Maraviroc Observational Study: The Impact of Expanded Resistance Testing and Clinical Considerations for Antiretroviral Regimen Selection in Treatment-Experienced Patients

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Abstract

Maraviroc (MVC) use has trailed that of other post-2006 antiretroviral therapy (ART) options for treatment-experienced patients. We explored the impact of free tropism testing on MVC utilization in our cohort and explored barriers to MVC utilization. The Maraviroc Outcomes Study (MOS) is an investigator-initiated industry-sponsored trial where consecutive ART-experienced patients receiving routine care with viral loads $\geq 1,000$ copies/ml, and whose provider requested resistance testing and received standardized resistance testing (SRT; phenotype, genotype, coreceptor/tropism). Sociodemographic, clinical, and ART characteristics of those receiving SRT were compared to a historical cohort (HC). Subsequently, providers were surveyed regarding factors influencing selection of salvage ART therapy. The HC ($n=165$) had resistance testing 7/08–9/09, while prospective SRT ($n=83$) patients were enrolled 9/09–8/10. In the HC, 92% had genotypes, 2% had tropism assays, and 62% ($n=102$) changed ART after resistance testing (raltegravir 37%, etravirine 25%, darunavir 24%, MVC 1%). In the SRT cohort, 57% ($n=48$) changed regimens after standardized resistance testing (darunavir 48%, raltegravir 40%, and etravirine 19%). CCR5-tropic virus was identified in 43% of the SRT group, and MVC was used in 10% [or 20% of R5 tropic patients who underwent a subsequent regimen change ($n=25$)], a statistically significant ($p=0.01$) increase in utilization. The factors most strongly influencing utilization were unique patient circumstances (60%), clinical experience (55%), and potential side effects (40%). The addition of routine tropism testing to genotypic/phenotypic testing was associated with increased MVC utilization, raising the possibility that tropism testing may present a barrier to MVC use; however, additional barriers exist, and merit further evaluation.

Introduction

DRAMATIC PROGRESS IN THE availability of new, efficacious, and well-tolerated HIV treatment options for antiretroviral therapy (ART)-experienced patients has taken place over the past decade.^{1–8} Since 2006, several new antiretroviral agents (ARVs) have been introduced for use among treatment-experienced patients, including raltegravir, etravirine, darunavir, and maraviroc. Raltegravir and maraviroc represent the vanguard agents of new therapeutic drug classes, while etravirine and darunavir are additions to existing classes that are active against viruses that harbor reduced

susceptibility to other agents in their respective classes. All have been shown to be efficacious and well tolerated, and have provided much needed expansion to the therapeutic options available to ART-experienced patients.^{1–9} With access to these newer agents, the goal of therapy is to suppress HIV viral load (VL) to below the limits of detection for all HIV-infected persons on treatment, including those with drug tolerance issues and multidrug resistance.¹⁰

Use of these new agents has varied considerably in our clinic practice. Raltegravir, darunavir, and etravirine experienced rapid uptake in our cohort while maraviroc utilization lagged behind, despite its proven efficacy and favorable

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toxicity profile. For example, by April 2008, 109 patients in our clinic had been prescribed raltegravir while only five were prescribed maraviroc, despite its earlier FDA-approval date. Different from other new drugs, prior to maraviroc use, providers must order a tropism test to determine a patient's HIV coreceptor status owing to the activity of maraviroc being restricted to patients with only CCR5-tropic virus.¹¹ We hypothesized that the requirement of ordering a tropism test was a financial (cost) and logistic (additional wait time prior to therapy) barrier to maraviroc use. To test this hypothesis and to learn more about factors influencing provider prescription of specific salvage therapies, we (1) determined maraviroc utilization in a historical cohort of ART-experienced patients, the majority of whom received only genotypic resistance testing, and compared treatment selection in a prospective cohort of ART-experienced patients, whose providers were provided with standardized resistance testing (SRT) that included tropism testing and a combined genotypic and phenotypic resistance assay, regardless of whether the clinician requested these assays, and (2) surveyed providers in our cohort to identify factors influencing provider prescription of specific salvage therapies among their treatment-experienced patients.

