Tackling Resistance: Managing Virologic Failure in Treatment-Experienced Patients

Austin Chan, MD
Division of Infectious Diseases
Morehouse School of Medicine

Disclosures

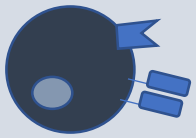
- No disclosures

Objectives

- Review the Considerations for Managing Treatment-Experienced Patients with Resistance
- Discuss Specific Clinical Considerations in Specific Scenarios
- Emphasize the Importance of the Therapeutic Alliance in Treatment Experienced Patients

The Benefits of Durable Viral Suppression

Improves immune function



Improves overall quality of life

Lowers the risk of both AIDS-defining and non-AIDS-defining complications

Prolongs life

Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed May 11, 2019.

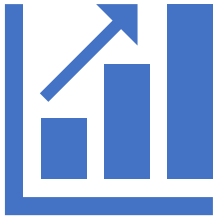
Why is achieving undetectable viremia important in treatment-experienced patients?

Successful outcomes in treatment-experienced patients are more difficult to achieve as a result of low CD4 count and multiple previous virologic failures

Patients on ART who do not achieve undetectable viremia can **develop resistance mutations**[1]

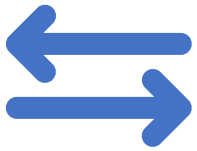
→ Further mutation accumulations restrict the already limited options in treatment-experienced patients[3]

Some studies indicate that viral load of >200 copies/mL is **predictive of virologic rebound**[1]



→ Getting this under control mitigates the higher risk of disease progression and mortality in treatment-experienced patients compared to treatment-naïve patients[3]

People with an undetectable viral load have effectively **no risk of transmitting HIV** to their HIV-negative sexual partners[2]



→ Transmission of resistance from treatment-experienced to treatment-naïve patients remains a significant problem[4]

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CDC, December 2018. Available at https://www.cdc.gov/hiv/pdf/risk/art/cdc-hiv-art-viral-suppression.pdf.
Sheikh V, et al. *N Engl J Med* 2018;379(7):605-607.
Günthard HF, et al. *Clin Infect Dis* 2019;68(2):177-187.

Let’s Meet Daniel MacGuffin.

- 57-year-old-male
- Comorbidities: type 2 diabetes mellitus and hypertension
- Has been receiving treatment since 2003

We will continue to learn more about Daniel throughout this presentation.

How might treatment-experienced patients with HIV like him differ?

Part 1: Considerations for Managing Treatment-Experienced Patients with Resistance

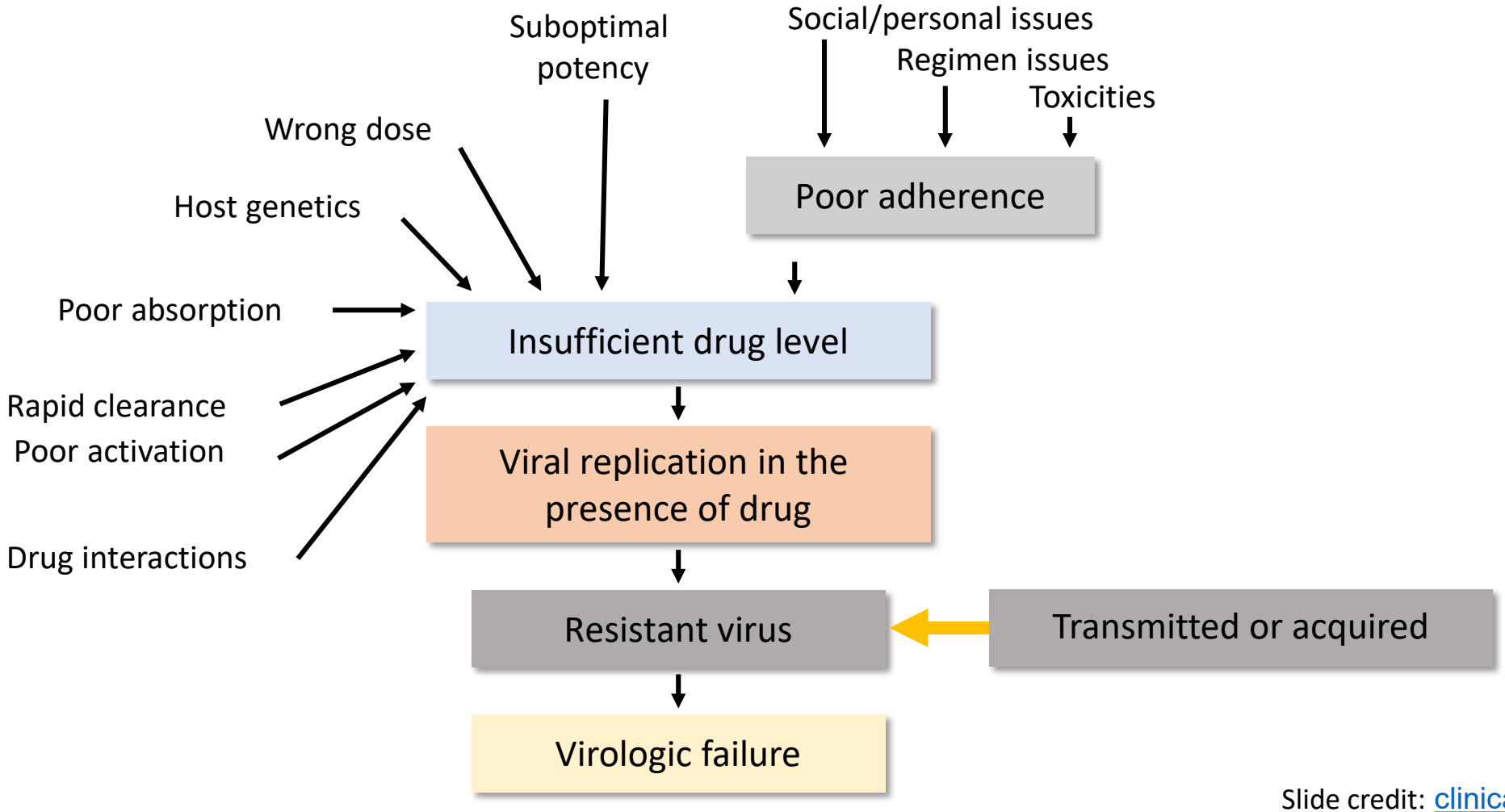
Revisiting Daniel MacGuffin, Our Treatment-Experienced Patient

