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Quality Assessment for Therapeutic Drug Monitoring in AIDS Clinical Trials Group (ACTG 5146): A Multicenter Clinical Trial

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Abstract

In a randomized trial, AIDS Clinical Trials Group (ACTG) protocol 5146 (A5146) investigated the use of TDM to adjust doses of HIV-1 protease inhibitors (PIs) in patients with prior virologic failure on PI-based therapy who were starting a new PI-based regimen. The overall percentage of “PI trough repeats”, such as rescheduled visits or redrawn PI trough specimens, increased from 2% to 5% to 10% as the process progressed from the clinical sites, the PSL, and the study team, respectively. Cumulatively, this represents a 17% rate of failure to obtain adequate PI trough sample. While targeting a turn-around of ≤ 7 days from sample receipt to a drug concentration report, 12% of the received specimens required a longer period to report concentrations. The implementation of dosing changes in the TDM arm were achieved within ≤ 7 days for 56% of the dose change events, and within ≤ 14 days for 77% of dose change events. This quality assurance analysis provides a valuable summary of the specific points in the TDM process that could be improved during a multicenter clinical trial including: [1] shortening the timeline of sample shipment from clinical site to the lab, [2] performing the collection of PI trough specimen within the targeted sampling window by careful monitoring of the last dose times and collection times by the clinicians [3] increasing patient adherence counseling to reduce the number of samples that are redrawn due to suspecting inconsistent adherence, and [4] decreasing the time to successful TDM-based dose adjustment. The application of some of these findings may also be relevant to single center studies or clinical TDM programs within a hospital.

INTRODUCTION

Therapeutic drug monitoring (TDM) is an accepted tool for optimizing highly active antiretroviral therapy (HAART) in HIV-infected individuals in certain countries. Although this approach is routine in Europe, other countries such as the United States recommend TDM in selected clinical situations rather than for routine management. (1,2) In a randomized trial, AIDS Clinical Trials Group (ACTG) protocol 5146 (A5146) investigated the use of TDM to adjust doses of HIV-1 protease inhibitors (PIs) in patients with prior virologic failure on PI-based therapy who were starting a new PI-based regimen.(3) The rationale for the focus on PIs in this study was their central role in recommended HAART regimens, the considerable pharmacokinetic variability that results during chronic dosing, and the potential for TDM to optimize drug exposure and reduce the development of resistance. (4–19) A5146 found that TDM was not associated with greater virologic suppression overall, although certain patient

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subgroups benefited from TDM, specifically patients with less PI resistance at baseline, as well as black and Hispanic patients(3).

As a strategy to optimize HAART, the value of TDM is dependent upon the quality of pharmacokinetic data that results from blood sample collection at clinical sites as well as the timeliness of dosage adjustments following receipt of TDM assay reports. Thus, the success of TDM is dependent on precise protocol compliance at the clinical site as well as in the operations of the site processing laboratory. In particular, commitment to the correct timing of sample collection relative to recent medication administration and the timeliness of sample shipment, drug assay, TDM result reporting and implementation of dose adjustments are vital. During the conduct of A5146, a central TDM pharmacology specialty laboratory (TDM PSL) monitored the collection of clinical samples with real-time review of prior PI dosing and blood sample collection as well as other critically important features related to sample collection and processing.

The objective of this report is to provide a quality analysis of the adherence to TDM requirements during A5146 at the clinical sites and the ACTG PSL with regard to: 1) clinical site protocol compliance and accuracy in PI trough blood sampling and timeliness of sample shipment, 2) the suitability and quality of samples that were received at the TDM PSL for analysis, 3) the turnaround time for PI trough assay and pharmacology report generation and 4) post-assay report interpretation by the protocol team and subsequent actions.

