

Adherence to HIV Therapeutic Drug Monitoring Guidelines in The Netherlands

Matthijs van Luin, PharmD,*†‡ Ferdinand W. Wit, MD, PhD,§ Colette Smit, PhD,||
 Irma M. Rigter, PharmD,¶ Eric J. F. Franssen, PharmD, PhD,** Clemens Richter, MD, PhD,††
 Frank Kroon, MD, PhD,‡‡ Frank de Wolf, MD, PhD,§§ and David M. Burger, PharmD, PhD*†

Background: Therapeutic drug monitoring (TDM) is recommended in several international HIV treatment guidelines. The adherence of clinicians to these recommendations is unknown. The authors evaluated the adherence to the Dutch TDM guideline of 2005.

Methods: From the ATHENA cohort study, three scenarios were selected for which the guideline recommended TDM: 1) start of a combination of lopinavir/ritonavir + efavirenz or nevirapine (drug–drug interaction); 2) start of efavirenz (routine TDM); and 3) use of nelfinavir during pregnancy. For each scenario, we determined the proportion of patients for whom TDM was performed. Multivariable logistic regression modeling was used to identify determinants for the use of TDM.

Results: The adherence to the TDM guideline was 46.7% in patients who started lopinavir/ritonavir plus efavirenz or nevirapine; 9.5% for patients who started efavirenz; and 58.5% for patients who used nelfinavir during pregnancy. Patients treated in clinics that had a TDM assay available locally and patients treated in academic clinics were more likely to receive TDM. A higher baseline HIV viral load was another significant predictor for the performing TDM.

Conclusion: The adherence of clinicians to the Dutch TDM guidelines varied from low to moderate for the three investigated TDM scenarios. This study identifies several determinants for the use

of TDM, which may be useful information for those responsible for generating TDM guidelines.

Key Words: therapeutic drug monitoring, guidelines, HIV
(Ther Drug Monit 2010;0:000–000)

INTRODUCTION

Therapeutic drug monitoring (TDM), meaning the use of plasma drug concentrations in the management of antiretroviral therapy, is used frequently in some European countries such as The Netherlands, Spain, and France. In addition, several international HIV treatment guidelines, including the US Department of Health and Human Services guidelines, recommend TDM for specific clinical scenarios such as in patients with drug–drug interactions, with drug concentration-dependent toxicities, or in patients with a lack of virologic response.¹

The scientific basis for TDM of antiretroviral drugs consists of three observations: first, the importance of sufficiently high plasma drug concentrations for adequate suppression of HIV replication^{2–6}; second, the large interindividual variability in plasma concentrations of protease inhibitors and nonnucleoside transcriptase inhibitors (NNRTIs) among patients taking the same dose^{3,7–9}; and third, data from two randomized controlled trials, which demonstrated better therapeutic outcome in treatment-naïve patients who received routine TDM of nelfinavir or indinavir.^{10,11}

Little is known about the adherence of clinicians to TDM recommendations in HIV treatment guidelines. In addition, the determinants of adherence to TDM recommendations are unknown. For instance, a potential determinant might be the local availability of a TDM assay in the hospital or an HIV outpatient clinic. By understanding which factors are associated with adherence to TDM guidelines, strategies can be developed to improve adherence of clinicians to the guidelines as well as improving the guidelines themselves.

To obtain more insight into the use of TDM and the determinants of its use, we evaluated the use of TDM in The Netherlands from 2004 to 2008. Within this period, in 2005, the Dutch Association of AIDS Physicians issued evidence-based guidelines for the treatment of HIV-infected patients, including recommendations for TDM.^{12,13} The guidelines were published,¹³ they were discussed at plenary Dutch

Received for publication July 29, 2010; accepted November 9, 2010.

From the *Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; †Nijmegen Institute for Infection, Inflammation and Immunity (N4i), Nijmegen, The Netherlands; ‡Department of Clinical Pharmacy, Alysia Zorggroep, Arnhem, The Netherlands; §Centre for Poverty-related Communicable Diseases, Amsterdam Institute for Global Health and Development, Academic Medical Centre, Amsterdam, The Netherlands; ||Stichting HIV Monitoring, Amsterdam, The Netherlands; ¶Department of Clinical Pharmacy, Academic Medical Centre, Amsterdam, The Netherlands; **Department of Clinical Pharmacy, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands; ††Department of Internal Medicine, Alysia Zorggroep, Arnhem, The Netherlands; ‡‡Department of Infectious Diseases, Leiden University Medical Centre, Leiden, The Netherlands; and §§Department of Infectious Disease Epidemiology, Imperial College, London, UK.

The authors declare no conflicts of interest.

Correspondence: Matthijs van Luin, PharmD, Department of Clinical Pharmacy, 864 Radboud University Medical Centre Nijmegen, Geert Grooteplein 10, 6525 GA Nijmegen, The Netherlands (e-mail: m.vanluin@akf.umcn.nl).