- First-line treatment: ddI/3TC/TDF/ABC
- Second-line treatment: T20, LPV/r and 3TC/ABC/ZDV
- Experiencing virologic failure on his third-line regimen of DRV/r/ETR/DTG BID (600/100/200/50 mg), FTC/TAF QD and ZDV QD (300 mg)
- His HCP attributed his virologic failure to several factors:
  - Difficulty tolerating the pill burden
  - Difficulty controlling his blood sugar
  - GI adverse effects

What are some other potential causes of virologic failure, particularly in treatment-experienced patients?

3TC, lamivudine; ABC, abacavir; ddI, didanosine; DTG, dolutegravir; ETR, etravirine; FTC, emtricitabine; GI, gastrointestinal; HCP, healthcare professional; LPV/r, lopinavir/ritonavir; r/DRV, darunavir/ritonavir; T20, enfuvirtide; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine

There Are Many Possible Causes of Virologic Failure



Slide credit: clinicaloptions.com

Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed June 7, 2019

Undetectability is Achievable:
Considerations for incomplete viral suppression…

For some ART-experienced patients with drug resistance, maximal virologic suppression may not be possible[1]

- **In this case, ART should be continued with regimens designed to minimize toxicity, preserve CD4 cell counts, and delay clinical progression**

- In some classes, incomplete activity can lead to **class-wide resistance,** a problem for treatment-experienced patients with limited options[2,3]

- **Potential for preservation** if failing regimens are modified early[2]

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Hatano H, et al. *J Acquir Immune Defic Syndr* 2010;54(4):389-393.
Spach DH and Kinney RG. https://www.hiv.uw.edu/go/antiretroviral-therapy/evaluation-management-virologic-failure/core-concept/all

Now back to Daniel…

Despite being on third-line therapy and demonstrating an extensive archived resistance mutation profile, Daniel was able to achieve virologic suppression on his third-line regimen, reaching HIV RNA <20 copies/mL

Daniel's resistance profile

NRTI: M41L, D67N, M184V, L210W, T215F/I/N/S/Y

NNRTI: K101Q, K103N, V108I, G190A

INI: None

PI: L10F/V, K20I, E35D, M36I, M46I, Q58E, I62V, A71V, L76V, I84V, I85V, L90M

Trofile: X4


Stanford University
HIV DRUG RESISTANCE DATABASE
A curated public database to represent, store and analyze HIV drug resistance data.
HOME
GENOTYPE-RX
GENOTYPE-PHENO
GENOTYPE-CLINICAL
HIVDB PROGRAM
ABOUT HIVDB
SUPPORT HIVDB!
HIVDB Algorithm Version 8.8
Feb 13, 2019
Reference Library: Dolutegravir Resistance
A body of literatures reviewed, annotated and searchable
Integrase DRMs for Transmitted Resistance Surveillance
DRMs proposed / Added to CPR analysis / Criteria and rational
SIERRA
Sierra 2.3.2
release notes / web service
Jul 17, 2019
Transmitted Resistance Surveillance Map
Published virus sequences from >95,000 ART-naïve persons over 120 countries
CPR Calibrated Population Resistance
INTERACTIVE MAP
Surveillance Mutations
Reference Library / Dolutegravir Resistance
Point-of-Care / Essential Mutations
HIVDB released on Jul 2, 2019
Query / Download
Genotype-treatment
ARV selection data comprising 165,194 protease, 174,533 RT and 21,345 integrase HIV-1 virus sequences from 184,328 persons; 915 protease, 715 RT and 269 integrase HIV-2 virus sequences from 954 persons.
Genotype-phenotype
Drug susceptibility data comprising 25,434 PI, 19,858 NRTI, 11,536 NNRTI and 4,606 INI susceptibility results from HIV-1 virus isolates
Genotype-clinical
Clinical outcome data comprising genotype, treatments, plasma HIV-1 RNA levels and CD4 counts from 13 clinical trials and >1500 Treatment-Change Episodes
References
1,661 references of genotype-treatment and/or genotype-phenotype data according to author-yr, including 138 references collected since 2019-01-01.
3,042 Genbank submission sets according to author-yr and submission title, including 42 new submissions from Genbank release on 2019-04-15.
HIVdb Program
Drug Resistance Summaries (Download PDF)
PIs
NRTIs
NNRTIs
INSTIs
HIVseq Program
HIValg Program
HIV-1 Genetic Variability for Drug Resistance
Single Genome Sequence Database