METHODS

To conduct therapeutic interventions within the A5146 study, the operation of three key organizations were managed: the clinical trial site where patients were enrolled into A5146, the PSL that provided drug assay for the PI plasma trough concentrations, and the protocol team which provided the NIQ report and recommendations for PI dose adjustments to the clinical sites. Figures 1 and 2 provide an overview of the protocol chronology and operational TDM events, respectively.

Protocol design and chronology of events

A5146 was an open-label, randomized clinical trial of TDM for PIs in antiretroviral-experienced, HIV-1-infected patients experiencing virologic failure on a PI-based regimen (3). Drug selection, randomization and recommended PI dose adjustments were based on a calculated normalized inhibitory quotient ($NIQ = \text{patient IQ} \div \text{reference IQ}$; $IQ = \text{PI trough concentration} \div \text{fold-change in baseline IC}_{50}$). During screening, samples were collected to assess HIV-1 resistance to PIs. On day 0 of Step 1, subjects initiated a new PI-containing ART regimen selected by the primary care physician on the basis of an NIQ calculated from the screening virtual phenotype (VircoType® HIV-1). At week 2, blood samples were collected for a PI trough assay. At Step 2 entry (week 4), subjects with an $NIQ \leq 1$ were randomized to receive either standard PI dosing (standard-of-care; SOC arm) or TDM-based adjustments to PI doses (TDM arm). After randomization at week 4, subjects in the TDM arm had additional trough PI concentration determined at weeks 6, 10 and 14. Subjects randomized to the TDM arm received real-time NIQ reports with recommended PI dose escalations at selected time points after Step 2 entry. The following procedures were scheduled to occur: PI trough sample collection, shipment of sample to the ACTG PSL, PI trough assay, pharmacology report to the team, team calculation of the NIQ with review of patient data, and a NIQ report to the site featuring NIQ result and PI dose adjustment recommendations. Based on these NIQ reports, patients received a new PI dose over a time period that was sufficient to attain a new steady-state. Subjects with an $NIQ > 1$ at week 2 were assigned to an observational standard-of-care arm (OBS) with fixed doses of PIs but no TDM. Subjects on any arm who experienced virologic

failure at week 24 or later were eligible to enter Step 3 and could undergo TDM intervention with PI dose escalation.

Clinical Site TDM Sampling

The first step in the TDM process was collection of the trough sample by the clinical site staff. If the patient did not arrive in time for the TDM sample to be obtained within ± 2 hours of the target trough sampling range for twice-daily PIs (i.e., 10–14 hours after the previous dose) and within ± 2 hours of the target for once daily PI dosing (22–26 hours), the TDM visit was rescheduled. Medication adherence over the three days prior to the TDM sample was evaluated; if adherence was unacceptable (any missed doses within 72 hours), the patient was counseled to take all medication doses and the visit rescheduled.

The clinical site local laboratory received, processed and shipped the PI trough sample. Here, the PI trough sample integrity as required by the protocol (e.g., sample type, trough collection timing, or PI adherence) was also inspected prior to shipment. If it was determined that the sample was not valid for PSL analysis, the clinical site rescheduled the visit and marked the collected specimen as “invalid for analysis” in the protocol specimen inventory. All shipments were to be shipped overnight the day of sample collection. If the following day was a Saturday or Sunday or holiday, shipments were held until Monday or the next possible shipment day.

PSL Sample processing

Upon receipt of each sample, and prior to sample assay, the PSL reviewed the sample collection data, evaluating a number of factors. The PSL provided an additional check for the appropriateness of the sample collection time relative to the PI dosing time and adherence for the three prior doses. Consistent with CLIA guidelines (20), the PSL was also responsible for determining the physical integrity of the sample received. In addition, the study required that the following information accompany all TDM samples: a listing of all concurrent medications, time of last food intake, and any medication changes since the last PI trough sample. The data were entered into the laboratory data management system (LDMS) by the TDM PSL, for later use during the core team assay interpretation and site report. All data entries were checked by a second technician for accuracy. If the sampling time was not within the protocol-specified trough collection windows and HAART therapy adherence criteria, the sample was considered invalid for assay and the clinical site was immediately contacted with a request to collect a repeat PI trough sample, citing reasons why the initial sample was not acceptable. If any of the data requirements were missing, the clinic was contacted and asked to fax the appropriate forms to the TDM PSL. If an error was discovered, a fax of the corrected form was required. Once sample integrity was confirmed for analysis, the PI concentration was determined.