Copyright © 2010 by Lippincott Williams & Wilkins

Association of AIDS Physicians meetings, and they were distributed by mail to all Dutch HIV physicians. We studied the use of TDM in three specific clinical scenarios for which TDM was recommended by the Dutch guideline.^{12,13} In addition, we studied whether TDM use was associated with therapeutic outcome.

The first scenario was the use of TDM in the setting of a drug–drug interaction, namely patients who started with the combination of the protease inhibitors lopinavir/ritonavir plus a NNRTI, either efavirenz or nevirapine. NNRTIs induce CYP3A-mediated metabolism of lopinavir, so an increase in the dose of lopinavir/ritonavir is recommended when concomitant use is indicated.¹⁴ TDM of lopinavir may be helpful to achieve optimal lopinavir plasma exposure in this situation.

The second scenario was the use of routine TDM in patients starting efavirenz in combination with two nucleoside analogue reverse transcriptase inhibitors (NRTIs). Although there was no formal evidence that routine TDM would benefit patient outcome for efavirenz, the scientific committee recommended it because efavirenz had similar pharmacologic characteristics as indinavir and nelfinavir (ie, large interindividual variability in pharmacokinetics and an established relationship between the plasma concentration of efavirenz and antiretroviral efficacy and toxicity³).

The third scenario was in patients who used a nelfinavir-containing regimen during pregnancy. When the guideline was introduced in 2005, nelfinavir in combination with lamivudine and zidovudine was a commonly used regimen for HIV-infected pregnant women in The Netherlands.¹² Nelfinavir plasma concentrations may be decreased during pregnancy,^{15,16} which may in turn lead to an increased risk of treatment failure.¹⁷ To ensure adequate nelfinavir plasma concentrations during pregnancy, the guideline recommended TDM of nelfinavir during pregnancy.

METHODS

Patients

All Dutch hospitals that provide antiretroviral treatment participate in the AIDS Therapy Evaluation in The Netherlands (ATHENA) observational cohort study. Currently, data from over 16,000 patients have been recorded anonymously in a central database that is maintained by the HIV Monitoring Foundation.¹⁸

We studied the use of TDM for the three scenarios given subsequently from January 1, 2004, to December 31, 2008. Because it is difficult to assess whether TDM would have been applied in patients who used the antiretroviral drug (combination) of interest for a relatively short time, we excluded those patients who had discontinued the drug of interest before TDM should have been applied for the specific TDM scenario (see subsequently).

Scenario 1: Drug Interaction Lopinavir + Efavirenz/ Nevirapine

From the ATHENA observational cohort study, we selected all adult patients who started lopinavir/ritonavir + efavirenz

or nevirapine. Adherence to the guideline was defined as the presence of a lopinavir plasma concentration in the ATHENA database between Weeks 1 and 12. Patients who discontinued the combination of lopinavir + efavirenz or nevirapine within 3 weeks were excluded.

Scenario 2: Routine Therapeutic Drug Monitoring of Efavirenz

We selected all adult patients who started efavirenz in combination with two NRTIs for the first time. For efavirenz, the guideline recommended measuring plasma concentrations at Week 4 and Week 24 after starting therapy. Therefore, we defined full adherence to the guideline as the presence of plasma concentrations of efavirenz in the ATHENA database between Weeks 2 and 8 and between Weeks 16 and 32. Because adherence to the TDM guideline was only possible in patients who still used efavirenz at Week 24, we excluded those patients who discontinued efavirenz within 32 weeks. Because many patients were thus excluded, we also defined “partial adherence,” defined as having an efavirenz plasma concentration measurement at Week 4. For this analysis, we only excluded patients who had discontinued efavirenz within 8 weeks.

Scenario 3: Therapeutic Drug Monitoring of Nelfinavir During Pregnancy

For Scenario 3, we selected all adult female patients who started nelfinavir during pregnancy or who became pregnant while using nelfinavir. We defined adherence to the guideline as the availability of at least one plasma concentration of nelfinavir during pregnancy. Patients who used nelfinavir for less than 8 weeks during pregnancy were excluded.

Statistics

Baseline Characteristics

Patient characteristics at the start of one of the three scenarios were tabulated for patients who received TDM according to the guideline and those who did not. Differences between groups were compared using chi square or Fisher exact tests for categorical data and Mann-Whitney *U* tests for continuous data. All tests were two-sided and a *P* value of < 0.05 was considered statistically significant.