Daniel MacGuffin's Stanford Profile

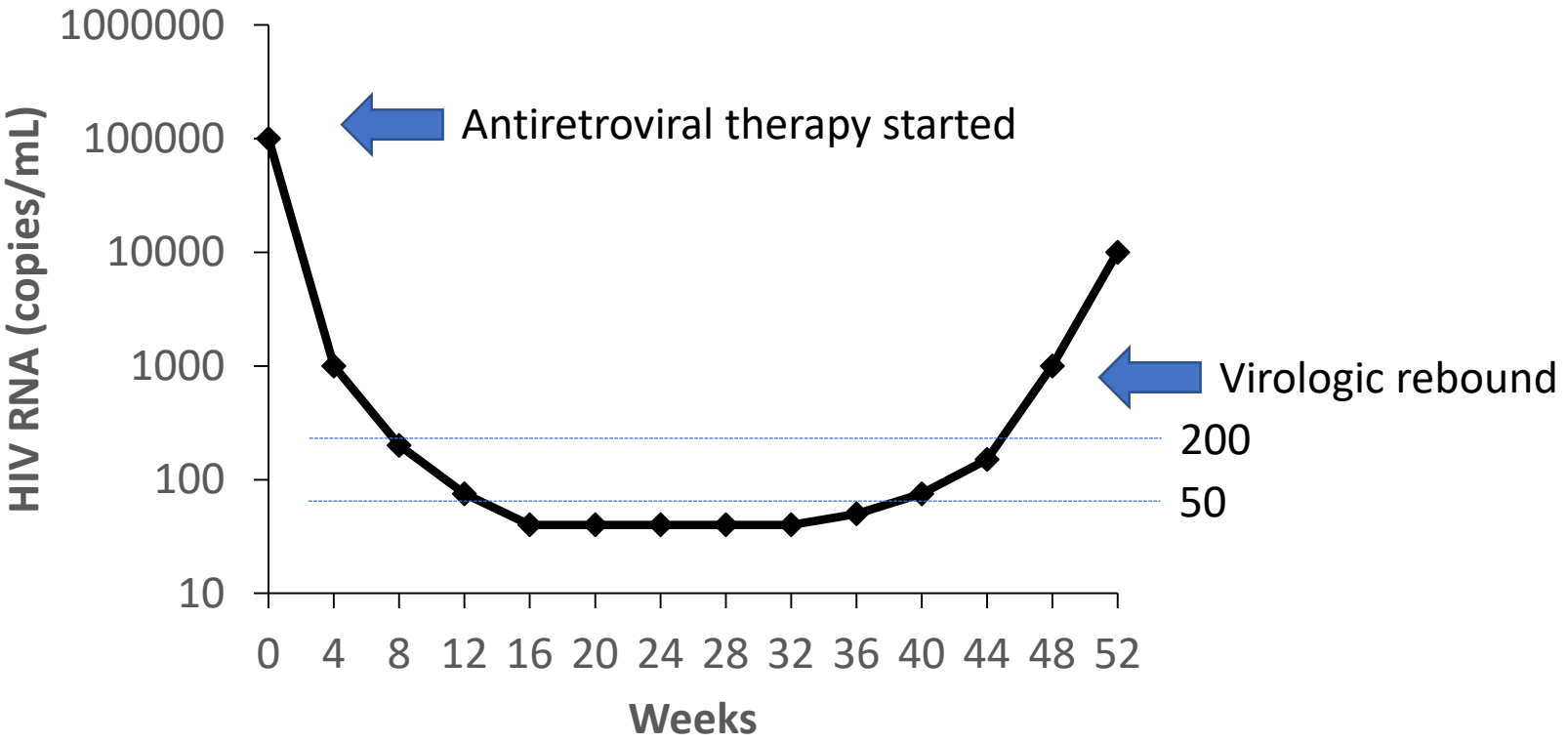
Mutation Scoring: RT

NRTI	ABC	AZT	FTC	3TC	TDF
M184V	15	-10	60	60	-10
L210W	5	15	0	0	5
L210W + T215FY	10	10	5	5	10
T215FY	10	40	0	0	10
M41L	5	15	0	0	5
M41L + L210W	10	10	0	0	10
M41L + L210W + T215FY	5	0	5	5	5
M41L + T215FY	15	10	5	5	10
M41L + D67N + T215FY	5	5	5	5	5
D67N	5	15	0	0	5
Total	85	110	80	80	55

NNRTI	DOR	EFV	ETR	NVP	RPV
V108I	10	10	0	15	0
K103N	0	60	0	60	0
G190A	0	45	10	60	15
Total	10	115	10	135	15

Virologic Failure Can Be Defined as Undetectability Not Maintained

- **Possible definition of virologic failure (2/2):** Undetectable plasma HIV RNA levels are achieved, but not maintained[1-3]



In treatment-experienced patients, the time to virologic failure is shorter[4]

Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Daar ES. *in*Practice®. Available at https://www.inpractice.com/Textbooks/HIV/Antiretroviral_Therapy/ch15_pt2_TxExp_Pts.aspx
Spach DH and Kinney RG. Available at https://www.hiv.uw.edu/go/antiretroviral-therapy/evaluation-management-virologic-failure/core-concept/all
Häggblom A , et al. *PLoS One* 2017;12(7): e0180140.

Low-Level Viremia Is Increasing, with Consequences for Treatment-Experienced Patients

DHHS: Confirmed, persistent **detectable** HIV RNA level <200 copies/mL (**50–199 copies/mL**)[1]

IAS-USA: Between limits of assay quantification **(20–50 copies/mL)** and **1000 copies/mL**[2]

- Resistance mutations can emerge with persistent HIV-1 RNA 100–200 copies/mL[3]
- Whether it is associated with potential virologic rebound remains controversial[1]

Treatment-experienced patients failing with LLV are at increased risk of death, despite comparable rates of AIDS diagnoses when compared with treatment-experienced patients who achieved maximal viral suppression[4]

DHHS, U.S. Department of Health and Human Services; IAS-USA, International Antiviral Society–USA; LLV, low-level viremia

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Günthard HF, et al. *Clin Infect Dis* 2019;68(2):177-187.
Daar ES. inPractice®. Available at https://www.inpractice.com/Textbooks/HIV/Antiretroviral_Therapy/ch15_pt2_TxExp_Pts.aspx
Chao C, et al. *AIDS Patient Care STDS* 2012;26(5):253-255.