Materials and Methods

Study setting and procedures

The maraviroc outcome study (MOS) is a prospective cohort study of maraviroc utilization among ART-experienced patients experiencing virologic failure (VL >1000) on their current ART regimen. The study was nested within the University of Alabama at Birmingham (UAB) 1917 Clinic Cohort and was an investigator initiated study sponsored by Pfizer, Inc. The UAB 1917 Clinic Cohort is an ongoing, institutional review board (IRB)-approved, prospective clinical cohort study that collects psychosocial, sociodemographic, and clinical information from patients receiving care at the UAB 1917 HIV/AIDS Clinic. The cohort data are 100% quality assured, whereby all provider notes are reviewed within 72 h of entry into the clinic electronic medical record to ensure appropriate data capture regarding diagnoses and medication use. This process to ensure data quality was recognized by the information integrity coalition for excellence in information integrity in 2007.

The present study was reviewed and approved by the UAB IRB and a waiver of informed consent was obtained. All ART-experienced patients whose providers ordered ARV resistance testing during the study period received a standardized set of resistance assays including a combined genotype and phenotype (protease and reverse transcriptase resistance assay PhenoSense GT, Monogram Biosciences) and a phenotypic coreceptor tropism assay (Trofile, Monogram Biosciences) with costs incurred by the study. These patients were then compared to a historical cohort that underwent resistance testing as ordered by providers. Subsequent regimen selection was determined and compared in both cohorts to determine if there were differences in subsequent ARV utilization. This study was observational in design and decisions regarding the need for ARV resistance testing and subsequent regimens were made by primary care providers, independent of research staff. The study provided standardized resistance testing as described above, but did not provide ARVs or

remuneration to patients or providers. All resistance testing was performed at Monogram Biosciences (South San Francisco, CA). This investigation was an investigator-initiated study supported by Pfizer, Inc. The sponsor did not participate in the study design, data interpretation, or manuscript preparation.

Study sample

Two patient groups were compared to investigate provider selection of agents for postresistance testing therapeutic regimens.

Historical cohort (HC). Patients were identified for inclusion in the historical cohort through a query of the 1917 Clinic Cohort database. Subjects subsequently underwent detailed review of medical records and HC inclusion required a patient to have (1) received an ARV resistance test in the time between the introduction of commercially available maraviroc (August 6, 2007) and the start date of the prospective cohort study (September 28, 2009), (2) been ART-experienced (≥ 1 ART regimen) at the time of the resistance test in order to meet the indications for maraviroc prescription at the time,¹⁰ (3) had a plasma HIV viral load ≥ 1000 copies/ml (threshold needed for completion of the Trofile assay), and (4) not been enrolled in a sponsored clinical trial, thus guaranteeing providers alone would have input into subsequent regimen selection.

Standardized resistance testing cohort (SRT). Between September 28, 2009 and August 16, 2010, all ART-experienced patients receiving routine care at the UAB 1917 Clinic with (1) viral load $\geq 1,000$ copies/ml and (2) whose providers requested a resistance test received standardized resistance testing, which included a combined genotypic and phenotypic resistance assay and a tropism assay per study protocol. Providers were not made aware that genotypic/phenotypic resistance testing and a tropism test would be ordered, but received tropism results via the electronic medical record at the same time that the PSGT results were reported.

Survey development and administration

After completion of prospective enrollment for the SRT cohort, a survey was administered to all our UAB 1917 Clinic healthcare providers who prescribed ART (attending physicians, infectious disease fellows, and nurse practitioners) during the study period. The survey was designed to gain insight into factors influencing provider selection of post-2006 treatment options for ART-experienced patients. The survey instrument was a modified version of prior surveys in the extant literature and consisted of two parts.¹² First, providers were asked to identify their confidence in the efficacy of raltegravir, etravirine, darunavir, and maraviroc, as well as their likelihood to prescribe each to a clinically eligible patient. Responses were quantified on a Likert scale ranging from 1 (not at all) to 7 (a great deal). Responses ≥ 5 indicated a positive response.

