Maraviroc in Treatment Experienced Patients Infected with CCR5 - Tropic HIV-1

FDA Advisory Committee
Silver Spring, MD
24th April 2007

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Agenda and Speakers

- Introductions, Background and Overview of Maraviroc
  Michael Dunne MD, Therapeutic Area Head, Development, Infectious Diseases
- Clinical Efficacy
  Howard Mayer MD, Global Clinical Leader, Pfizer
- Safety and Toleration
  Steve Felstead MB ChB, Maraviroc Team Leader, Pfizer
- *In vitro* and *in vivo* Tropism and Resistance Evaluation
  Mike Westby PhD, Virology Team Leader, Pfizer
- Medical Need and Place in HIV Armamentarium
  Dan Kuritzkes MD, Brigham and Women's Hospital, Harvard Medical School, Boston
- Conclusions
  Michael Dunne MD

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Proposed Indication

Maraviroc, in combination with other antiretroviral agents, is indicated for treatment-experienced adult patients infected with CCR5-tropic HIV-1

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Maraviroc

This data review has some important characteristics:

- The chemotype is from a novel chemical class
- The antiviral target is a human receptor
- The receptor engages immune mediators
- Successful inhibition of the underlying HIV infection will also effect the immune system
- Inherent tropism of the virus potentially selects for a second pathway of resistance, with virus that may behave differently

The most integrated basis upon which to generate a risk / benefit assessment will be derived from human data collected from trials in the target population

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Chemokine Receptors and HIV Cell Entry

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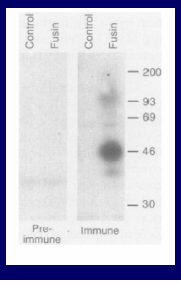
Discovery of CCR5 and Impact on HIV Pathogenesis

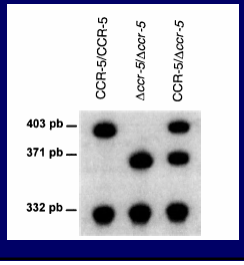
HIV-1 Entry Cofactor: Functional cDNA Cloning of a Seven-Transmembrane, G Protein-Coupled Receptor

Yu Feng, *et al. Science 1996;* 272; 872-877.



Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene

Samson, *et al. Nature 1996;* 382: 722 – 725.



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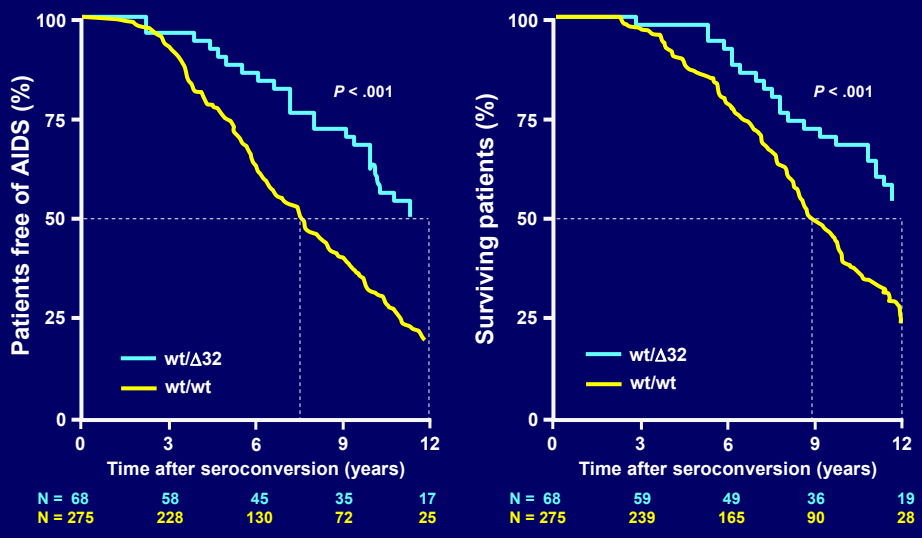
Patients Heterozygous for CCR5 Δ32 Have Slower Progression to AIDS and Death



Adapted from de Roda Husman A-M, et al. *Ann Intern Med.* 1997;127:882-890.