Sample analysis at PSL

Prior to routine use of the PI assay method for A5146, the PSL validated the method for rigor, accuracy, specificity, sensitivity, and reproducibility (21,22). The methods were submitted to the New York State Department of Health Clinical Laboratory Evaluation Program (NYS DOH CLEP), which approved the assay for use in the PSL. During routine use of the method, the laboratory maintained operations in a CLIA certified and CLIA-compliant environment. CLIA criteria included participation in two proficiency testing programs, the ACTG/IMPAACT Proficiency Testing (PT) Program (23,24) and the International Inter-laboratory Quality Control program (IQC) (25,26). The accuracy of the assays performed at the PSL was monitored by proficiency scores with a required accuracy of $\pm 20\%$ of the target value. Throughout the A5146 study, the PSL maintained successful proficiency testing standing. The PSL assayed samples once weekly and with a targeted turnaround time of ≤ 7 days from sample receipt.

PSL Reporting

The PI trough pharmacology report was prepared by the PSL and sent to the core study team. The report consisted of a patient identifier, sample date and time, time of and interval between the last three doses prior to the blood sample collection, a listing of concomitant medications, changes in dosing since the last visit, and analyte concentration(s). These data were used by the core team to interpret the PI trough concentration(s). Prior to sending the pharmacology report, the draft report was inspected for consistency with the source documents. Other information as required by CLIA, such as laboratory contact information, was also provided.

Pharmacology Report: Core Team Interpretation and Intervention

Prior to recommending TDM interventions (PI dose escalation), the pharmacology report provided by the PSL lab was assessed by core team pharmacologists, physician investigators, and other key personnel by reviewing sample specific information that identified the time interval between the three doses (adherence) and the interval preceding the PI trough sample (appropriate trough collection). Additional factors that were reviewed and considered with each report were recent food intake, concomitant medications, previous dose changes that were implemented, timing of dose changes; elapsed time between receipt of the NIQ report at the site and the dose change implementation; and the time elapsed between study entry and dose change implementations. To ensure pharmacokinetic steady-state, the time elapsed between dose initiation/change and the visit was calculated and summarized separately by step, week and nature of intervention (e.g., initial/repeat). The team had the option to request rescheduled visits if the trough drug concentration was undetectable, above the expected C_{min} upper limit concentration or the subject conditions such as concomitant medications or timing between doses or adherence were questionable. For those patients in the TDM arm in Step 2 or in Step 3, PI dose adjustments were recommended based on an $NIQ \leq 1$. For those patients entering Step 2 or 3 and receiving the PI dose adjustment recommendations, the clinicians could decide on the implementation of the dose change. In any case, if the dose change was implemented, the clinical site provided the date of patient specific therapeutic changes on the protocol specific case report forms.

In the A5146 study, all ARVs including individual PI agents and ritonavir pharmacokinetic enhancing doses were issued by prescription at the local research site. There was no research pharmacy immediately dispensing revised PI dosing medications upon receipt of the NIQ report. The site was required to review the NIQ report and PI dose adjustment recommendations with the site principal investigator and provider; review the report with the study patient to assess for any toxicity on the current PI dosing regimen; and issue new prescriptions to be dispensed at local or mail-order pharmacies.

