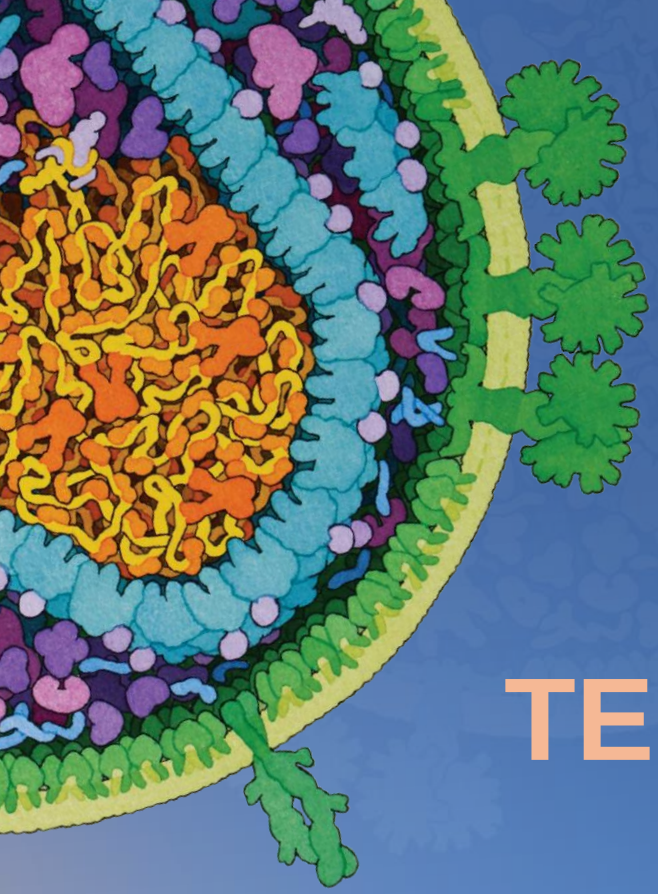

SCIENCE SPOTLIGHT™

REDUCED SUSCEPTIBILITY TO TEMSAVIR IS NOT LINKED TO IBA OR MVC RESISTANCE

Burt Rose,[1] Margaret Gartland,[2] Eugene Stewart,[3] Mark Cockett,[1] Peter Ackerman,[1] Max Lataillade,[1] Cyril Llamoso,[1] Mark Krystal[1]

[1]ViiV Healthcare, Branford, CT, USA; [2]ViiV Healthcare, Research Triangle Park, NC, USA; [3]GlaxoSmithKline, Philadelphia, PA, USA

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Background and Methods

- Temsavir (TMR), the active agent of the HIV-1 attachment inhibitor fostemsavir (FTR), the CD4-directed inhibitor ibalizumab (IBA), and the CCR5 antagonist maraviroc (MVC) are ARV agents that inhibit different steps in HIV-1 viral entry by targeting key HIV (FTR) or human immune targets (IBA and MVC)
- Although the mechanisms of inhibition of the 3 agents are different, all 3 ARVs exhibit context-dependent effects on susceptibility, so it is important to understand whether there is any overlap in susceptibility patterns
  - Mutations in the *gp120* gene have been associated with reduced susceptibility to these agents (e.g. C3-5, V3, V5 regions)
  - Previously published *in vitro* data suggest that there is no overlap in profiles for reduced susceptibility[1]
  - The current analysis examines clinical specimens derived from participant isolates
- Envelope sequences from samples at screening and protocol-defined virologic failure (PDVF) were assessed from participants in the FTR phase 3 BRIGHTE trial who were co-dosed with IBA or MVC
- Envelopes from select participants in the MOTIVATE trials (MVC registrational trials) who met PDVF criteria were regenerated and assessed for cross-resistance to TMR
- Site-directed mutations were performed on targeted site positions to assess cross-resistance

1. Li et al. *Antimicrob Agents Chemother*. 2013;57:4172-4180.

No Cross-resistance Was Observed in Participants Receiving FTR and IBA in BRIGHTE

- No participants in the Randomized Cohort received IBA as part of their initial OBT
- 15 participants in the Non-randomized Cohort received IBA as part of their initial OBT, and 5 met criteria for PDVF
  - Of the 5 who met PDVF criteria, there were 4 with available PDVF samples; all had decreased susceptibility to IBA, and 3 had decreased susceptibility to TMR
- When polymorphisms associated with the potential for reduced susceptibility to TMR were reverted to wild-type, TMR susceptibility was rescued while no substantial change to IBA susceptibility was observed

Participant	Sample	Type	TMR gp120 polymorphisms	TMR IC_{50} (nM)	IBA IC_{50} (nM)	IBA MPI (%)
1	Baseline	Population	S375T	10.89	0.11	100
	Week 108	Population	S375T_M426L	>5000	0.45	72
	Week 108	Clone	S375T_M426L	>2000	2.39	71
	Week 108	SDM clone	None	10.72	2.66	69
2	Baseline	Population	None	0.47	0.15	93
	Week 36	Population	S375H/N_M426M/L	>5000	0.47	74
	Week 36	Clone	S375N_M426L	>2000	1.56	87
	Week 36	SDM clone	None	1.16	1.47	64
3	Baseline	Population	M426M/T	0.89	0.11	64
	Week 36	Population	S375N_M475I	>5000	9.93	62
	Week 36	Clone	S375N_M475I	>2000	>800	25
	Week 36	SDM clone	None	5.61	>800	38

IC_{50}, half-maximal inhibitory concentration; MPI, maximum percent inhibition; SDM, site-directed mutagenesis.