In Some Treatment-Experienced Patients, Viral Blips May Occur

- After virologic suppression is achieved, a detectable HIV RNA level (typically low level) occurs during **a single measurement** and subsequently **returns to undetectable levels**[1,2]
- The source and clinical relevance of viral blips are unknown, and may reflect:[3]

Technical variability

Real biologic processes

In one study, patients on second-line therapy who required a switch to third-line therapy **had a higher frequency of viral blips** than those who did not switch[4]

Current guidelines do not include recommendations for treatment modification based on the presence of a blip[1]

Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Daar ES. *in*Practice®. Available at https://www.inpractice.com/Textbooks/HIV/Antiretroviral_Therapy/ch15_pt2_TxExp_Pts.aspx
Günthard HF, et al. *Clin Infect Dis* 2019;68(2):177-187.
Evans D, et al. *AIDS Res Ther* 2018;15(1):10

Key Treatment Considerations

Are drugs with partial activity effective in treatment-experienced patients?

ARVs with partial activity are those predicted to reduce HIV RNA, but to a lesser extent than when there is no underlying drug resistance[1]

ARVs with partial activity can be used selectively in combination with fully active agents[2]

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Daar ES. inPractice®. Available at https://www.inpractice.com/Textbooks/HIV/Antiretroviral_Therapy/ch15_pt2_TxExp_Pts.aspx.

Treatment-Experienced Patients Should Receive at Least Two, Preferably Three, Fully Active ARTs

- Fully-active agents are expected to have uncompromised activity on the basis of the patient's:
  - ART history
  - Current drug resistance test results
  - Past drug resistance test results
- A fully active agent may also have a novel mechanism of action

Adding a single ARV agent to a failing regimen is not recommended
- **This may risk the development of resistance to all drugs in the regimen to which treatment-experienced patients may already have several mutations**

PK, pharmacokinetics

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In Treatment-Experienced Patients, Fully-Active ARV Options Are Limited with Each Successive Failure[1]

- Using a "new" drug that a patient has never used previously does not ensure that the drug will be fully active[2]
  - Potential for cross-resistance among drugs from the same class

Phenotypic drug susceptibility

Weeks in culture

Resistance mutation	DTG	EVG	RAL	MK-2048
G118R	1	0.9	0.8	0.4
G118R, E138K	1.7	4.1	4.4	139
G118R, E138K, T66A	6.5	6.6	4.6	175
G118R, E138K, T66A, L74M, V151I	8.0	10.0	11.3	300

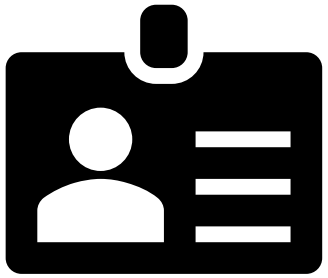
Example: G118R resistance pathway conferring cross-resistance to integrase inhibitors[3]

EVG, elvitegravir

Clinical Care Options Available at https://www.clinicaloptions.com/hiv/programs/managing-mdr-hiv.
Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed June 7, 2019.
Brenner BG, et al. *J Antimicrob Chemother* 2016;71(7):1948-1953.

Key Treatment Consideration: Performing and Interpreting Resistance Testing

- Test for HIV drug-resistance when changing ART regimens in patients with:
  - Virologic failure and HIV RNA levels >1000 copies/mL
  - HIV RNA levels >500 copies/mL but <1000 copies/mL, drug-resistance testing may be unsuccessful but should still be considered
  - Suboptimal viral load reduction



All prior and current drug-resistance testing results should be reviewed and considered when designing a new regimen for a patient experiencing virologic failure

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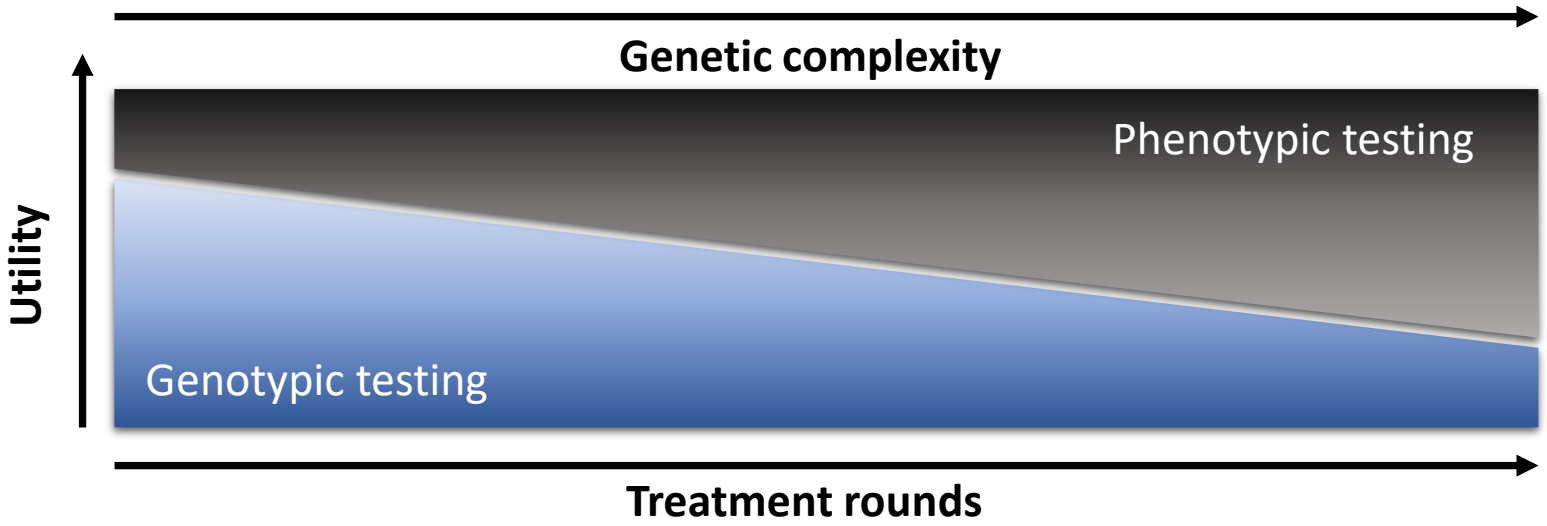
As The Treatment-Experienced Patient Progresses, Different Resistance Testing Needed To Construct New Regimen