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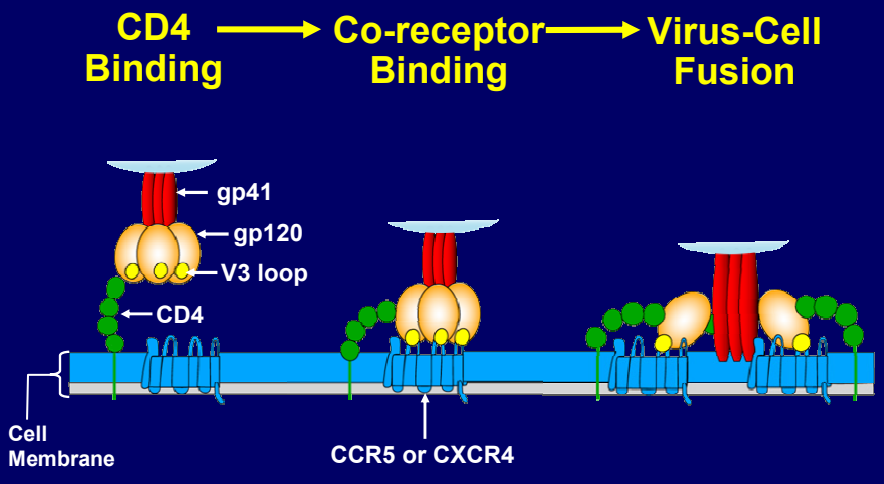
After Attachment to CD4 - Fusion Occurs When the V3 Loop Binds to Either CCR5 or CXCR4



Adapted from Moore JP *et al.* PNAS 2003;100:10598-10602.

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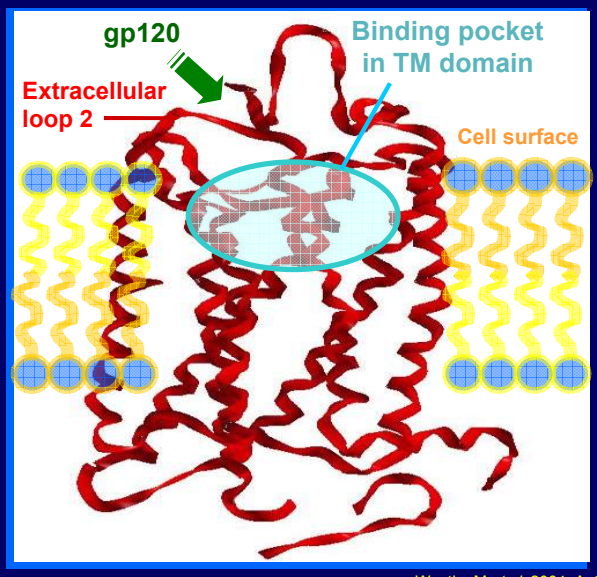
Molecular Model of CCR5, gp120 and Maraviroc Binding Sites