Adherence to the Guidelines

We used multivariable logistic regression modeling to investigate the relationship of the following factors with use of TDM: 1) time period of starting therapy, ie, a) preintroduction of guideline (2004), b) introduction of guideline (2005–2006), and c) postintroduction of guideline (2007–2008); 2) context of outpatient clinic. Outpatient clinics were categorized as follows: a) small academic HIV outpatient clinics, b) large academic outpatient clinics, c) small nonacademic outpatient clinics, and d) large nonacademic outpatient clinics. Outpatient clinics were classified as large or small if they had greater or fewer than the median number of patients for academic (*n* = 354) and nonacademic HIV outpatient clinics (*n* = 221), respectively; 3) regular presence of a clinical pharmacist at multidisciplinary HIV treatment-team meetings;

and 4) availability of a TDM assay in the hospital laboratory of the outpatient clinic.

In addition, we evaluated the influence of several patient-related factors, namely gender, country of birth (as a surrogate for ethnicity), age, body mass index (calculated as the weight in kilograms divided by the square of the height in meters), hepatitis B and C status, HIV transmission risk group, CD4 count, HIV viral load at the start of the regimen of interest, specific NRTI backbone, and pretreated status at the start of therapy. Pretreated status was categorized as follows: 1) treatment-naïve patients; 2) treatment-experienced patients with an undetectable viral load (less than 50 copies/mL) at the start of the regimen of interest; and 3) treatment-experienced patients with a detectable viral load at the start of the regimen of interest.

Effect of Adherence to the Guidelines on Virologic Response and Toxicity-Driven Drug Discontinuations

To assess whether adherence to the TDM guideline affected therapeutic outcome, we investigated the effect of adherence to the TDM guideline on virologic response and toxicity-driven drug discontinuations.

For Scenarios 1 and 2, virologic response was defined as a viral load below 50 copies/mL at Week 48. For Scenario 3 (nelfinavir use during pregnancy), virologic response was a viral load below 50 copies/mL at the last viral load measurement before delivery. For the latter scenario, we included the time on nelfinavir as an extra independent variable in our logistic regression models.

We used an observed failure approach in which patients who discontinued their regimen as a result of failure to suppress viral replication were considered failures at subsequent time points, whereas patients who discontinued as a result of other reasons were censored from that moment onward. Multivariable logistic regression association models were constructed to adjust for potential confounders. All patient-related factors that were used in the analysis for guideline adherence were tested for confounding. We used a stepwise selection procedure by which a parameter was identified as a confounder if its addition to the model resulted in a greater than 10% change of the regression coefficient of TDM on virologic response.

Cox proportional hazards analysis was used to assess the impact of adherence to the TDM guideline on drug discontinuations resulting from toxicity or the patient's choice within the first year of therapy. Patients who discontinued the drug of interest for other reasons were censored from the moment of discontinuation. Confounding was assessed for the same parameters and in the same manner as for the analysis of virologic response.

All data were analyzed with SPSS for MS Windows, Version 16.0.1 (SPSS Inc, Chicago, IL).

RESULTS

Table 1 presents some key characteristics of the Dutch HIV outpatient clinics that were considered potentially relevant for the uptake of the TDM recommendations. Academic

outpatient clinics were generally larger than nonacademic outpatient clinics. In addition, academic outpatient clinics had a TDM assay available locally more frequently.

Scenario 1: Drug Interaction Lopinavir + Efavirenz/Nevirapine

Three hundred four patients started cART, which contained lopinavir/ritonavir plus efavirenz or nevirapine. Within the first 3 weeks, 47 patients (15.5%) discontinued the use of this combination. The main reasons for early discontinuation of the combination of lopinavir + efavirenz/nevirapine were as follows: toxicity ($n = 15$ [31.9%]), unknown reason ($n = 11$ [23.4%]), and regimen simplification ($n = 5$ [10.6%]).

The remaining 257 patients were included in the analysis, of which the majority (158 [61.5%]) used efavirenz in combination with lopinavir. A total of 120 of the 257 patients (46.7%) had a plasma lopinavir concentration determined as recommended by the guideline. As shown in Table 2, baseline characteristics for the TDM and non-TDM group were mostly similar.

The use of TDM increased from 32.4% in 2004 (preguideline) to 55.3% during introduction of the guideline in 2005–2006. In 2007–2008, the use of TDM remained stable (49.0%). Multivariable logistic regression analysis demonstrated that patients in large nonacademic outpatient clinics were significantly less likely to receive TDM compared with patients in academic clinics (Table 3). Furthermore, treatment-experienced patients were more likely to receive TDM compared with treatment-naïve patients, especially those treatment-experienced patients with detectable viral loads at baseline (Table 3).

Forty-eight weeks after baseline, 79.6% of the patients who received TDM had a viral load below 50 copies/mL compared with 73.9% of the patients who were not monitored by TDM ($P = 0.50$). In the univariable logistic regression analysis, baseline CD4 count and baseline viral load were significantly associated with virologic response at Week 48. After adjusting for these and other factors that confounded the effect of adherence to the guideline (namely gender, body mass index, hepatitis B status, pretreated status, and NRTI backbone), patients who received TDM had an adjusted odds ratio (OR) of 1.77 (95% confidence interval [CI], 0.36–8.37; $P = 0.48$) for achieving virologic response at Week 48. At Week 24, adherence to the guideline was also not associated with virologic response (data not shown).