Prior Virologic Failure on MVC Was Not Associated With Decreased Response to FTR at Day 8

- 15/18 (83%) participants with virologic failure on an MVC-containing regimen experienced virologic success at Day 8 of FTR functional monotherapy
  - 8/8 (100%) participants with CCR5-tropic virus had virologic success on FTR at Day 8 with a median 1.1 log_{10} c/mL decline in HIV-1 RNA
  - 7/10 (70%) participants with dual/mixed- or CXCR4-tropic virus had virologic success on FTR at Day 8 with a median 1.3 log_{10} c/mL decline in HIV-1 RNA
    - Median TMR IC_{50} values were similar in CCR5- (1.229 nM, n=225), dual/mixed- (0.787 nM, n=339), and CXCR4-tropic (1.109 nM, n=43) pre-treatment isolates in BRIGHTE, indicating that viral tropism does not appear to influence phenotypic susceptibility to TMR[1]

Tropism	Day 8 success*	Change in HIV-1 RNA from Day 1 to Day 8 (log_{10} c/mL)	TMR IC_{50} at baseline (nM)
CCR5	Y	−0.942	6.38
	Y	−0.700	1.99
	Y	−1.778	0.07
	Y	−0.785	9.27
	Y	−1.921	>5000
	Y	−0.753	0.25
	Y	−1.235	0.37
	Y	−2.020	19.18

Tropism	Day 8 success*	Change in HIV-1 RNA from Day 1 to Day 8 (log_{10} c/mL)	TMR IC_{50} at baseline (nM)
Non-CCR5 (dual/mixed or CXCR4)	N	0.048	0.11
	Y	−1.080	0.56
	Y	−1.248	1.60
	Y	−2.696	0.45
	Y	−1.513	0.25
	Y	−1.387	0.43
	Y	−1.336	19.41
	Y	−1.311	2.19
	N	−0.434	15.94
	N	−0.187	31.36

FC, fold change; IC_{50}, half-maximal inhibitory concentration.

*Day 8 success defined as ≥0.5 log_{10} c/mL change in HIV-1 RNA from Day 1 to Day 8.

Day 8 population excludes participants with baseline HIV-1 RNA <1000 c/mL and/or change from screening to baseline of HIV-1 RNA >0.3 log_{10} c/mL.

1. Gartland et al. *J Antimicrob Chemother*. 2020 [Epub ahead of print].

In BRIGHTE Participants Co-dosed With FTR and MVC, Reduced Susceptibility to TMR Is Not Linked to MVC Resistance

- There were 2 participants co-dosed with FTR and MVC who met PDVF criteria

		TMR gp120 polymorphisms				
Participant	Week	Baseline	At PDVF	TMR EC_{50} (nM)	MVC EC_{50} (nM)	MVC MPI (%)
1	Baseline	M426L	NA	234.1	135.9	88.8
	Baseline	None (SDM)	NA	1.1	169.5	91.1
	Week 48	—	M426L	788.9	89.6	93.5
	Week 48	—	None (SDM)	1.3	166.2	93.8

		TMR gp120 polymorphisms				
Participant	Week	Baseline	At PDVF	TMR EC_{50} (nM)	MVC EC_{50} (nM)	MVC MPI (%)
2	Baseline	M434T	NA	69.7	>5000	−13.9
	Baseline	None (SDM)	NA	2.2	>5000	6.7
	Week 13	—	M434T, M426L	>2000	>5000	−2.6
	Week 13	—	M434T (SDM)	432.2	>5000	−7.3
	Week 13	—	M426L (SDM)	171.3	>5000	−2.2
	Week 13	—	None (SDM)	5.9	>5000	−8.1

EC_{50}, half-maximal effective concentration; MPI, maximum percent inhibition; NA, not applicable; PDVF, protocol-defined virologic failure; SDM, site-directed mutagenesis.

CCR5-Tropic MVC Resistance Was Not Predictive of Reduced Susceptibility to TMR in MOTIVATE-1 and -2

- No clinical samples from MOTIVATE were available, although gp120 sequences were accessible
- Sequences of envelopes from 5 participants who exhibited CCR5-tropic MVC resistance were used to regenerate functional envelopes
- All 5 exhibited resistance to MVC (and were CCR5-tropic), while 4/5 were fully susceptible to TMR
- The 1 envelope with reduced susceptibility to TMR contained an M426L polymorphism
- Site-directed mutagenesis reverting the virus back to M426 resulted in full sensitivity to TMR while MVC resistance remained

Envelope	TMR EC_{50} (nM)	MVC EC_{50} (nM)
MP5.7	1.00	>5000
MP35.2	1.00	>5000
MP49.20	1.56	>5000
MP53.36	0.51	>5000
MP11.38 (M426L)	412.7	>5000
MP11.38 (M426M; SDM)	0.98	>5000

EC_{50}, half-maximal effective concentration; SDM, site-directed mutagenesis.

Conclusions

- Data from BRIGHTE and MOTIVATE strongly suggest that there is no correlation between IBA or MVC resistance and a meaningful reduction in TMR susceptibility
- From BRIGHTE:
  - In participants co-dosed with FTR and IBA who demonstrated reduced susceptibility to both agents, susceptibility to TMR could be restored without restoring IBA susceptibility
  - A failing regimen with MVC did not impact virologic success of functional FTR monotherapy at Day 8
- From MOTIVATE:
  - Susceptibility to TMR was not indicative of susceptibility to MVC
  - The envelope with reduced susceptibility to TMR contained an M426L polymorphism; when reverted to M426M, susceptibility to TMR was rescued while susceptibility to MVC was unchanged

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