Westby M *et al.* 2004, Antiviral Therapy, **9**, S10

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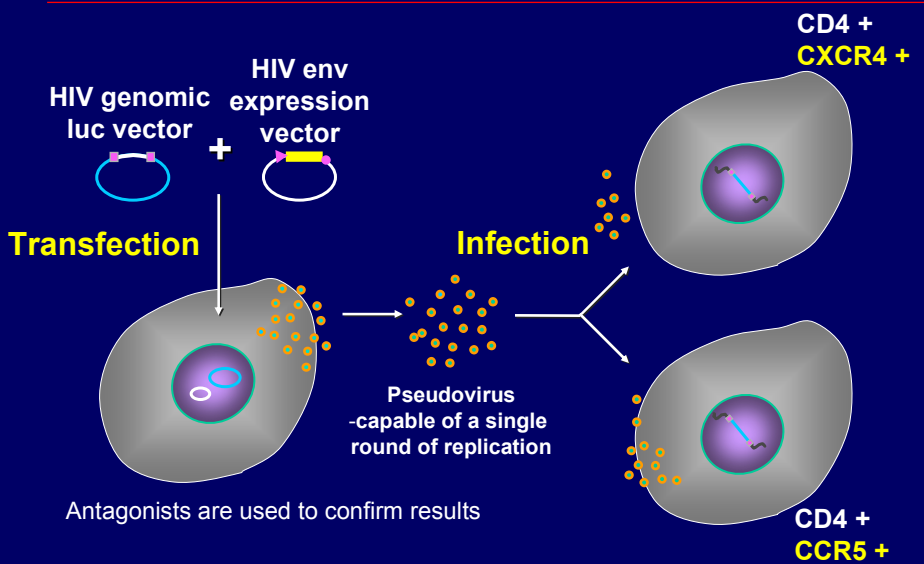
Trofile™ HIV Entry Cell Assay



Antagonists are used to confirm results

Adapted from Petropoulos CJ, et al. *Antimicrob Agents Chemother.* 2000;44:920-8. Full Public Slide #19

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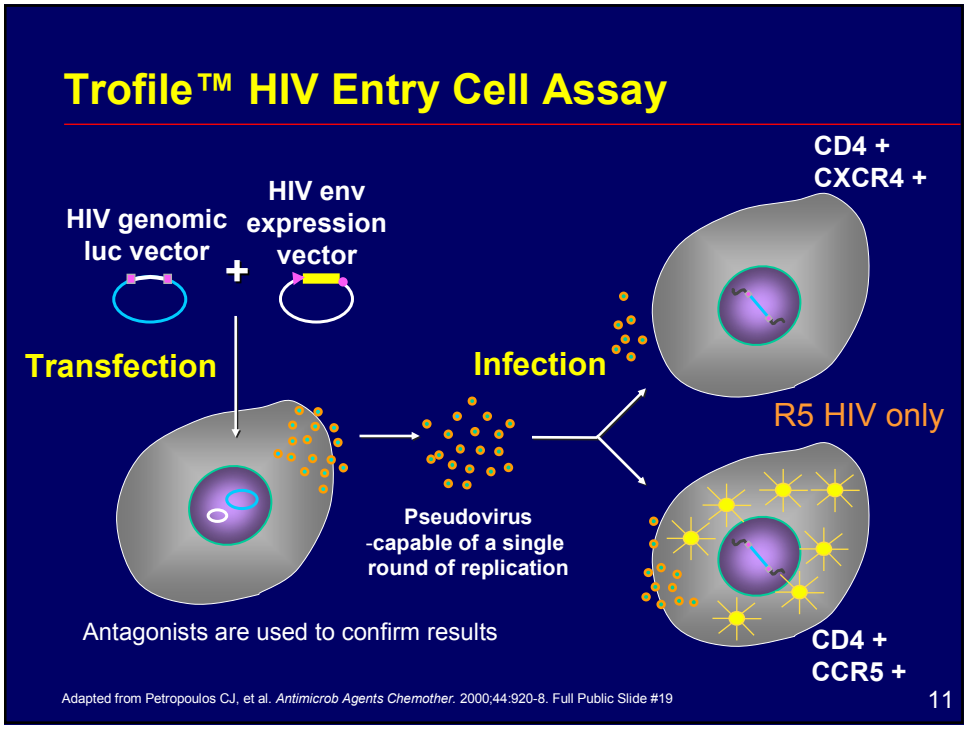
Trofile™ HIV Entry Cell Assay
HIV genomic luc vector
+
HIV env expression vector
Transfection
Infection
CD4 + CXCR4 +
R5 HIV only
Pseudovirus -capable of a single round of replication
Antagonists are used to confirm results
CD4 + CCR5 +
Adapted from Petropoulos CJ, et al. Antimicrob Agents Chemother. 2000;44:920-8. Full Public Slide #19
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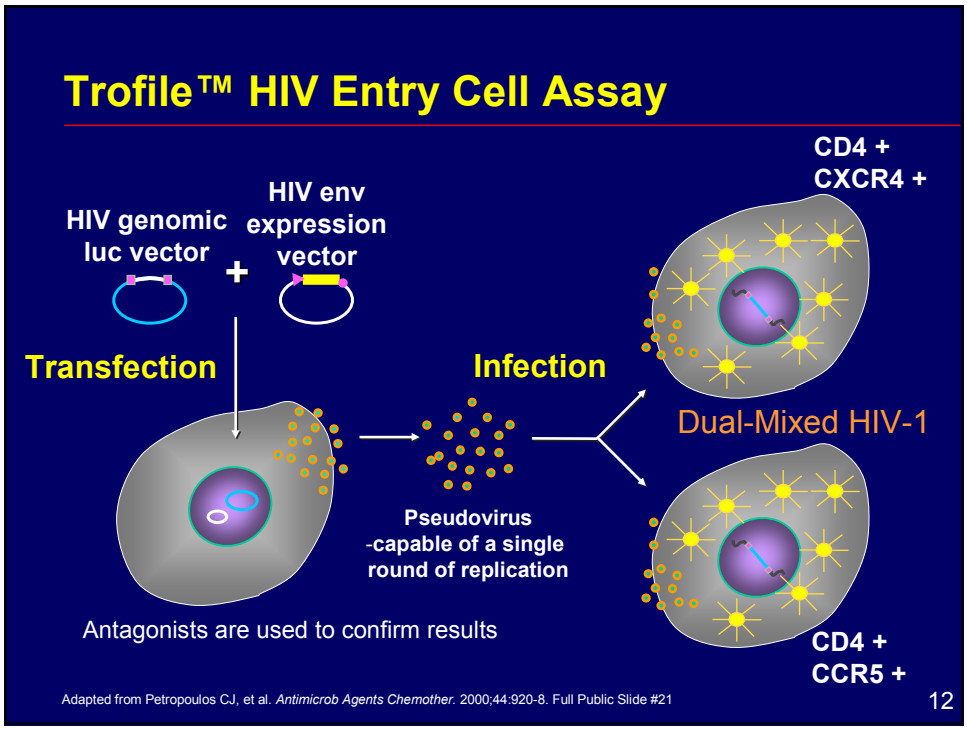
Trofile™ HIV Entry Cell Assay
HIV genomic luc vector
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CD4 + CCR5 +
Adapted from Petropoulos CJ, et al. Antimicrob Agents Chemother. 2000;44:920-8. Full Public Slide #21
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Terms Used to Define Tropism

