0.9)	0.30	2.7 (0.1)	3.2 (0.1)	<0.001	2.5 (0.9)	2.6 (1)	0.86
TG, mmole/L; mean (SD)	3.3 (2.4)	2.7 (1.4)	0.13	2.1 (0.1)	2.6 (0.2)	<0.001	2 (1)	1.9 (1.3)	0.79
Lipid-lowering drug	19 (46)	21 (51)	0.16	24 (20)	26 (21)	0.56	2 (15)	3 (23)	0.32

*Seventy patients stopped DBPIs during the study period and 41 were analyzed (3 died, 14 stopped treatment during >30 days, 12 underwent treatment switch at the end of the study period and so did not have 48-week data by May 2011, date of data extraction).

†One hundred eight-seven patients stopped triple NRTIs during the study period and 121 were analyzed (9 died, 1 emigrated, 32 stopped treatment during >30 days, 24 underwent treatment switch at the end of the study period and so did not have 48-week data by May 2011, date of data extraction).

‡Eighteen patients stopped ddI plus d4T during the study period and 13 were analyzed (4 stopped treatment during >30 days, 1 did not have 48-week data posttreatment switch).

§≥50 copies per milliliter.

‖Forgetting on ≥1 occasion per month.

DBPI, double-boosted protease inhibitor; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

single-tablet regimen (efavirenz/TDF/emtricitabine) became available in August 2010, 4 years after its availability in the United States.

We observe an association between clinical characteristics, such as CV events and diabetes and changes of cART in the DBPI and triple-NRTI groups, suggesting that clinicians observe recommendations when they become 'relevant' to patients. Rather than being influenced by CV risk factors such as lipid values or CV risk assessment tools such as the Framingham score, clinicians seem to react to an event once it has happened, rather than switch cART as primary prevention, if patients exhibit good virological and immunological control.

The reason for switching DBPIs or discontinuing cART altogether was driven primarily by the physician's decision, in some cases specified as observance of treatment recommendations. The main reason for switching triple NRTIs was concern regarding abnormal fat distribution. A subanalysis of this group showed that concern of CV disease and physician's decision increased slightly as reasons for switching after publication of the D:A:D study data,[21] suggesting that large studies may influence cART choice. The switch from ddI plus d4T to another regimen was driven mainly by the physician's decision and concern of abnormal fat distribution, in accordance with recommendations. The patients' clinical course posttreatment switch agrees with the IAS-USA recommendations: Cholesterol values were slightly lower after DBPI switch, and the number of patients with detectable VL was lower[28] after triple-NRTI switch. These results highlight the importance of treatment recommendation observance, supported further by the Swiss and US cohort studies cited above in which patients on recommendation-appropriate cART obtained significant virological benefit compared with patients on nonrecommended regimens.[13,16]

Our study has several limitations. Regarding reasons for treatment changes, although we were able to study why patients were switched, we were not able to assess why patients were continued on nonrecommended regimens. For the reasons themselves, we were restricted by the established SHCS classifications, notably *physician's decision*, as there is no classification entitled *response to treatment recommendations*. Although some clinicians annotated *physician's decision* by specifying that they were following treatment recommendations, many did not. Indeed, we observed some discrepancy between the 'reasons for switch,' as documented in the patient notes, and the 'factors associated with switch,' as determined from our analyses, and it is possible

that we have overestimated the number of patients who changed cART as a result of treatment recommendations. Another limitation is that patient inclusion began in September 2006, after the August 2006 IAS-USA recommendations. Although this was appropriate for patients on DBPIs, it is likely that some patients on the other 2 nonrecommended regimens were already on different cART by 2006, in response to earlier recommendations, notably the 2004 IAS-USA recommendations. This would explain the small size of the ddI/d4T group, reducing the power of our study of these patients. Finally, although this was not the principal endpoint, it is difficult to draw conclusions regarding the outcome in patients who switched from nonrecommended to other cART: as alternative regimens were diverse, the postswitch patients represent a group that is sufficiently heterogeneous for it to be difficult to make meaningful comparisons between their preswitch and postswitch statuses.

In conclusion, we observe that, for some regimens, clinicians are guided more by the clinical, immunological, and virological course of individual patients than by recommendations, and that patients who are switched to recommended cART regimens have an improved clinical and virological course. Although cART choice can be a complex process, particularly in experienced patients whose treatment history is highly heterogeneous, our results demonstrate the benefit of observing available cART recommendations and suggest that recommendations should be observed even in well-controlled patients.

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