- **Genotypic** and **phenotypic** resistance assays are used to assess viral strains and select treatment strategies[1]



Some specific resistance tests may need to be **ordered separately**:[1]

- INSTI-resistance
- Fusion inhibitor resistance
- Coreceptor tropism

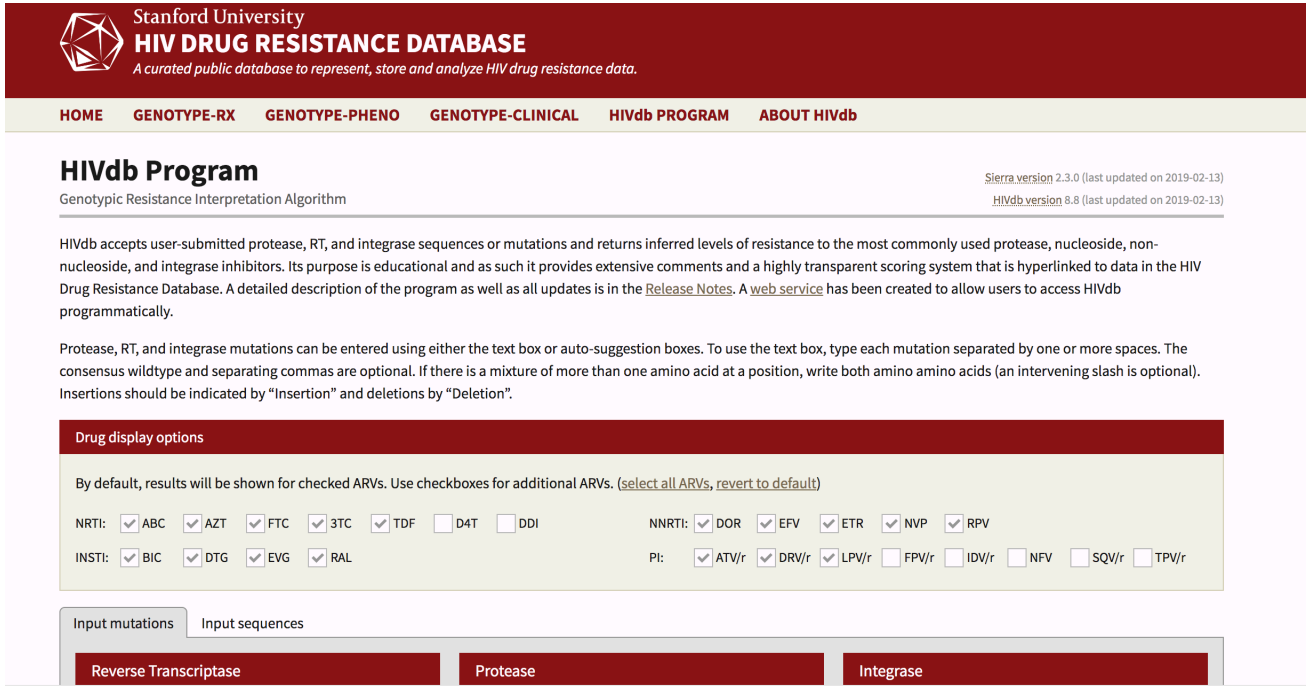
- A **standard genotypic resistance assay** is preferred for first- or second-line regimen failure[1]
- Phenotypic testing can provide **additional useful information** in patients with **complex** drug resistance mutation patterns[1]

Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed June 7, 2019

Figure from: WHO AIDS/HIV. Available at https://www.who.int/hiv/pub/drugresistance/HIVDR_Mod_1_Intro_to_HIVDR.ppt?ua=1. Accessed June 9, 2019

Resources Can Help Interpret Resistance Testing

- Various tools are available to assist providers in interpreting resistance test results, such as the Stanford HIV Drug Resistance Database (HIVDB)[1]



In treatment-experienced patients, the accumulation of resistance mutations to NRTIs, NNRTIs, and PIs is considered common[2]

Therefore, appropriate interpretation of resistance testing is essential when selecting a new regimen[2]

Stanford University. HIV Drug Resistance Database. Available at: https://hivdb.stanford.edu. Accessed June 9, 2019.
Imaz A, et al. *AIDS Rev* 2011 Jul-Sep;13(3):180-93.

Regimen Selection in Treatment-Experienced Patients Is More Challenging

- INSTIs have become a main component of first- and second-line treatment[1]
- Newer INSTIs, BIC and DTG, have **higher barriers to resistance** than other agents in this class (RAL or EVG)[1]
  - Although DTG and BIC have lower barriers once secondary or accessory mutations are present

However, this higher barrier to resistance was observed in vitro or in ART-naïve studies.