Analysis of PSL Procedures and Outcomes

The study database provided information to calculate the following outcomes: the number of PI trough visits/events, the number and percent of rescheduled visits, and the number of days the patient was on the ARV regimen prior to PI trough sampling. The LDMS at FSTRF (Frontier Science and Technology Research Foundation) was used to track the date of sample collection, receipt, and assay while report dates were tracked by e-mail records. The number of days between sample collection at the clinical site and receipt at the PSL were tabulated to assess the expediency of shipments. To assess the performance of the PSL, the number of days between the blood sample receipt and assay report date were determined as well as the number of days between receipt and assay date, and the assay date to report date. As mentioned above, the core team had the option to verify questionable assay results by requesting the site to collect an additional PI trough sample. The percentage of these requests was determined by enumerating the number of reports generated for the same scheduled event. Using the site communication records and the study database, the time between the PSL report and the dose

change was calculated as a measure of the timeliness of those dose changes when a dose change was implemented.

Statistical methods—Statistical analysis was performed using SAS software version 9.1. Comparisons over time (between Steps 1 and 2, between Steps 2 and 3) were performed using Fisher's Exact test (StatXact-5) for the following selected benchmark measures: percent of samples received by the PSL lab within 1 day of sample collection, percent of samples for which no more than 7 days elapsed between receipt at the PSL and distribution of the TDM report, percent of samples deemed valid and percent of samples deemed plausible.

RESULTS

General Outcomes

A total of 743 subjects were assessed for eligibility for the A5146 TDM protocol. Of these, 411 subjects entered Step 1 from 45 clinical sites and satellites/subunits, which mandated collection of a PI trough sample two weeks after initiation of a new PI-containing regimen. Of the 214 subjects with an NIQ ≤ 1 , 91 were randomized into the SOC arm (no TDM) and 92 into the TDM arm. Fifty subjects with NIQ > 1 were assigned to the OBS arm.

Clinical Site PI Trough Sampling

Table 1 summarizes the TDM steps undertaken at each clinical site. Clinic staff determined that the subject was not adequately compliant for Step 1 PI trough sampling in 2% of the initial sampling visits and 2% of the rescheduled visits. For Steps 2 and 3, the incidence of rescheduled PI trough visits remained consistent at 2%. For all steps and weeks, PI trough samples were collected a median of 14 days after the subject initiated the most recent PI dose. At the time of Step 1 PI trough sampling, 92% of subjects were on their regimen for ≥ 14 days, and 100% of subjects were on the regimen for ≥ 7 days. After Step 2 entry, 64%, 55% and 67% of subjects were on their current regimen for ≥ 14 days at the week 6, 10 and 14 visits, respectively, and 99%, 93% and 100% were on the regimen for ≥ 7 days. Of the Step 3 PI trough samples, 83% were collected ≥ 14 days and all were collected ≥ 7 days after current regimen initiation. On Steps 1, 2 and 3 the median time from PI trough sample collection to receipt at the PSL was 2, 1 and 1 days, respectively. Combining samples from all arms, 51% of PI trough samples received were received within 1 day of specimen collection, and 86% were received within 5 days. Of the PI trough samples collected for Steps 1, 2 and 3, 49%, 54% and 54% were received by the next day, respectively. The differences in the proportion of samples between the steps were not statistically significant.

Sample processing at the PSL

Table 2 summarizes handling of samples at the PSL. Combining all samples, the median time between receipt and assay was 4 days, and 96% of samples were assayed within 7 days of receipt. The median time between assay and reporting was 1 day; 99% of results were reported within 7 days. Overall, the median time from sample receipt to pharmacology report distribution to the protocol team was 5 days, with 88% of the reports sent within 7 days of the sample arriving at the PSL. There was no difference in performance between Steps of the protocol.