In the second portion of the survey, providers were asked to identify factors most likely to be considered when prescribing each of these drugs. For each factor, providers identified whether or not it was considered "Not at all," "Not very much," "Some," or a "Great deal." Queried factors included

clinical knowledge and experience, patient's unique situation, peer-reviewed journals, potential medication side effects, clinical practice guidelines, colleagues' and peers' experiences, patient's insurance coverage and drug formulary, information from pharmaceutical companies, patient opinion, and associated laboratory testing. The survey was distributed electronically via email and returned anonymously to a locked drop box located in the clinic.

Independent variables

At study enrollment, the following sociodemographic and clinical data were obtained about all HC and SRT cohort participants: age, sex, race, insurance status (private, public, uninsured), substance abuse history, alcohol abuse history, history of depression/anxiety, tobacco use, HIV risk factor, county of residence, baseline HIV viral load (copies/ml), and baseline CD4⁺ T-lymphocyte cell count (cells/mm³) at study entry. Antiretroviral treatment history (number of previously prescribed ARVs, number of ARV classes previously experienced) was determined by an electronic database search and confirmed by medical record abstraction.

Following the implementation of SRT, the types and results of all resistance tests ordered for each cohort (HC vs. SRT) were identified via medical chart abstraction. If a regimen change (change in ≥ 1 antiretroviral) occurred following resistance testing, these subsequent regimens were identified and the number of active medications included in each subsequent ART regimen was determined using the Stanford Genotype Database (<http://hivdb.stanford.edu/>).^{13,14} Using the Stanford Genotype Database, each drug in the subsequent regimen was assigned a score of zero to one ("0" for those with intermediate- or high-level resistance; "0.5" for those with low-level resistance; or "1" for those with that were susceptible or had potential low-level resistance) based on the results. Ritonavir used for "boosting" the activity of other protease inhibitors in a regimen was not considered an active agent. Raltegravir was given a score of "1" for those with no previous exposure to raltegravir and/or for those with a susceptible integrase inhibitor resistance test and a score of "0" for those with an integrase inhibitor resistance test showing reduced susceptibility (none in the current population). The sum of the scores of all component drugs was used to calculate the genotypic susceptibility score (GSS) for the subsequent ART regimen in accordance to prior reports.^{15,16}

Outcome variables

The primary outcome of interest was maraviroc utilization (yes/no) following the implementation of SRT at our clinic. To determine this outcome, the number of individuals prescribed maraviroc in the 6 months following ARV resistance testing was determined via medical record abstraction for both the HC and SRT cohorts. Factors influencing provider prescription of different post-2006 antiretroviral treatment options were determined through survey administration.

Statistical analysis

Descriptive analyses were performed to evaluate sociodemographic, clinical, and regimen level characteristics and to ensure assumptions for statistical tests were met. Bivariate analysis (*t*-test, chi square) was performed to evaluate

differences between the historical and SRT cohorts, as well as differences in prescribing patterns after implementation of SRT. Descriptive analyses were also performed to evaluate provider opinions regarding post-2006 ARV treatment options for ART-experienced patients. All statistical analyses were performed using SAS software version 9.1.3.

Results

A total of 248 patients received a resistance test during the study period and met inclusion criteria for either the HC or SRT cohorts. In both the HC ($n=165$) and SRT ($n=83$) cohort, minority race (HC=67%; SRT=72%) and male sex (HC=75%; SRT=66%) predominated. The average age of patients was 41.9 years and a majority (67%) lived within the same county where the UAB 1917 Clinic is located (Jefferson County, Alabama). Half of participants were publically insured (51%), while 27% were uninsured. There were no significant differences in baseline HIV viral load, CD4⁺ T-lymphocyte cell count, or prior antiretroviral drug and class experience ($p>0.05$) between HC and SRT patients. Only a history of depression/anxiety differed between the cohorts, with depression/anxiety being more prevalent (HC=21%, SRT=55%; $p<0.001$) in SRT patients (Table 1).