There are no clinical trial data to guide therapy for INSTI failures[1]

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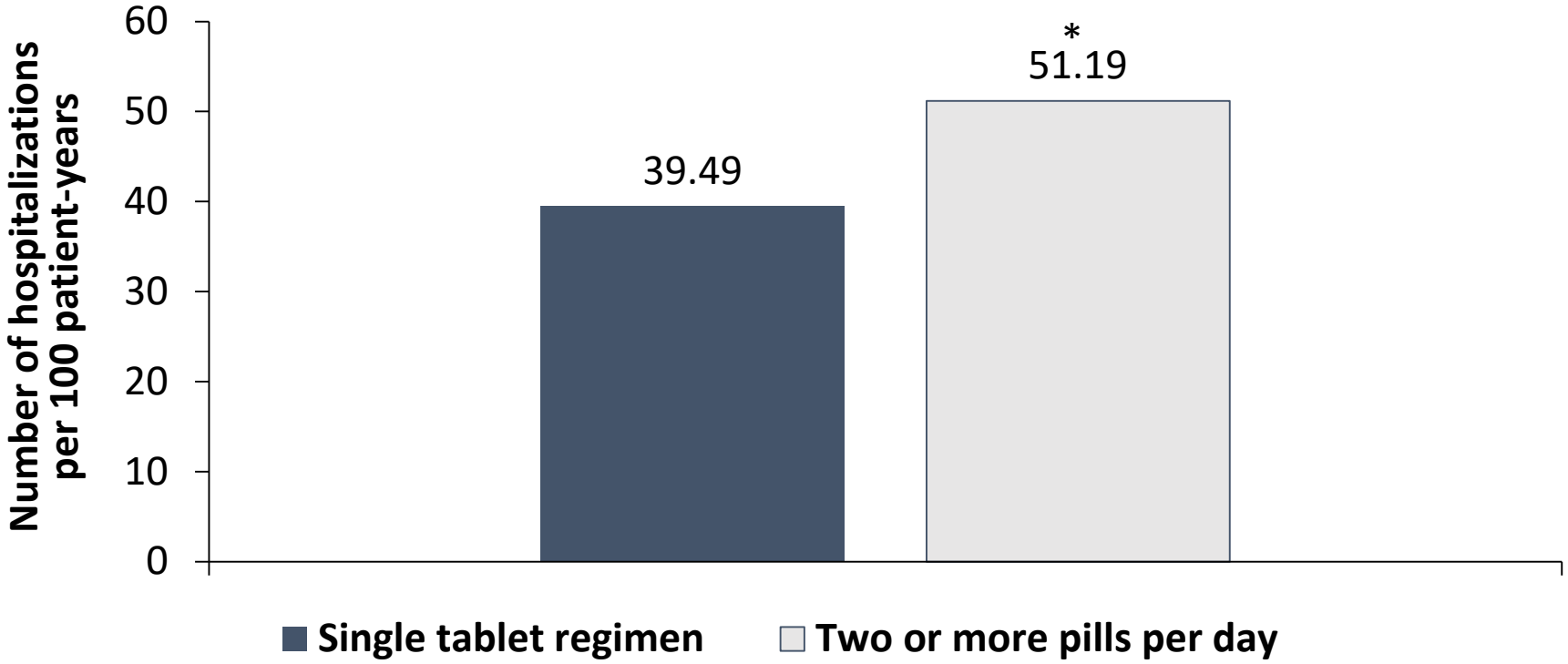
Patient Factors Are Also Important Drivers of Success in Treatment-Experienced Patients



*p<0.001

Multiple pill burden is linked to lower rates of complete adherence and increased hospitalizations[1]

Revisiting Daniel…

As mentioned, Daniel is failing his third-line regimen – his HIV-1 RNA has increased from 20 copies/mL, to 87 copies/mL, and most recently was measured at 654 copies/mL

What would you do next for Daniel?

Part 2: Managing Virologic Failure in Different Clinical Scenarios

Overview: Recommended Treatments for Virologic Failure – First Regimen Failure

Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
NNRTI plus 2 NRTIs	Most likely resistant to NNRTI +/3TC/FTC (i.e. NNRTI mutations +/- M184V/I).[c] Additional NRTI mutations may also be present	• Boosted PI plus 2 NRTIs (at least 1 active) **(AIII)**; or • DTG[d] plus 2 NRTIs (at least 1 active) **(AI)**; or • Boosted PI plus INSTI **(AIII)**	Resuppression
Boosted PI plus 2 NRTIs	Most likely no resistance, or resistance only to 3TC/FTC (i.e. M184V/I, without resistance to other NRTIs)[c]	• Continue same regimen **(AII)**; or • Another boosted PI plus 2 NRTIs (at least 1 active) **(AII)**; or • INSTI plus 2 NRTIs (at least 1 active; if only 1 of the NRTIs is fully active, or, if adherence is a concern, DTG[d] is preferred over the other INSTIs) **(AIII)**; or • Another boosted PI plus INSTI **(BIII)**	Resuppression
INSTI plus 2 NRTIs	No INSTI resistance (can have 3TC/FTC resistance, i.e. only M184V/I, usually without resistance to other NRTIs)[c]	• Boosted PI plus 2 NRTIs (at least 1 active) **(AIII)**; or • DTG[d] plus 2 NRTIs (at least 1 active) **(AIII)**; or • Boosted PI plus INSTI **(BIII)**	Resuppression
	EVG or RAL +/- 3TC/FTC resistance Resistance to first-line BIC or DTG is rare	• Boosted PI plus 2 NRTIs (at least 1 active) **(AIII)**; or • DTG[d,e] twice daily (if patient is sensitive to DTG) plus 2 active NRTIs **(AIII)**; or • DTG[d,e] twice daily (if patient is sensitive to DTG) plus a boosted PI **(AIII)** • BIC has not been studied in this setting and **cannot be recommended**	Resuppression

a There are insufficient data to provide a recommendation for the continuation of 3TC/FTC in the presence of M184V/I. **b** When switching an ARV regimen in a patient with HIV/HBV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage. **c** If other NRTI resistance mutations are present, use resistance test results to guide NRTI usage in the new regimen. **d** Preliminary data from Botswana suggested that there is an increased risk of NTDs in infants born to those who were receiving DTG at the time of conception. Pregnancy testing should therefore be performed for those of childbearing potential prior to initiation of DTG. **e** Response to DTG depends on the type and number of INSTI mutations.