Table 3 summarizes problematic PI trough samples. The PSL received a total of 775 samples during the study period. Over all steps and weeks, 95% of samples were identified, upon receipt at the PSL, as valid for assay. For the remaining 5% of samples judged invalid for PI trough assay determination (due to inadequate dosing and/or improper timing of sample collection relative to the preceding dose), sites were instructed to have subjects return for a repeat PI trough sample. For Steps 1, 2 and 3, 94%, 97% and 98%, respectively, of samples were valid,

suggesting improvement over time. The difference between Steps 1 and 2 for the percentage of valid samples was not statistically significant ($p=0.176$); the difference between Steps 1 and 3 was significant ($p=0.042$).

PSL and Sample Analysis

The PSL participated in 15 rounds of proficiency testing for different PIs during the course of the A5146 protocol analyses; 8 were within the ACTG/IMPAACT proficiency testing program and seven were within the IQC program. Initially, 5 PIs were monitored by 2 assays and by the end of the A5146 study 7 PIs were monitored by 3 assays. Overall, 765 proficiency testing concentration results were reported within these programs over <4 years. The PSL maintained assay $\pm 20\%$ accuracy of its drug concentration measurements and with no reporting of false positives, as evaluated by these two proficiency testing monitoring programs throughout the period from 2002–2007.

Protocol Team Interventions

Table 3 summarizes the incidence of requests for repeat trough specimen collections by the core team. The core team accepted the drug concentration result as plausible in 90% of cases overall, and in 87%, 96% and 93% of PI trough assay results in patients on Steps 1, 2 and 3, respectively. The difference in percent plausible between Steps 1 and 2 was statistically significant ($p=0.001$).

Table 4 summarizes the elapsed time between the report specifying a PI concentration and the date at which the PI dose adjustment was initiated. Overall, the median number of days from drug concentration report date to dose change implemented was 7 and 96% of the dosage changes were accomplished within 28 days or less (range was 0 to 76 days). Elapsed time was ≤ 7 days for 56% of Step 2 recommendations and was ≤ 14 days for 77% of Step 2 recommendations.

DISCUSSION

With the increasing clinical use of plasma concentration monitoring in certain countries, our analysis of the quality assurance aspects of A5146 provides clinicians and researchers with an assessment that can be used to prospectively design new studies and prioritize resources for TDM program implementation in HIV treatment practices. Although some reports have identified patients who may benefit from TDM, other studies have not clearly confirmed these benefits. Thus, it is likely that additional research will be needed to further investigate the optimal use of TDM in clinical practice. None of the previous TDM studies have reported a quality assurance analysis that summarizes the overall success of a planned TDM intervention strategy. Therefore, our findings provide important results relevant to the design of future TDM trials. With regard to clinical centers that may have a laboratory as a part of their central facilities, some of the items we identified may not be a concern, particularly related to sample shipment. However, the quality assurance practices of the clinic staff and laboratory staff remain important to all antiretroviral TDM programs.

We identified the need for quality data management and sample integrity assessments at each step of the TDM process including the clinic, the PSL and expert evaluation of the PI trough assay. Our results indicate that the overall percentage of “PI trough repeats”, such as rescheduled visits or redrawn PI trough specimens, increased from 2% to 5% to 10% as the process progressed from the clinical sites, the PSL, and the study team, respectively. Cumulatively, this represents a 17% rate of failure to obtain adequate PI trough sample. While it would be difficult to address each of these critical assessments, we would recommend developing quality improvement strategies, such as patient and staff education and training

that would modify these percentages.(27) Early identification of the need for re-sampling by the clinic would shorten the process of obtaining an accurate PI trough specimen from the patient and thus, reduce the risk for developing either resistance or concentration-related toxicity. It should be considered that even with optimal education and training, certain barriers to accurate reporting by patients will remain a potential barrier. (28)

A reduced time required for TDM sample analysis and reporting is another goal we identified as a potential quality improvement. Although the A5146 clinical research sites were able to assure that most shipments were sent and received within one day, this is unlikely to be the routine practice at many medical centers. Even in a research network where we were targeting a turn-around of ≤ 7 days from sample receipt to a drug concentration report (Table 2), 12% of the received specimens required a longer period to report concentrations. Areas for quality improvement in the reporting step would also be advantageous. Providing more frequent PI trough assays, as well as complete data with the sample (such as amounts, date and time of dose and previous doses) would shorten the turn-around time and prevent delays in the interpretation of results. Some of these items can be addressed through protocol design or the use of standard operating procedures while information technology applications such as bar-coding may avoid the omission of key patient data.