Resistance assays ordered for HC patients were mostly genotypes (92%), while tropism assays were rare (2%). All HC patient tropism tests ($n=4$) reported dual/mixed-tropic virus. A majority of HC patients ($n=102$, 62%) changed ART following resistance testing. Raltegravir (37%), etravirine (25%), and darunavir (24%) were the most commonly prescribed agents, while maraviroc was prescribed for only one patient (1%) with dual-mixed virus (Table 2). In contrast, all SRT cohort patients received a combined phenotype/genotype and tropism testing per the SRT protocol. Following resistance testing, 48 (58%) SRT patients underwent an ART regimen change. Subsequent ART regimens in SRT patients most commonly included darunavir ($n=25$, 52%), raltegravir ($n=19$, 40%), and etravirine ($n=9$, 19%). CCR5-tropic virus was identified in 43% ($n=36$) of the SRT group. Five SRT patients were prescribed maraviroc, four of whom were CCR5-tropic; one patient with dual/mixed-tropic virus was prescribed maraviroc erroneously, leading to the total use of maraviroc for 10% ($n=5$) of SRT patients who underwent a regimen change ($n=25$): a modest yet statistically significant ($p=0.01$) increase in maraviroc utilization when compared to the HC. Darunavir prescriptions were also more common in the SRT cohort (HC 24% vs. SRT 48%, $p<0.01$). There was no difference in the number of active drugs in subsequent ART regimens in the HC or SRT cohort (HC=3.0, SRT=3.0; $p=0.33$).

A total of 98 (40%) patients in the HC and SRT cohorts did not undergo an ART regimen change following ARV resistance testing. Among these patients, 42% ($n=37$) had pan-sensitive virus, 28% ($n=25$) had sensitivity to their current ART regimen, and 30% ($n=26$) reported other reasons ($p>0.001$), including failure to attend a clinic visit within 6 months of ARV resistance testing ($n=19$), preemptive initiation of new ART prior to receiving ARV resistance test results ($n=9$), and nonadherence to ART ($n=6$) (Table 2).

A total of 19 out of 21 providers completed the survey regarding their opinions on currently available antiretrovirals for use in salvage HIV therapy (the three providers involved

TABLE 1. CHARACTERISTICS OF HIV-POSITIVE PATIENTS

	Overall n = 248	HC (7/9/08–9/27/09) n = 165	SRT (9/28/09–8/16/10) n = 83	p-value ^a
Sociodemographic characteristics				
Age (year) ^b				
Mean ± SD	41.92 ± 9.69	41.28 ± 9.91	43.19 ± 9.16	0.13
Sex, <i>n</i> (%)				
Male	179 (72.2%)	124 (75.1%)	55 (66.3%)	0.14
Female	69 (27.8%)	41 (24.9%)	28 (33.7%)	
Race, <i>n</i> (%)				
White	77 (31.0%)	54 (32.7%)	23 (27.7%)	0.42
Black/other	171 (69.0%)	111 (67.3%)	60 (72.3%)	
Insurance, <i>n</i> (%) ^b				
Private	56 (22.6%)	38 (23.0%)	18 (21.7%)	0.49
Public	126 (50.8%)	87 (52.7%)	39 (47.0%)	
Uninsured	66 (26.6%)	40 (24.3%)	26 (31.3%)	
Substance abuse, <i>n</i> (%)				
No	189 (76.2%)	130 (78.8%)	59 (71.1%)	0.18
Yes	59 (23.8%)	35 (21.2%)	24 (28.9%)	
Alcohol abuse, <i>n</i> (%)				
No	205 (82.7%)	137 (83.0%)	68 (81.9%)	0.83
Yes	43 (17.3%)	28 (17.0%)	15 (18.1%)	
Depression/anxiety, <i>n</i> (%)				
No	168 (67.7%)	131 (79.4%)	37 (44.6%)	< 0.001
Yes	80 (32.3%)	34 (20.6%)	46 (55.4%)	
Tobacco use, <i>n</i> (%)				
No	141 (56.9%)	94 (57.0%)	47 (56.6%)	0.96
Yes	107 (43.1%)	71 (43.0%)	36 (43.4%)	
HIV risk factor, <i>n</i> (%)				
IVDU	19 (7.0%)	14 (8.5%)	5 (2.0%)	0.59
MSM	116 (47.0%)	79 (47.9%)	37 (44.6%)	
Heterosexual	112 (45.3%)	71 (43.0%)	41 (49.4%)	
Residence, <i>n</i> (%) ^b				
Jefferson County	167 (67.3%)	107 (64.9%)	60 (72.3%)	0.24
Outside of Jefferson County	81 (32.7%)	58 (35.1%)	23 (27.7%)	
Clinical and regimen characteristics				
Baseline HIV viral load (log ₁₀ HIV viral load)	4.54 ± 0.95	4.58 ± 0.86	4.47 ± 1.11	0.41
Baseline CD4 cell count (cells/ μ l)				
Mean ± SD	205 ± 210	191 ± 190	232 ± 244	0.36
≤ 200	150 (60.5%)	103 (62.4%)	47 (56.6%)	
200–350	48 (19.4%)	33 (20.0%)	15 (18.1%)	
≥ 350	50 (20.1%)	29 (17.6%)	21 (25.3%)	
Previous antiretrovirals				
Median (Q1, Q3)	7.0 (4.0, 9.5)	7.0 (4.0, 10.0)	7.0 (4.0, 9.0)	0.45
Number of ART class experienced, <i>n</i> (%)				
≤ 2 class experienced	108 (43.5%)	73 (44.2%)	35 (42.2%)	0.76
≥ 3 class experienced	140 (56.5%)	92 (55.8%)	48 (57.8%)	