At Week 48, 15 of the 137 patients who did not receive TDM had discontinued lopinavir as a result of toxicity or the patient's choice (TOXP) compared with three of the 120 patients who did receive TDM ($P = 0.008$, log-rank test). In bivariable Cox proportional hazards models, only baseline CD4 count significantly (greater than 10%) modified the effect of adherence to the guideline on the risk of TOXP discontinuations. After adjusting for this parameter, patients who received TDM still had a significantly lower risk of toxicity-induced lopinavir discontinuations (adjusted hazard ratio, 0.16; 95% CI, 0.036–0.71; $P = 0.016$).

TABLE 1. TDM-Related Characteristics of the 24 Dutch HIV Outpatient Clinics

	Academic		Nonacademic		P Value
	No.	Percent	No.	Percent	
All	8		16		
Presence of a clinical pharmacist at multidisciplinary HIV treatment-team meetings					
Never	2	25.0	8	50.0	0.39†
Regularly	6	75.0	8	50.0	
Presence of a local HIV TDM assay					
Present	5	62.5	5	31.3	0.20†
Not present	3	37.5	11	68.8	
	Median	Range	Median	Range	
Number of patients under care at January 1, 2006	354	255–1636	221	69–1490	0.032*

*Mann-Whitney test.

†Fisher exact test.

TDM, therapeutic drug monitoring.

Scenario 2: Routine Therapeutic Drug Monitoring of Efavirenz

A total of 3057 patients started antiretroviral treatment with efavirenz in combination with two NRTIs between 2004 and 2008. Within the first 36 weeks, 588 patients (19.2%) discontinued efavirenz, which left 2469 patients for analysis. The main reasons for discontinuation of efavirenz before Week 36 were as follows: unknown reasons ($n = 326$ [55%]), toxicity ($n = 146$ [24.8%]), and the patient's decision ($n = 51$ [8.7%]).

Two hundred thirty-four of the 2469 patients (9.5%) who used efavirenz for at least 32 weeks had a plasma efavirenz concentration determined at Weeks 4 and 24, as recommended by the guideline. As shown in Table 2, patients who received TDM had generally lower CD4 counts and higher viral loads at baseline compared with patients who did not receive TDM.

The use of TDM of efavirenz decreased significantly from 15.8% in 2004 (preguideline) to 11.5% during introduction of the guideline in 2005–2006. In 2007–2008, the adherence to the guideline decreased further to 5.7%. As for Scenario 1, patients treated in nonacademic outpatient clinics were less likely to receive TDM than patients in academic settings. In addition, large academic clinics had lower adherence to the guideline compared with small academic clinics. The presence of a clinical pharmacist at multidisciplinary team meetings resulted in lower adherence to the 2005 TDM guideline, whereas the local availability of a TDM assay resulted in greater adherence to the guideline. Finally, patients with higher baseline viral loads were more likely to receive efavirenz TDM (Table 3).

For the analysis of partial adherence to the guideline, we excluded the 307 patients who had discontinued efavirenz within 8 weeks. This left 2750 patients for this analysis. Of these patients, 836 (30.4%) had a plasma efavirenz concentration measured at Week 4. Partial adherence was stable over time (30.8% in 2004, 30.7% in 2005–2006, and 30.0% in 2007–2008). Baseline viral load, hospital type, the presence of a local TDM assay, and the presence of a clinical pharmacist at multidisciplinary team meetings predicted partial adherence in the same manner as they did for full adherence to the guideline (data not shown).

Forty-eight weeks after baseline, 89.5% of the patients in the group of patients who received TDM according to the guidelines had a viral load below 50 copies/mL compared with 93.3% of the patients who did not receive TDM ($P = 0.054$). After adjusting for factors that confounded the effect of adherence to the guideline on virologic response (body mass index and baseline CD4 count), patients who received TDM were less likely to achieve virologic response (adjusted OR, 0.49; 95% CI, 0.29–0.85; $P = 0.010$). Patients who received TDM of efavirenz at Week 4 (ie, partial adherence to the guideline) were also less likely to achieve virologic response (adjusted OR, 0.59; 95% CI, 0.39–0.89; $P = 0.013$).