Tropism	Definition
R5-tropic	Only CCR5-tropic virus detected in the assay
X4-tropic	Only CXCR4-tropic virus detected in the assay
D/M (dual/mixed) tropic	Both CCR5-tropic and/or CXCR4-tropic and/or Dual Tropic virus detected in the assay

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Percentage of HIV Co-receptor Usage

Study/Source	Population	N	R5	X4	R5/X4
Homer cohort[1]	Naïve	979	82%	<1%	18%
C & W cohort[2]	Naïve	402	81%	<1%	19%
Demarest[3]	Naïve	299	88%	0%	12%
TORO 1/2[4]	Experienced	612	50%	4%	46%
Monogram[5]	Experienced	>2000	48%	2%	50%
ACTG 5211[6]	Experienced	391	49%	4%	47%

* This table may not include all available reported data. Majority of data are generated in the developed world (subtype B)

[1]Brumme ZL, et al. *J Infect Dis.* 2005;192:466-474. [2]Moyle GJ, et al. *J Infect Dis*. 2005;191:866-872. [3]Demarest J, et al. *ICAAC* 2004. Abstract H-1136. [4] Melby *J Infect Dis.* 2006;194:238-46 [5]previously Virologic; Paxinos EE, et al. *ICAAC* 2002. Abstract 2040. [6]Wilkin T, *et al.* Clinical Infectious Diseases 2007; 44:591–5.