Patients at the University of Alabama at Birmingham 1917 clinic receiving antiretroviral drug resistance assays who were antiretroviral-experienced at the time of testing with a most recent previous viral load ≥ 1000 copies/ml and who were not enrolled in a clinical trial at the time.

^aChi-square or *t*-test.

^bOn the date that the resistance testing sample was drawn.

HC, historical cohort; SRT, standardized resistance testing cohort; ART, antiretroviral therapy; IVDU, intravenous drug use; MSM, men who have sex with men.

in the design of this study were not surveyed). One provider did not respond to questions pertaining to darunavir. The number of years, including formal training, for which these providers made medical decisions for HIV-infected individuals ranged from 1 to 30 years, with the average being 10 years. Providers were most confident in the efficacy of raltegravir (*n* = 19, 100%), etravirine (*n* = 18, 94%), and darunavir (*n* = 17, 94%). Additionally, while most providers also expressed confidence regarding the efficacy of maraviroc

(*n* = 15, 79%), they stated they were less likely to prescribe maraviroc (68%) than etravirine (84%), darunavir (94%), or raltegravir (100%). Overall, when prescribing post-2006 ARV treatment options, factors most strongly influencing our providers' consideration (provider response = "Great deal") were unique patient circumstances (60%), clinical knowledge and experience (55%), and potential side effects (40%). Providers most often reported no influence (provider response = "Not at all") on prescription practices for the

TABLE 2. RESULTS OF INTRODUCTION OF ROUTINE TROPISM RESISTANCE TESTING

	Overall n = 248	HC ^a n = 165	SRT n = 83	p-value ^b
Resistance assay ordered, ^c n (%)				
Trofile				
Yes	87 (35.1%)	4 (2.4%)	83 (100.0%)	<0.001
PhenoSense GT				
Yes	114 (46.0%)	31 (18.8%)	83 (100.0%)	<0.001
GeneSeq HIV				
Yes	151 (61.1%)	151 (91.5%)	0 (0.0%)	<0.001
PhenoSense HIV				
Yes	20 (8.1%)	20 (12.1%)	0 (0.0%)	0.001
PhenoSense Integrase				
Yes	15 (6.1%)	7 (4.2%)	8 (9.6%)	0.10
Trofile results, n (%)				
CCR5	36 (14.5%)	0 (0.0%)	36 (43.4%)	
Dual mixed (D/M)	51 (60.5%)	4 (2.4%)	47 (56.6%)	0.14
Change in ART regimen per resistance testing results, n (%)				
Yes	150 (60.5%)	102 (61.8%)	48 (57.9%)	
No	79 (31.9%)	53 (32.1%)	26 (31.3%)	
Patient no-show	19 (7.7%)	10 (6.1%)	9 (10.8%)	0.89
GSS ^d of subsequent regimen with stanford HIVdb				
Median (Q1,Q3)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	0.33
Of new regimens (n=147), strategy, n (%)				
Darunavir				
Yes	47 (31.3%)	24 (23.5%)	23 (47.9%)	
No	103 (68.7%)	78 (76.5%)	25 (52.1%)	0.01
Raltegravir				
Yes	57 (38.0%)	38 (37.3%)	19 (39.6%)	
No	93 (62.0%)	64 (62.8%)	29 (60.4%)	0.78
Etravirine				
Yes	34 (22.7%)	25 (24.5%)	9 (18.8%)	
No	116 (77.3%)	77 (75.5%)	39 (81.3%)	0.43
Maraviroc				
Yes	6 (4.0%)	1 (1.0%)	5 (10.4%)	
No	144 (96.0%)	101 (99.0%)	43 (89.6%)	0.01
Of regimens unchanged (n=100), reasons for continuing regimen, n (%)				
No mutations	37 (42.1%)	33 (52.4%)	4 (16.0%)	
Mutations do not affect current ART	25 (28.4%)	18 (28.6%)	7 (28.0%)	
Other	26 (29.5%)	12 (19.0%)	14 (56.0%)	<0.001