Lastly, the implementation of dosing changes in the TDM arm were achieved within ≤ 7 days for 56% of the dose change events, and within ≤ 14 days for 77% of dose change events. For this study, delay in review of the team's recommendations by the site could have been a contributing factor. In addition, contributing factors could also include delayed receipt of a new prescription, delayed communication with the pharmacy to provide the new dosage, time delay in receiving the new prescription, this process represents an important area for potential improvement. As the duration of time from the awareness that an individual has suboptimal drug exposure to the time that a new dosage change is implemented may be a key component to preventing resistance, the exact time period is unknown. For subjects with suboptimal exposure, prolonged time to accomplish any step in the TDM process would likely delay the time to achieve increased systemic PI exposure which underlies the anticipated benefit of TDM. In fact, A5146 was designed to shorten the time to initial trough sample collection and analysis in comparison to overcome the limitations in earlier TDM reports (29,30). To address this point, communication between the clinic and the pharmacy could be facilitated so that individuals with suboptimal trough concentrations would receive rapid provision of the new prescription to provide the new PI dosage. This quality assurance analysis provides a valuable summary of the specific points in the TDM process that could be improved during a multicenter clinical trial including: [1] shortening the timeline of sample shipment from clinical site to the lab, [2] performing the collection of PI trough specimen within the targeted sampling window by careful monitoring of the last dose times and collection times by the clinicians [3] increasing patient adherence counseling to reduce the number of samples that are redrawn due to suspecting inconsistent adherence, and [4] decreasing the time to successful TDM-based dose adjustment. The application of some of these findings may also be relevant to single center studies or clinical TDM programs within a hospital.

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Carol Greisberger RN BSN and Jane Reid RNC MS-University of Rochester (Site 1101) CTU Grant # U01AI069511-02 (as of 2/12/08); CRC: 5-MO1 RR00044

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Kim Whitely, R.N. and Robert C Kalayjian, M.D. -MetroHealth (Site 2503) CTU Grant # AI069501

Mary Albrecht, MD and Neah Kim, FNP- Beth Israel Deaconess (Partners/Harvard) (Site 103) CTU Grant # U01 AI069472-04