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Maraviroc Overview

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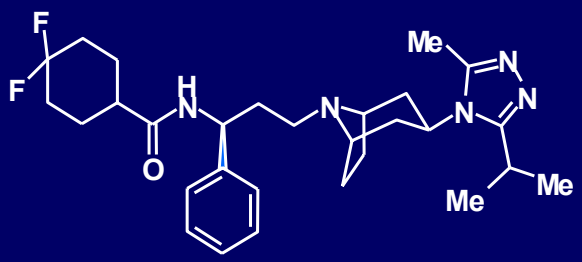
Pre-clinical Profile



- Selective, functional, reversible CCR5 antagonist
  - Antagonises binding of endogenous CCR5 ligands
- Active *in vitro* versus R5-tropic HIV-1
  - Inactive versus X4-tropic or R5X4-tropic HIV-1
  - Serial passage found R5 resistant isolates emerging slowly
- Cross-clade potency against primary CCR5-tropic isolates
- Mean IC_{90} = 2.0 nM

Dorr P et al. *10th CROI* 2003; Oral Presentation 12. Macartney et al. *43rd ICAAC* 2003; Poster H-875.

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Absorption and Distribution

- Absorption is non-linear at doses <100 mg
  - Increasingly linear thereafter
- Distribution is widespread
  - High concentrations in lymph nodes
  - CSF concentration is 10% of plasma (rat)

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Metabolism and Excretion

- Maraviroc is extensively metabolised via CYP3A4
  - No effect on other cytochrome p450 enzyme pathways
  - No CYP3A4 induction/inhibition
  - No effect of maraviroc on other drugs
    - midazolam, β-OH-cortisol/cortisol
- Maraviroc is a p-glycoprotein substrate
- Excretion is primarily fecal
  - 23% of drug related material excreted in the urine
- Metabolites have no activity/affinity at/for any receptor at relevant concentrations

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Human Pharmacokinetics

- Rapid absorption with T_{max} 0.5 - 4.0 hours
- Modelled terminal $T_{1/2}$ of 17 hours
- PK similar across gender, race, patients/volunteers
- Limited accumulation on multiple dosing (<20%)
- High fat meal reduces exposure with blunting of C_{max} (↓33%)
  - C_{min} and AUC correlate best with efficacy

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Drug-Drug Interaction Program

Effect of 'other drugs' on maraviroc

- Ketoconazole
- Saquinavir (± rtv)
- Lopinavir/ritonavir
- Ritonavir
- Atazanavir (± rtv)
- Darunavir/ritonavir
- Efavirenz
- Rifampicin
- Lopinavir/ritonavir + efavirenz
- Saquinavir/ritonavir + efavirenz
- Tipranavir/ritonavir
- HAART (SD probe study)
  - Efavirenz + lamivudine/zidovudine (Combivir)
  - Lopinavir/ritonavir + lamivudine + stavudine
  - Efavirenz + didanosine EC + tenofovir N
  - Nevirapine + lamivudine + tenofovir
- Sulfamethoxazole/trimethoprim
- Tenofovir

Effect of maraviroc on 'other drugs'

- Oral Contraceptives
  - Ethinylestradiol
  - Levnorgestrel
- Midazolam
- Debrisoquine metabolic ratio
- 6beta-hydroxycortisol/cortisol ratio
- Zidovudine/lamivudine (Combivir)

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CYP3A4 Drugs Can Affect Metabolism

- CYP3A4 inhibitors increase maraviroc exposure
  - Ketoconazole, protease inhibitors, delavirdine
    - AUC (↑3-10x) and C_{max} (↑2-5x)
  - But no change with tipranavir/ritonavir
- CYP3A4 inducers decrease maraviroc exposure
  - AUC and C_{max} decreased by 50-70%
    - Efavirenz, rifampin
- Combinations of inhibitors/inducers lead to inhibition
  - Saquinavir/ritonavir + efavirenz; Kaletra® + efavirenz
- Renal substrates/inhibitors do not affect maraviroc PK
  - Co-trimoxazole, tenofovir