Testing at the UAB 1917 Clinic for antiretroviral-experienced patients with a most recent previous viral load ≥ 1000 copies and who were not enrolled in a clinical trial at the time.

^aOn the date that the Resistance Testing sample was drawn.

^bChi-square or *t*-test.

^cTrofile test identifies HIV-1 viral tropism as either CCR5 only, CXCR4 only, or dual/mixed tropism and is used to determine efficacy of maraviroc; PhenoSense GT is a resistance test that combines the PhenoSense HIV, GeneSeq HIV, and Replication Capacity tests to give a complete picture of phenotypic and genotypic resistance in protease and reverse transcriptase; GeneSeq HIV is a genotypic HIV resistance assay; PhenoSense[®] HIV is a phenotypic HIV resistance assay; PhenoSense Integrase is a phenotypic resistance assay that measures viral susceptibility to integrase inhibitors.

^dGenotypic susceptibility score.

HC, historical cohort; SRT, standardized resistance testing cohort.

following factors: information from pharmaceutical companies ($n=37\%$), associated laboratory testing (13%), and peer-reviewed journals (11%). When specifically identifying factors influencing maraviroc prescription, providers most often identified patient's unique situation (68%), potential side effects (37%), patient insurance status (37%), and associated laboratory testing (35%) as factors they considered a great deal when prescribing maraviroc. Similar concerns regarding the cost of associated laboratory testing for protease, reverse transcriptase, and integrase inhibitors were observed as well, albeit at somewhat reduced levels (Table 3). Clinical knowledge and experience were factors considered most often when

prescribing darunavir (72%) and raltegravir (74%) and least often when prescribing maraviroc (21%). Furthermore, colleague and peer experience was also considered less often when prescribing maraviroc (26%) than when prescribing darunavir (44%), raltegravir (37%), and etravirine (37%) (Table 3).

Discussion

The lifespan of HIV-infected individuals has increased markedly in the ART era leading to a commensurate increase in longitudinal exposure to ART.¹⁷ To provide lifelong viable