Because there were only a few patients who discontinued efavirenz because of TOXP after Week 32, we examined the association between partial adherence to the guideline (at least a Week 4 efavirenz plasma sample available) and TOXP-driven discontinuations. Within 48 weeks, 11 of the 836 patients in the TDM group (2.5%) had discontinued efavirenz because of TOXP versus 41 of the 1915 (3.5%) of the patients in the non-TDM group ($P = 0.19$, log-rank test). After adjusting for confounding factors in a multivariable Cox proportional hazards analysis (baseline CD4 count and the NRTI backbone), patients who received TDM had an adjusted hazard ratio (95% CI) of 0.72 (0.44–1.18; $P = 0.19$) for TOXP discontinuations of efavirenz.

Scenario 3: Therapeutic Drug Monitoring of Nelfinavir During Pregnancy

A total of 161 patients started antiretroviral treatment with nelfinavir during pregnancy or before becoming pregnant. Of these patients, 135 used nelfinavir for more than 8 weeks during pregnancy. The great majority of these patients ($n = 130$ [96.3%]) started nelfinavir during pregnancy; five patients had already started nelfinavir before they became pregnant.

Table 2 shows that the majority of women ($n = 79$ [58.5%]) had at least one plasma concentration of nelfinavir determined during pregnancy. There were no statistically significant differences in baseline characteristics between patients who did or did not receive TDM during pregnancy (Table 2).

TABLE 2. Patient Characteristics at the Time of Starting the Regimen of Interest

	Lopinavir + NNRTI					Efavirenz				
	TDM		No TDM		<i>P</i>	TDM		No TDM		<i>P</i>
	No.	Percent	No.	Percent		No.	Percent	No.	Percent	
All	120	46.7	137	53.3		234	9.5	2235	90.5	
Gender										
Male	96	80.0	113	82.8	0.61†	194	82.9	1827	81.7	0.66†
Female	24	20.0	24	17.5		40	17.1	408	18.3	
Region of origin										
Western Europe	86	71.7	78	56.9	0.067†	145	62.0	1413	63.2	0.75†
Caribbean/Latin America	13	10.8	16	11.7		28	12.0	247	11.1	
Sub-Saharan Africa	13	10.8	27	19.7		41	17.5	349	15.6	
Other	8	6.7	16	11.7		20	8.5	226	10.1	
Pretreatment status										
Treatment-naïve	40	33.3	47	34.3	0.22†	161	68.8	1516	67.8	0.034†
Treatment-experienced, VL < 50 copies/mL	19	15.8	32	23.4		36	15.4	462	20.7	
Treatment-experienced, VL > 50 copies/mL	61	50.8	57	41.6		37	15.8	251	11.2	
	Median	IQR	Median	IQR		Median	IQR	Median	IQR	
Age (years)	43	37–51	42	36–59	0.37*	40	35–48	41	35–48	0.38*
Date of starting therapy	06/06	06/05–10/07	04/06	10/04–11/07	0.31*	12/05	10/04–03/07	12/06	07/05–01/08	<0.001*
Body mass index (kg/m ²)	22.5	20–25	22.9	21–25	0.65*	22.7	21–25	23.1	21–25	0.051*
CD4 count (/mm ³)	230	120–463	300	140–440	0.63*	210	100–310	245	160–350	<0.001*
Viral load (log ₁₀ copies/mL)‡	4.7	3.6–5.8	4.5	3.4–5.5	0.27*	5.0	4.6–5.3	4.9	4.4–5.3	0.051
	Nelfinavir									
	TDM		No TDM		<i>P</i>	TDM		No TDM		<i>P</i>
	No.	Percent	No.	Percent		No.	Percent	No.	Percent	
All	79	58.5	56	41.5						
Gender										
Male	NA	—	NA	—		NA	—	NA	—	
Female	79	58.5	56	41.5						
Region of origin										
Western Europe	15	19.0	4	7.1	0.065†	4	7.1	7.1	0.065†	
Caribbean/Latin America	13	16.5	5	8.9		5	8.9	8.9		
Sub-Saharan Africa	45	57.0	44	78.6		44	78.6	78.6		
Other	6	7.6	3	5.4		3	5.4	5.4		
Pretreatment status										
Treatment-naïve	66	83.5	44	78.6	0.61†	44	78.6	78.6	0.61†	
Treatment-experienced, VL < 50 copies/mL	7	8.9	8	14.3		8	14.3	14.3		
Treatment-experienced, VL > 50 copies/mL	6	7.6	4	7.1		4	7.1	7.1		
	Median	IQR	Median	IQR		Median	IQR	Median	IQR	
Age (years)	29	25–32	29	25–33	0.67*	29	25–33	29	25–33	0.67*
Date of starting therapy	06/05	09/04–02/06	02/05	08/04–04/06	0.74*	02/05	08/04–04/06	02/05	08/04–04/06	0.74*
Body mass index (kg/m ²)	24.7	23–30	26.2	24–28	0.85*	26.2	24–28	26.2	24–28	0.85*
CD4 count (/mm ³)	410	283–565	390	281–518	0.51*	390	281–518	390	281–518	0.51*
Viral load (log ₁₀ copies/mL)‡	3.9	3.3–4.5	4.0	3.1–4.4	0.96*	4.0	3.1–4.4	4.0	3.1–4.4	0.96*

*Mann-Whitney test.