BIC, bictegravir; NTD, neural tube defects; Rating of Recommendations: A = Strong; B = Moderate; C = Optional; Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

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Different Mechanism of Action Is Recommended for Second Regimen Failure and Beyond

Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
Drug resistance with active treatment options	Use past and current genotypic +/- phenotypic resistance testing and ART history in designing new regimen	• At least 2, and preferably 3, fully active agents **(AI)** • Partially active drugs may be used when no other options are available • Consider using an ARV with a different mechanism of action	Resuppression
Multiple or extensive drug resistance with few treatment options	Use past and current genotypic and phenotypic resistance testing to guide therapy Consider viral tropism assay if use of MVC is considered Consult an expert in drug resistance, if needed	• Identify as many active or partially active drugs as possible based on resistance test results • Consider using an ARV with a different mechanism of action • Consider enrolment into clinical trials or expanded access programs for investigational agents, if available • Discontinuation of ARVs is not recommended	Resuppression, if possible; otherwise, keeping viral load as low as possible and CD4 cell count as high as possible

a There are insufficient data to provide a recommendation for the continuation of 3TC/FTC in the presence of M184V/I.; **b** When switching an ARV regimen in a patient with HIV/HBV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.

MVC, maraviroc; Rating of Recommendations: A = Strong; B = Moderate; C = Optional; Rating of Evidence: I = One or more randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Panel on Antiretroviral Guidelines for Adults and Adolescents.

An Overview of the Data in Treatment-Experienced Patients

Agent	Study	Week 24	Week 48	First line failure	2nd line failure & Beyond
ENF	TORO 1+2[1-3]	16	18	√	√
DTG	VIKING-44[4]	47	40	√	√
IBA	TMB-301, TMB-311[5,6]	43	59*		√
DRV/r	POWER 1+2[7]	45	45	√	√
RAL	BENCHMRK 1+2[8]	62	62	√	√
ETR	DUET 1+2[9]	61	61	√	√
MVC	MOTIVATE 1+2[10]	45	47	√	√

*Completer analysis

ALT, alanine transaminase; AST, aspartate aminotransferase; VL, viral load

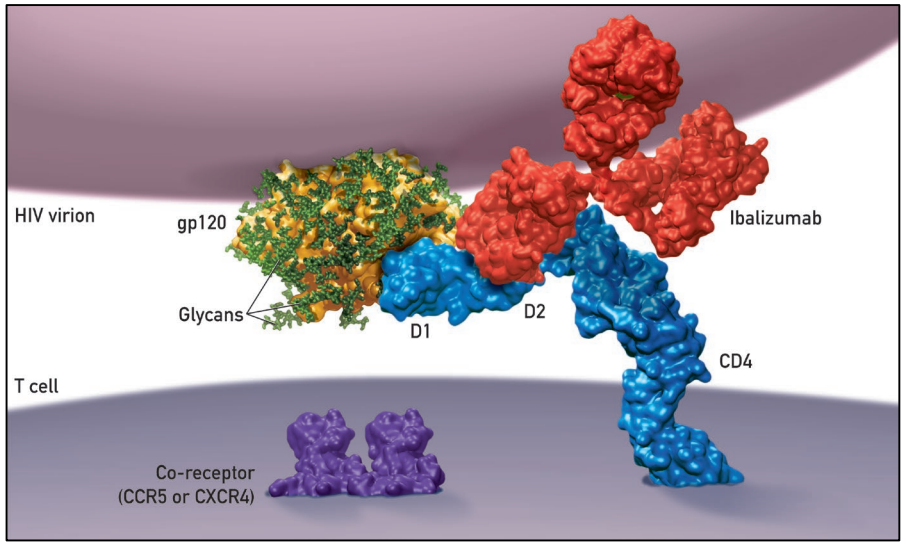
1. Nelson M, et al. *J Acquir Immune Defic Syndr* 2005;40(4):404-412. 2. Lalezari JP, et al. N *Engl J Med* 2003;348(22):2175-2185. 3. Lazzarin A, et al. *N Engl J Med* 2003;348(22):2186-2195. 4. Akil B, et al. *Antiviral Ther*2015;20(3):343-348. 5. Emu B, et al. *N Engl J Med* 2018;379(7):645-654. 6. Emu B, et al. O345 *JIAS* 2018, 21(S8):e25187. 7. Clotet B, et al. *Lancet* 2007;369(9568):1169-1178. 8. Katlama C, et al. *AIDS* 2009;23(17):2289-2300. 9. Steigbigel RT, et al. *N Engl J Med*

Approved Agents for Treatment-Experienced Patients With Virologic Failure

Ibalizumab Approved Agent for 2nd Line Regimen Failure

ibalizumab – approved by the FDA in March 2018

- Humanized monoclonal antibody (IgG4 backbone) that binds to domain 2 of CD4
- Therapeutic class: CD4-directed post-attachment HIV-1 inhibitor



First long-acting, IV monoclonal antibody approved for HIV

Infusion every 2 weeks dosed for a minimum duration of 15 minutes

- Prevents conformational changes induced by gp120-CD4 interaction via steric hindrance
- gp120 binds CD4 in the presence of ibalizumab