TABLE 3. FACTORS CONSIDERED BY PROVIDERS WHEN PRESCRIBING SALVAGE ANTIRETROVIRAL AGENTS

	<i>Not at all</i>	<i>Not very much</i>	<i>Some</i>	<i>A great deal</i>
Clinical knowledge and experience				
Darunavir ^a	0 (0.0%)	0 (0.0%)	5 (27.8%)	13 (72.2%)
Maraviroc	2 (10.5%)	1 (5.3%)	12 (63.2%)	4 (21.1%)
Raltegravir	0 (0.0%)	0 (0.0%)	5 (26.3%)	14 (73.7%)
Etravirine	0 (0.0%)	1 (5.3%)	8 (42.1%)	10 (52.6%)
Patient's unique situation				
Darunavir	0 (0.0%)	1 (5.6%)	6 (33.3%)	11 (61.1%)
Maraviroc	1 (5.3%)	0 (0.0%)	5 (26.3%)	13 (68.4%)
Raltegravir	0 (0.0%)	0 (0.0%)	10 (52.6%)	9 (47.4%)
Etravirine	0 (0.0%)	0 (0.0%)	7 (36.8%)	12 (63.2%)
Peer-reviewed journals				
Darunavir	2 (11.1%)	2 (11.1%)	5 (27.8%)	9 (50.0%)
Maraviroc	2 (10.5%)	2 (10.5%)	11 (57.9%)	4 (21.1%)
Raltegravir	2 (10.5%)	0 (0.0%)	12 (63.2%)	5 (26.3%)
Etravirine	2 (10.5%)	1 (5.3%)	11 (57.9%)	5 (26.3%)
Potential medication side effects				
Darunavir	0 (0.0%)	2 (11.1%)	7 (38.9%)	9 (50.0%)
Maraviroc	1 (5.3%)	3 (15.8%)	8 (42.1%)	7 (36.8%)
Raltegravir	3 (15.8%)	3 (15.8%)	6 (31.6%)	7 (36.8%)
Etravirine	1 (5.3%)	2 (10.5%)	9 (47.4%)	7 (36.8%)
Clinical practice guidelines				
Darunavir	1 (5.6%)	2 (11.1%)	8 (44.4%)	7 (38.9%)
Maraviroc	1 (5.3%)	2 (10.5%)	11 (57.9%)	5 (26.3%)
Raltegravir	1 (5.3%)	1 (5.3%)	10 (52.6%)	7 (36.8%)
Etravirine	2 (10.5%)	1 (5.3%)	12 (63.2%)	6 (31.6%)
Colleague and peer experiences				
Darunavir	1 (5.6%)	2 (11.1%)	7 (38.9%)	8 (44.4%)
Maraviroc	1 (5.3%)	1 (5.3%)	12 (63.2%)	5 (26.3%)
Raltegravir	1 (5.3%)	2 (10.5%)	9 (47.4%)	7 (36.8%)
Etravirine	1 (5.3%)	3 (15.8%)	8 (42.1%)	7 (36.8%)
Patient insurance coverage/formulary				
Darunavir	1 (5.6%)	2 (11.1%)	9 (50.0%)	6 (33.3%)
Maraviroc	1 (5.3%)	3 (15.8%)	8 (42.1%)	7 (36.8%)
Raltegravir	1 (5.3%)	3 (15.8%)	7 (36.8%)	8 (42.1%)
Etravirine	1 (5.3%)	4 (21.1%)	7 (36.8%)	7 (36.8%)
Information from pharmaceutical companies				
Darunavir	7 (38.9%)	8 (44.4%)	2 (11.1%)	1 (5.6%)
Maraviroc	7 (36.8%)	9 (47.4%)	3 (15.8%)	0 (0.0%)
Raltegravir	7 (36.8%)	10 (52.6%)	1 (5.3%)	1 (5.3%)
Etravirine	7 (36.8%)	7 (36.8%)	3 (15.8%)	2 (10.5%)
Patient opinion				
Darunavir	1 (5.6%)	5 (27.8%)	7 (38.9%)	5 (27.8%)
Maraviroc	1 (5.3%)	4 (21.1%)	10 (52.6%)	4 (21.1%)
Raltegravir	1 (5.3%)	4 (21.1%)	9 (47.4%)	5 (26.3%)
Etravirine	1 (5.3%)	4 (21.1%)	8 (42.1%)	6 (31.6%)
Associated laboratory testing				
Darunavir	3 (16.7%)	3 (16.7%)	7 (28.9%)	5 (27.8%)
Maraviroc	1 (5.3%)	5 (26.3%)	6 (35.3%)	6 (35.3%)
Raltegravir	4 (21.1%)	5 (26.3%)	5 (29.4%)	4 (21.1%)
Etravirine	2 (10.5%)	4 (21.1%)	10 (52.6%)	3 (15.8%)

^aNote that for all responses pertaining to Darunavir, $n = 18$. For all other responses, $n = 19$.

ART, the judicious use of all drugs in our therapeutic arsenal will be needed. We noted that despite being both efficacious and tolerable, maraviroc was minimally used in our cohort and we hypothesized that the integration of routine tropism testing would lead to an increased utilization of this drug.

The provision of free, routine tropism assays as part of a standardized resistance testing package resulted in a modest but statistically significant increase in maraviroc utilization at our clinic. Thus, our findings suggest that addressing the additional costs and logistics related to delivering tropism test data to the point of care may favorably impact maraviroc utilization, although the numbers herein represent a limited dataset.