Linda Meixner, R.N. and Dee Dee Pacheco-UCSD (Site 701) CTU Grant # AI 69432

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TDM SAMPLE PROCESS

Figure 2.
Quality assurance monitoring in ACTG 5146

Table 1

Collection of TDM samples at the clinical site

Study step	Study week	Arm	Purpose of sample	Inadequate compliance, visit rescheduled			Days on ARV regimen at time of sample collection				Days elapsed between sample collection and receipt by TDM lab				
				Total visits	Visits rescheduled	(%)	N	Median (Range)	≥14 days	≥10 days	≥7 days	N	Median (Range)	≤1 day	≤5 days
1	Week 2	All	NIQ for arm assignment/randomization	477	8	(2%)	.	.	.	.	.	469	2 (1, 30)	228 (49%)	403 (86%)
1	Initial sample	All	(as above)	390	6	(2%)	383	14 (10, 35)	351 (92%)	383 (100%)	383	2 (1, 30)	186 (49%)	326 (85%)	
1	Repeat sample	All	(as above)	87	2	(2%)	.	.	.	.	86	2 (1, 30)	42 (49%)	77 (90%)	
2	All weeks	TDM (B)	NIQ for TDM	193	4	(2%)	.	.	.	.	184	1 (1, 20)	100 (54%)	162 (88%)	
2	Week 6	TDM (B)	NIQ after 1 st dose adjustment	96	1	(1%)	80	14 (6, 33)	51 (64%)	76 (95%)	79 (99%)	94	1 (1, 20)	49 (52%)	84 (89%)
2	Week 10	TDM (B)	NIQ after 2 nd dose adjustment (when required)	83	3	(4%)	44	14 (5, 27)	24 (55%)	34 (77%)	41 (93%)	78	1 (1, 8)	42 (54%)	67 (86%)
2	Week 14	TDM (B)	NIQ after 3 rd dose adjustment (when required)	14	1	(0%)	6	14 (9, 42)	4 (67%)	5 (83%)	6 (100%)	12	1 (1, 8)	9 (75%)	11 (92%)
2	Initial sample	TDM (B)	(NIQ for TDM)	176	4	(2%)	.	.	.	.	.	167	1 (1, 20)	94 (56%)	147 (88%)
2	Repeat sample	TDM (B)	(NIQ for TDM)	17	.	(0%)	.	.	.	.	.	17	2 (1, 7)	6 (35%)	15 (88%)
3	All weeks	All	NIQ for selection of salvage regimen	127	2	(2%)	41	14 (7, 37)	34 (83%)	39 (95%)	41 (100%)	122	1 (1, 15)	66 (54%)	102 (84%)
All	All weeks	All	--	797	14	(2%)	.	.	.	.	.	775	1 (1, 30)	394 (51%)	667 (86%)

All shipments were to be sent overnight and on dry ice; shipments from Hawaii required two days.

Table 2

Handling of TDM samples at the ACTG TDM lab

Study step	Study week	Arm	Purpose of sample	...receipt and assay			...assay and TDM report				...receipt and TDM report					
				N	Median (Range)	≤7 days	≤14 days	N	Median (Range)	≤1 day	≤3 days	≤7 days	N	Median (Range)	≤7 days	≤14 days
1	Week 2	All	NIQ for arm assignment/randomization	440	4 (0, 23)	420 (95%)	439 (100%)	436	1 (0, 29)	301 (69%)	389 (89%)	432 (99%)	438	6 (1, 31)	383 (87%)	436 (100%)
Ther Drug Monit	First sample	All	(as above)	360	4 (0, 23)	347 (96%)	359 (100%)	357	1 (0, 9)	239 (67%)	313 (88%)	354 (99%)	358	6 (1, 24)	315 (88%)	357 (100%)
	Repeat sample	All	(as above)	80	5 (0, 11)	73 (91%)	80 (100%)	79	1 (0, 29)	62 (78%)	76 (96%)	78 (99%)	80	6 (1, 31)	68 (85%)	79 (99%)
	All weeks	TDM (B)	NIQ for TDM	176	4 (0, 13)	170 (97%)	176 (100%)	176	1 (0, 13)	120 (68%)	155 (88%)	174 (99%)	178	5 (0, 16)	153 (86%)	117 (99%)
Author manuscript; available in PMC 2011 August 1	Week 6	TDM (B)	NIQ after 1 st dose adjustment	88	3.5 (0, 13)	85 (97%)	88 (100%)	88	1 (0, 7)	61 (69%)	78 (89%)	88 (100%)	89	5 (1, 16)	77 (87%)	88 (99%)
	Week 10	TDM (B)	NIQ after 2 nd dose adjustment (when required)	76	4 (0, 9)	73 (96%)	76 (100%)	76	1 (0, 13)	55 (72%)	70 (92%)	74 (97%)	77	5 (0, 13)	68 (88%)	77 (100%)
	Week 14	TDM (B)	NIQ after 3 rd dose adjustment (when required)	12	4 (1, 7)	12 (100%)	12 (100%)	12	2 (0, 6)	4 (33%)	7 (58%)	12 (100%)	12	6 (3, 11)	8 (67%)	12 (100%)
August 1, 2011	First sample	TDM (B)	(NIQ for TDM)	159	4 (0, 12)	155 (97%)	159 (100%)	159	1 (0, 13)	107 (67%)	139 (87%)	157 (99%)	161	5 (0, 14)	138 (86%)	161 (100%)
	Repeat sample	TDM (B)	(NIQ for TDM)	17	2 (0, 13)	15 (88%)	17 (100%)	17	1 (1, 4)	13 (76%)	16 (94%)	17 (100%)	17	5 (1, 16)	15 (88%)	16 (94%)
	All weeks	All	NIQ for selection of salvage regimen	118	2.5 (0, 13)	115 (97%)	118 (100%)	118	1 (0, 14)	93 (79%)	112 (95%)	117 (99%)	120	4.5 (0, 18)	109 (91%)	119 (99%)
All	All weeks	All	--	734	4 (0, 23)	705 (96%)	733 (100%)	730	1 (0, 29)	514 (70%)	656 (90%)	723 (99%)	736	5 (0, 31)	645 (88%)	732 (99%)