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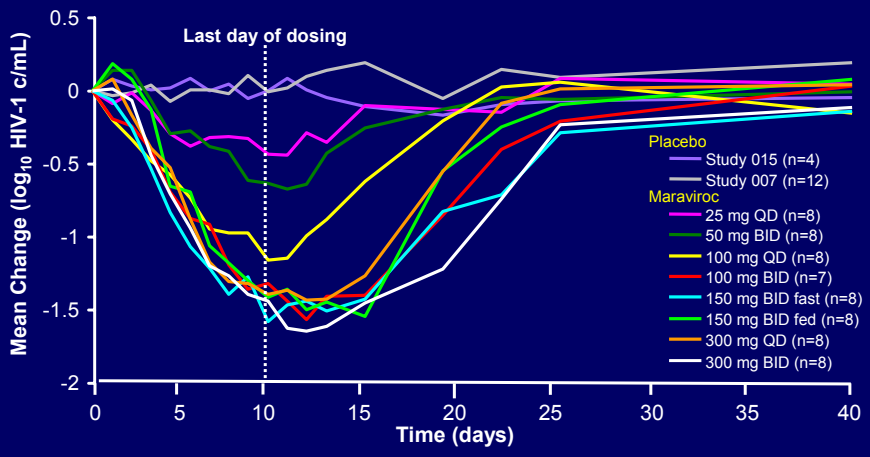
Rationale for Dose Selection
Phase 2a Monotherapy



Study population: asymptomatic, CD4 >250, R5-tropic (N=82); BL VL ~42K

Fätkenheuer G, et al. *Nat Med.* 2005;11:1170-1172.

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Rationale for Dose Selection and Adjustment

- Maraviroc was very well tolerated to 300 mg BID
  - Postural hypotension observed at 600 mg, related to C_{max}
- 300 mg QD and BID at plateau of antiviral effect
- Drugs which affect CYP3A4 can influence maraviroc concentrations
  - Dose adjustment to 150 mg for CYP3A4 inhibitors is, overall, most clinically appropriate
    - Corrects for C_{max}; under corrects for AUC
  - Dose adjustment to 600 mg for CYP3A4 inducers corrects for both C_{max} and AUC

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Phase 2b/3 Program

	ARV-naïve	ARV-experienced		
	R5 Patients	R5 Patients		Non R5 Patients
Study	1026	1027	1028	1029
Phase	2b→3	2b/3	2b/3	2b
Design	MVC vs. EFV +CBV	OBT add-on		
Randomization	1:1:1	2:2:1	2:2:1	1:1:1
Primary Endpoint	%<400/<50 wk 48/96	Δ VL at wk 24/48		
Enrollment	917	601	475	190
Received Maraviroc		467	373	124

ARV – antiretroviral, EFV - efavirenz (Sustiva), VL - viral load
OBT - optimized background therapy, CBV - Combivir

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Phase 2b/3 Program

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Summary of Patient Exposure

	Maraviroc	Comparator
Phase 1		
Single dose	299	-
Multiple dose	333	-
Phase 2a	66	16
Total Short Term Studies	698	16
Phase 2b/3		
Treatment Experienced R5 patients (1027 & 1028)	840	209
Treatment Experienced nonR5 patients (1029)	124	62
Total Treatment Experienced patients	964	271
Open Label from placebo (1027 & 1028)	74	-
Naïve, QD regimen (1026)	174	-
Total	1910	287

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Issues to Be Addressed Regarding Virology

- Switch to CXCR4 virus predominance
  - A consequence of selection or mutation?
    - V3 alignment and phylogenetic analyses
- R5 viral resistance to maraviroc
  - Phenotypic and genotypic markers
  - Identification of associated point mutations

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- Medical Need and Place in HIV Armamentarium
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- Conclusions
  Michael Dunne MD

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