It is important to note that in our HC, none of the patients tested had CCR5 tropic virus so maraviroc utilization was not indicated. However, the limited number of Trofile tests ordered and the contemporaneous high utilization of other newer therapeutic options in that time period suggest underuse of maraviroc. The observed increase in the prescription of maraviroc in the SRT cohort suggests that the current practice requiring an additional tropism assay prior to its use may pose a barrier to maraviroc utilization. However, 80% ($n = 20/25$) of individuals found to be CCR5-tropic in the SRT cohort and who subsequently underwent a regimen change were not prescribed maraviroc. Despite existing literature showing maraviroc to be a safe, efficacious treatment option for ART-experienced patients, our provider survey showed only 64% of our clinicians were likely to prescribe maraviroc to clinically eligible patients. In contrast, 94% of our clinicians stated that they were both highly confident in the efficacy of darunavir and were more likely to prescribe darunavir to an eligible patient. This reported confidence coincides with a significant increase in darunavir utilization in the SRT cohort as compared to the HC (HC = 24%, SRT = 48%, $p < 0.001$). Despite having addressed cost and logistical barriers to Trofile testing, our modest uptake in maraviroc utilization suggests additional barriers affect its uptake by clinicians and merit further investigation.

Our providers identified patients' unique situations as a primary factor considered when prescribing maraviroc, along with potential side effects, patient insurance status, and associated laboratory testing. In contrast, those factors influencing the prescription of raltegravir and darunavir, the most commonly prescribed salvage therapies in our cohort, were clinical knowledge and experience, patient's unique situation, potential side effects, clinical practice guidelines, and colleague/peer experiences. Maraviroc seems to be used by our providers once patient-specific factors limit the use of other post-2006 ARV treatment options. Additionally, given the importance of clinical knowledge and experience indicated by providers when prescribing post-2006 ARVs, the slow uptake of maraviroc by our providers, and its limited use in our cohort, may have affected confidence in and subsequent utilization of maraviroc. Efforts beyond accessibility to tropism testing will be needed for maraviroc to gain acceptance to the degree of other post-2006 treatment options.

The results of our study should be interpreted with respect to its limitations. As a single-site, observational cohort study, our experiences may not be applicable to other settings. Also, some issues in comparability between the HC and SRT may beget other limitations: the HC study was established just after MVC approval in 2006, during a period with less information and experience available for prescription of MVC, whereas the SRT cohort was initiated in late 2009, a time with more visibility, information, and experience available for MVC.

Additionally, as with all observational studies, our results may identify associations between tropism availability and

maraviroc use but cannot attribute causality. Furthermore, while providers were not made aware of the provision of free tropism testing as part of a research protocol, some may have realized that their prescribing patterns were being observed, thereby influencing their ART choices.

In summary, this study demonstrates that maraviroc utilization was increased by integrating routine tropism testing and providing these data to providers at the decision-making point of care. While acquisition of a tropism assay is a financial and logistical barrier to the use of maraviroc, other barriers to maraviroc use likely exist and merit further study before the utilization of this therapeutic option, and subsequent members of this drug class, can be maximized in the continued efforts to provide lifelong antiretroviral therapy to HIV-infected patients.

Acknowledgments

The authors acknowledge Karina Defaria and Yolanda Lie from Monogram Biosciences for facilitation, monitoring, and data reporting for this study and Agnes Paquet (Monogram Biosciences) for manuscript review. The Monogram Biosciences Clinical Reference Laboratory performed all Monogram assays.

Author Disclosure Statement

Supported by Pfizer, Inc. J.H.W. has received research support from the Bristol-Myers Squibb Virology Fellows Research Program for the 2006–2008 academic years, Pfizer, Tibotec Therapeutics, and Definicare, and has consulted for Bristol-Myers Squibb, Definicare, and Gilead Sciences. M.J.M. has received recent research support from Tibotec Therapeutics, Merck Foundation, and Pfizer and has consulted for Bristol-Myers Squibb and Gilead Sciences. L.A.N. is an employee of Monogram Biosciences and its parent company, LabCorp, and owns LabCorp stock. M.S.S. has received research support or served as a consultant for Ardea, Avexa, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Merck, Monogram Biosciences, Progenics, Tibotec Therapeutics, and Vertex.

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