†Chi square test.

‡Includes only data from patients with a detectable viral load at baseline.

NNRTI, nonnucleoside transcriptase inhibitor; TDM, therapeutic drug monitoring; VL, viral load; IQR, interquartile range; NA, not applicable.

TABLE 3. Factors Predictive of Adherence to the Dutch TDM Guidelines in Multivariable Logistic Regression Analyses

	Adjusted OR	95% CI	P
Scenario 1: lopinavir + NNRTI drug interaction			
Treatment period			0.004
Preintroduction (2004)	0.24	0.10–0.56	0.001
Guideline introduction (2005–2006)	1.00		
Postintroduction (2007–2008)	0.52	0.23–1.20	0.12
Context of outpatient clinic			0.004
Academic	1.00		
Nonacademic, small (less than 221 patients)	0.49	0.18–1.34	0.16
Nonacademic, large (more than 221 patients)	0.24	0.098–0.57	0.001
Pretreatment status			0.058
Naive	1.00		
Treatment-experienced, VL < 50 copies/mL	1.16	0.42–3.26	0.082
Treatment-experienced, VL > 50 copies/mL	2.62	1.08–6.40	0.034
Scenario 2: routine TDM of efavirenz at Week 4 and Week 24			
Treatment period			<0.001
Preintroduction (2004)	1.65	1.15–2.37	0.007
Guideline introduction (2005–2006)	1.00		
Postintroduction (2007–2008)	0.48	0.34–0.67	<0.001
Context of outpatient clinic			<0.001
Academic, small (less than 354 patients)	1.00		
Academic, large (more than 354 patients)	0.20	0.13–0.29	<0.001
Nonacademic, small (less than 221 patients)	0.076	0.035–0.17	<0.001
Nonacademic, large (more than 221 patients)	0.13	0.089–0.19	<0.001
Presence of a local TDM assay for efavirenz			
Not present	1.00		
Present	2.06	1.31–3.26	0.002
Presence of a clinical pharmacist at HIV MDT meetings			
Not present	1.00		
Regularly present	0.56	0.37–0.86	0.009
Baseline viral load (copies/mL) (per ¹⁰ log increase)	1.17	1.06–1.29	0.003
Scenario 3: nelfinavir during pregnancy			
Context of outpatient clinic			0.004
Academic	1.00		
Nonacademic, small (less than 221 patients)	0.39	0.12–1.24	0.11
Nonacademic, large (more than 221 patients)	0.18	0.066–0.49	0.001
Presence of a local TDM assay for nelfinavir			
Not present	1.00		
Present	3.79	1.45–9.87	0.006

TDM, therapeutic drug monitoring; OR, odds ratio; CI, confidence interval; NNRTI, nonnucleoside transcriptase inhibitor; VL, viral load; MDT, multidisciplinary team.

The use of TDM increased slightly from 54.9% in 2004 (preguideline) to 61.8% during the introduction of the guideline in 2005–2006. After introduction of the guideline, in 2007–2008, the use of TDM decreased (50.0%). In the multivariable logistic regression model, patients treated in large nonacademic outpatient clinics were less likely to receive TDM than patients in academic clinics. In addition, the local availability of a TDM assay was associated with more use of TDM during pregnancy (Table 3).

At the last viral load measurement before delivery, 94.2% in the group of patients who received TDM during pregnancy had a viral load below 50 copies/mL compared with 94.1% of the patients who did not receive TDM ($P = 1.00$). After adjusting for confounders (baseline CD4, baseline viral

load, and time on nelfinavir), the adjusted OR (95% CI) to achieve an undetectable load was 1.45 (0.18–11.73; $P = 0.73$) for patients who received TDM. There were two TOXP discontinuations of nelfinavir during pregnancy in the TDM group and two in the non-TDM group ($P = 1.00$).

DISCUSSION

The main goal of this study was to evaluate the adherence of clinicians to the Dutch TDM guidelines of 2005. The adherence to the recommendations varied from low for routine TDM of efavirenz (full adherence 9%; partial adherence 30%), to moderate for nelfinavir in pregnancy (59%), and lopinavir concomitantly used with an NNRTI (47%).

We cannot compare these results with those of other countries or databases because this is, to our knowledge, the first evaluation of HIV physician adherence to TDM guidelines. Part of the explanation for the moderate adherence to the TDM recommendations might be that most recommendations were based on expert opinion. The only exceptions are nelfinavir and indinavir.^{10,11} In agreement with this, adherence to the TDM recommendations was highest for the nelfinavir scenario. HIV therapy is changing rapidly and improving as a result of continuous drug development. Between 2004 and 2008, the antiretroviral armamentarium was extended with several potent and relatively well-tolerated drugs. Therefore, physicians have increased opportunities for switching therapy instead of managing drug-related problems with TDM. This may form a second explanation for the moderate adherence to the TDM recommendations.