Table 3

Quality of obtained TDM samples and achieved PI concentrations

Study step	Study week	Arm	Purpose of sample	Review of form at ACTG TDM lab indicates sample is valid		Review of PI concentration by study team indicates result is plausible	
				Total	Valid	Total	Plausible
1	Week 2	All	NIQ for arm assignment/randomization	469	440 (94%)	469	410 (87%)
1	First sample	All	(as above)	383	358 (93%)	383	330 (86%)
1	Repeat sample	All	(as above)	86	82 (95%)	86	80 (93%)
2	All weeks	Arm B	NIQ for TDM	184	178 (97%)	184	176 (96%)
2	Week 6	Arm B	NIQ after 1 st dose adjustment	94	89 (95%)	94	89 (95%)
2	Week 10	Arm B	NIQ after 2 nd dose adjustment (when required)	78	77 (99%)	78	75 (96%)
2	Week 14	Arm B	NIQ after 3 rd dose adjustment (when required)	12	12 (100%)	12	12 (100%)
2	First sample	Arm B	(NIQ for TDM)	167	161 (96%)	167	159 (95%)
2	Repeat sample	Arm B	(NIQ for TDM)	17	17 (100%)	17	17 (100%)
3	All weeks	All	NIQ for selection of salvage regimen	122	120 (98%)	122	113 (93%)
All	All weeks	All	--	775	738 (95%)	775	699 (90%)

Table 4

Days elapsed between reporting and subsequent action

Study step	Study week	Arm	Purpose of sample	N	Median (Range)	≤7 days (49%)	≤14 days (90%)	≤28 days (95%)
1	Week 2	All	NIQ for arm assignment/randomization	79	8 (0, 65)	39	71	75
1	First sample	All	(as above)	60	8 (0, 53)	28 (47%)	56 (93%)	58 (97%)
1	Repeat sample	All	(as above)	19	7 (2, 65)	11 (58%)	15 (79%)	17 (89%)
2	All weeks	TDM (B)	NIQ for TDM	62	7 (1, 76)	35 (56%)	48 (77%)	60 (97%)
2	Week 6	TDM (B)	NIQ after 1 st dose adjustment	50	7 (1, 76)	29 (58%)	37 (74%)	48 (96%)
2	Week 10	TDM (B)	NIQ after 2 nd dose adjustment (when required)	12	7.5 (4, 20)	6 (50%)	11 (92%)	12 (100%)
2	First sample	TDM (B)	(NIQ for TDM)	54	7 (1, 76)	31 (57%)	43 (80%)	52 (96%)
2	Repeat sample	TDM (B)	(NIQ for TDM)	8	9.5 (5, 18)	4 (50%)	5 (63%)	8 (100%)
All	All weeks	All	--	141	7 (0, 76)	74 (52%)	119 (84%)	135 (96%)