The adherence to the recommendation to perform routine TDM of efavirenz at Week 4 and Week 24 was extremely low and declined from 16% in 2004 to 6% in the period 2007–2008. At present, there is international consensus among clinical pharmacologists that TDM should be applied selectively and not routinely.^{19–21} It is possible that during our study period, an increasing number of Dutch HIV physicians as well as clinical pharmacists (Table 3) became convinced that TDM is only indicated in selected situations. This may explain the declining rates for routine TDM of efavirenz between 2004 and 2008.

A second important goal of this study was to identify determinants of TDM use. The data from our study indicate that Dutch HIV physicians are more likely to use TDM in patients with a higher baseline viral load (efavirenz scenario) or in treatment-experienced patients who start therapy with a detectable viral load (lopinavir scenario). Thus, TDM is used in the most vulnerable patients who have the highest a priori chance of failure to suppress viral load. Other patient-related determinants of TDM use were not identified.

Independent of the context of the outpatient clinic, the local availability of an analytical assay for the measurement of antiretroviral drug concentrations was associated with increased use of TDM. The availability of a local assay would probably ease TDM logistics, thereby shortening the time delay between the time of blood sampling and the TDM result. As a consequence, HIV physicians might become more ready to use TDM, which in turn will lead to increased experience with TDM.

Another health-system related determinant of TDM use was the context of the HIV outpatient clinic. Academic centers were more likely to use TDM than nonacademic centers for all investigated TDM scenarios. It is difficult to explain this result, which is probably caused by multiple factors. One factor might be that academic HIV physicians are more willing to adhere to expert opinion-based recommendations. A second possible explanation might be the presence of trainees who specialize in infectious diseases in academic clinics. These trainees were actively educated on the Dutch TDM guidelines and they may have propagated the use of TDM in their outpatient clinics.

Finally, the time period in which therapy was initiated was associated with TDM use for efavirenz (discussed previously) and for lopinavir. For only lopinavir in combination with efavirenz or nevirapine, the results from our study suggest that the introduction of the TDM recommendations led to increased use of TDM.

The ATHENA database offers unique opportunities for TDM research because it comprises detailed information on TDM results as well as clinical information. Although not the primary goal of our analysis, we were also interested in whether adherence to the TDM guidelines was associated with virologic response or drug toxicity (the latter being deduced from toxicity or the decision of a patient to discontinue a drug).

For the lopinavir scenario, patients who received TDM appeared less likely to discontinue lopinavir because of toxicity or from patient choice. For efavirenz, patients who received TDM were less likely to achieve an undetectable viral load at Week 48. One should interpret both results cautiously, because our study design is observational. Thus, patients were not randomized to a TDM or a non-TDM group; they may have received TDM for a particular reason, which might be associated with the likelihood of achieving the studied outcome. Given the low adherence to the efavirenz routine TDM guideline, it is most probable that efavirenz TDM was applied selectively rather than routinely. As described, TDM was applied mostly in those patients who had the highest a priori chance of failure to suppress viral load. In our analysis, we attempted to adjust for such a selection bias (eg, by including baseline viral load in the regression model), but there certainly remain residual confounding variables (eg, preferential use of TDM in patients suspected of non-adherence). Confounding by indication is in our view the most likely explanation for the worse virologic outcome in patients who received TDM of efavirenz.

The lower discontinuation rate of lopinavir in the TDM group might be caused by dose reduction of lopinavir in patients with lopinavir adverse effects and high plasma lopinavir concentrations. Five patients in the TDM group had their lopinavir dose reduced after initially starting an increased dose, which may have prevented some toxicity-induced lopinavir discontinuations in the TDM group. High plasma lopinavir concentrations have been related to hypercholesterolemia²² and, anecdotally, to gastrointestinal symptoms such as nausea and abdominal pain.

Although this study evaluated the adherence to the Dutch TDM guidelines of 2005, drug–drug interactions (lopinavir scenario) and pregnancy (nelfinavir scenario) are still regarded as valid scenarios for TDM by current international HIV treatment guidelines.^{1,21} Present-day HIV treatment guidelines do not recommend unselected routine use of TDM any more. However, efavirenz is one of the few antiretroviral drugs with a high likelihood of concentration-related adverse effects, which is still a valid indication for TDM.^{3,23}

In conclusion, the adherence of clinicians to the Dutch TDM guideline varied from low to moderate for the three investigated TDM scenarios. This study identifies several determinants for the use of TDM, which may be useful information for those responsible for generating TDM guidelines.

REFERENCES

1. DHHS Panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents 2009 (updated December 1, 2009). Available at: <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>. Accessed July 29, 2010.

2. Baxter JD, Merigan TC, Wentworth DN, et al. Both baseline HIV-1 drug resistance and antiretroviral drug levels are associated with short-term virologic responses to salvage therapy. *AIDS*. 2002;16:1131–1138.
3. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS*. 2001;15:71–75.
4. Veldkamp AI, Weverling GJ, Lange JMA, et al. High exposure to nevirapine in plasma is associated with an improved virological response in HIV-1-infected individuals. *AIDS*. 2001;15:1089–1095.
5. Acosta EP, Kakuda TN, Brundage RC, et al. Pharmacodynamics of human immunodeficiency virus type 1 protease inhibitors. *Clin Infect Dis*. 2000;30(Suppl 2):S151–S159.
6. Vries-Sluijs TE, Dieleman JP, Arts D, et al. Low nevirapine plasma concentrations predict virological failure in an unselected HIV-1-infected population. *Clin Pharmacokinet*. 2003;42:599–605.
7. Barry MG, Merry C, Lloyd J, et al. Variability in trough plasma saquinavir concentrations in HIV patients—a case for therapeutic drug monitoring. *Br J Clin Pharmacol*. 1998;45:501–502.
8. Regazzi MB, Villani P, Maserati R, et al. Pharmacokinetic variability and strategy for therapeutic drug monitoring of saquinavir (SQV) in HIV-1 infected individuals. *Br J Clin Pharmacol*. 1999;47:379–382.
9. Marzolini C, Buclin T, Decosterd LA, et al. Nelfinavir plasma levels under twice-daily and three-times-daily regimens: high interpatient variability and low inpatient variability. *Therapeutic Drug Monitoring*. 2001;23:394–398.
10. Fletcher CV, Anderson PL, Kakuda TN, et al. Concentration-controlled compared with conventional antiretroviral therapy for HIV infection. *AIDS*. 2002;16:551–560.
11. Burger D, Hugen P, Reiss P, et al. Therapeutic drug monitoring of nelfinavir and indinavir in treatment-naïve HIV-1-infected individuals. *AIDS*. 2003;17:1157–1165.
12. Werkgroep antiretrovirale behandeling van de Nederlandse Vereniging van Aids Behandelaren. Herziened richtlijn Antiretrovirale Behandeling (updated December 2007). Available at: www.nvab.org. Accessed July 29, 2010.
13. Revised guideline 'Antiretroviral Treatment.' *Ned Tijdschr Geneesk*. 2005;149:2399–2405.
14. FDA. Kaletra; Prescribing information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2007/021226s022lbl.pdf. Accessed July 29, 2010.
15. Nellen JF, Schillevoort I, Wit FW, et al. Nelfinavir plasma concentrations are low during pregnancy. *Clin Infect Dis*. 2004;39:736–740.
16. Villani P, Floridia M, Pirillo MF, et al. Pharmacokinetics of nelfinavir in HIV-1-infected pregnant and nonpregnant women. *Br J Clin Pharmacol*. 2006;62:309–315.
17. Angel JB, Khaliq Y, Monpetit ML, et al. An argument for routine therapeutic drug monitoring of HIV-1 protease inhibitors during pregnancy. *AIDS*. 2001;15:417–419.
18. Gras L, Van Sighem AI, Smit C, et al. Monitoring of human immunodeficiency virus (HIV) infection in The Netherlands. Report 2009. Available at: www.hiv-monitoring.nl. Accessed July 29, 2010.
19. Van Luin M, Kuks PF, Burger DM. Use of therapeutic drug monitoring in HIV disease. *Curr Opin HIV AIDS*. 2008;3:266–271.
20. Khoo SH, Lloyd J, Dalton M, et al. Pharmacologic optimization of protease inhibitors and nonnucleoside reverse transcriptase inhibitors (POPIN)—a randomized controlled trial of therapeutic drug monitoring and adherence support. *J Acquir Immune Defic Syndr*. 2006;41:461–467.
21. Anonymous. BHIVA Guidelines for the treatment of HIV-infected adults treated with antiretroviral therapy (updated 10 June 2008). Available at: www.bhiva.org/documents/Guidelines/Treatment%20Guidelines/Current/TreatmentGuidelines2008.pdf. Accessed July 29, 2010.
22. Gutierrez F, Padilla S, Navarro A, et al. Lopinavir plasma concentrations and changes in lipid levels during salvage therapy with lopinavir/ritonavir-containing regimens. *J Acquir Immune Defic Syndr*. 2003;33:594–600.
23. Van Luin M, Gras L, Richter C, et al. Efavirenz dose reduction is safe in patients with high plasma concentrations and may prevent efavirenz discontinuations. *J Acquir Immune Defic Syndr*. 2009;52:240–245.