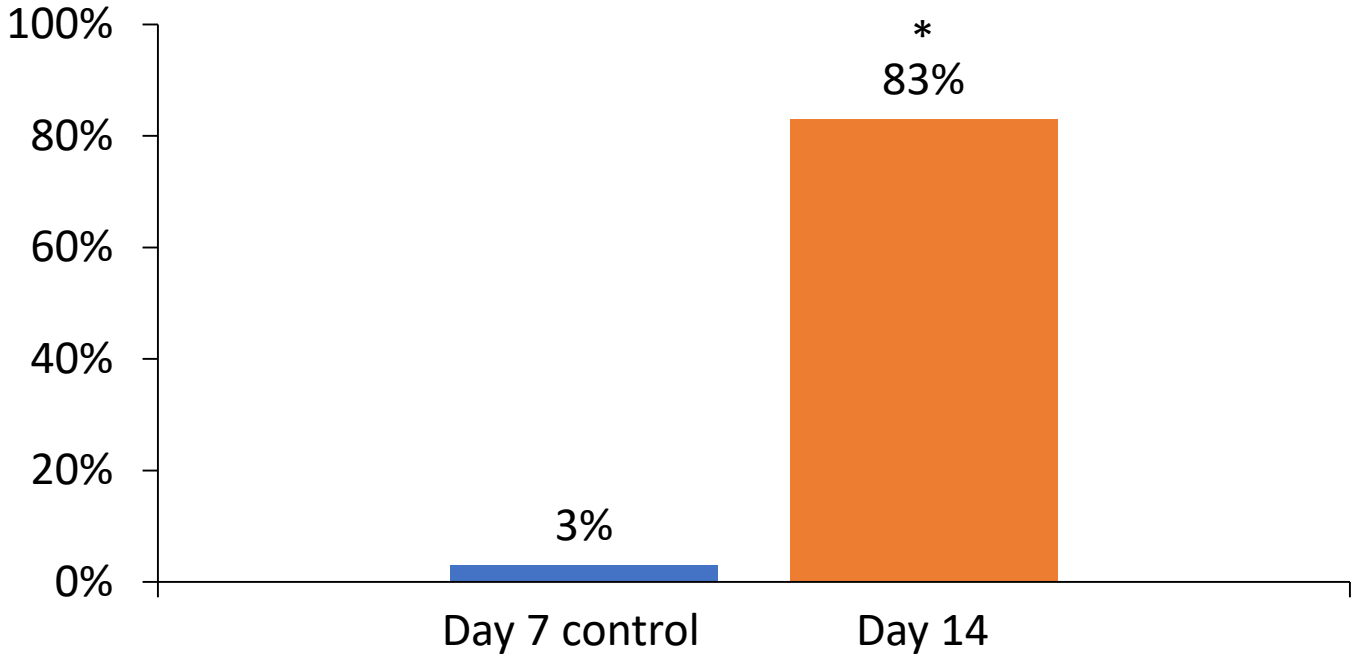
Based on ibalizumab's mechanism of action and target-mediated drug disposition, drug-drug interactions are not expected

Trogarzo (ibalizumab) Prescribing Information, May 2015.

Ibalizumab Demonstrated a Significant Reduction in Viral Load During the Functional Monotherapy Period

24-week Phase 3 study TMB-301

Primary endpoint: Proportion of patients achieving ≥0.5log$_{10}$ decrease in viral load at Day 14



*p<0.0001

Emu B, et al. *N Engl J Med 2018;*379(7):645-654.

Ibalizumab Maintained Viral Suppression Over 25 Weeks in Treatment-Experienced Patients

- Patients began their OBR on Day 14
- Patients received maintenance dose of 800 mg every 2 weeks as of Day 21

	ITT-MEF (N=40)	Completer (N=31)
Mean (± SD) VL reduction	1.7 ± 1.5 $\log_{10}$	2.2 ± 1.4 $\log_{10}$
Median VL reduction	1.8 $\log_{10}$	2.5 $\log_{10}$
Percent with VL<50 copies	43%	55%
Percent with VL<200 copies	50%	65%
Percent with ≥1.0 $\log_{10}$ reduction	58%	74%
Percent with ≥2.0 $\log_{10}$ reduction	48%	61%

OBR, optimized background regimen

Emu B et al. O345 *JIAS* 2018, 21(S8):e25187. Results presented in abstract but not on product label.

All Patients <50 copies/mL at Week 25 Maintained Viral Suppression with Ibalizumab to Week 48

TMB-311:

- Patients received maintenance dose of 800 mg every 2 weeks until Week 48
- Week 48 corresponds to weeks from beginning of ibalizumab dosing in TMB-301

	ITT-MEF (N=27)	Completer (N=24)
Mean (± SD) VL reduction	2.1 ± 1.6 $\log_{10}$	2.3 ± 1.4 $\log_{10}$
Median VL reduction	2.8 $\log_{10}$	2.9 $\log_{10}$
Percent with VL<50 copies	59%	67%
Percent with VL<200 copies	59%	67%
Percent with ≥1.0 $\log_{10}$ reduction	67%	75%
Percent with ≥2.0 $\log_{10}$ reduction	59%	67%

Emu B, et al. O345 *JIAS* 2018, 21(S8):e25187. Results presented in abstract but not on product label.

Patients Maintained Viral Suppression to Week 96

Efficacy:

- At Week 96,

56% (15 of 27) had VL <50 copies/mL

2.8 log_{10} Median VL reduction from baseline (of TMB-301)

Safety:

- Treatment-related adverse reactions – mild to moderate
- No safety concerns emerged between Week 25 and 96
- No patient developed anti-ibalizumab antibodies

TMB-311 expanded access: Week 96* safety, efficacy results

- Patients (n=27) who completed Week 25 in Study TMB-301 were enrolled
- Patients continued to receive 800 mg every 2 weeks until Week 96
- 22 of 27 (82%) completed study to Week 96

* Week 96 corresponds to weeks from beginning of ibalizumab dosing in TMB-301

Emu B, et al. CROI 2019, Abstract #485. Results presented in abstract but not on product label.

Revisiting Daniel …

- First-line treatment: ddI/3TC/TDF/ABC
- Second-line treatment: T20, LPV/r and 3TC/ABC/ZDV
- Third-line treatment: DRV/r/ETR/DTG BID (600/100/200/50 mg), FTC/TAF QD and ZDV QD (300 mg)

- Daniel was started on ibalizumab (2000 mg followed by 800 mg Q2WK) as well as DTG 50 mg BID, doravirine 100 mg QD, and FTC/TAF 200/25 mg QD

- He is getting infused at home, and he prefers it over previous treatment

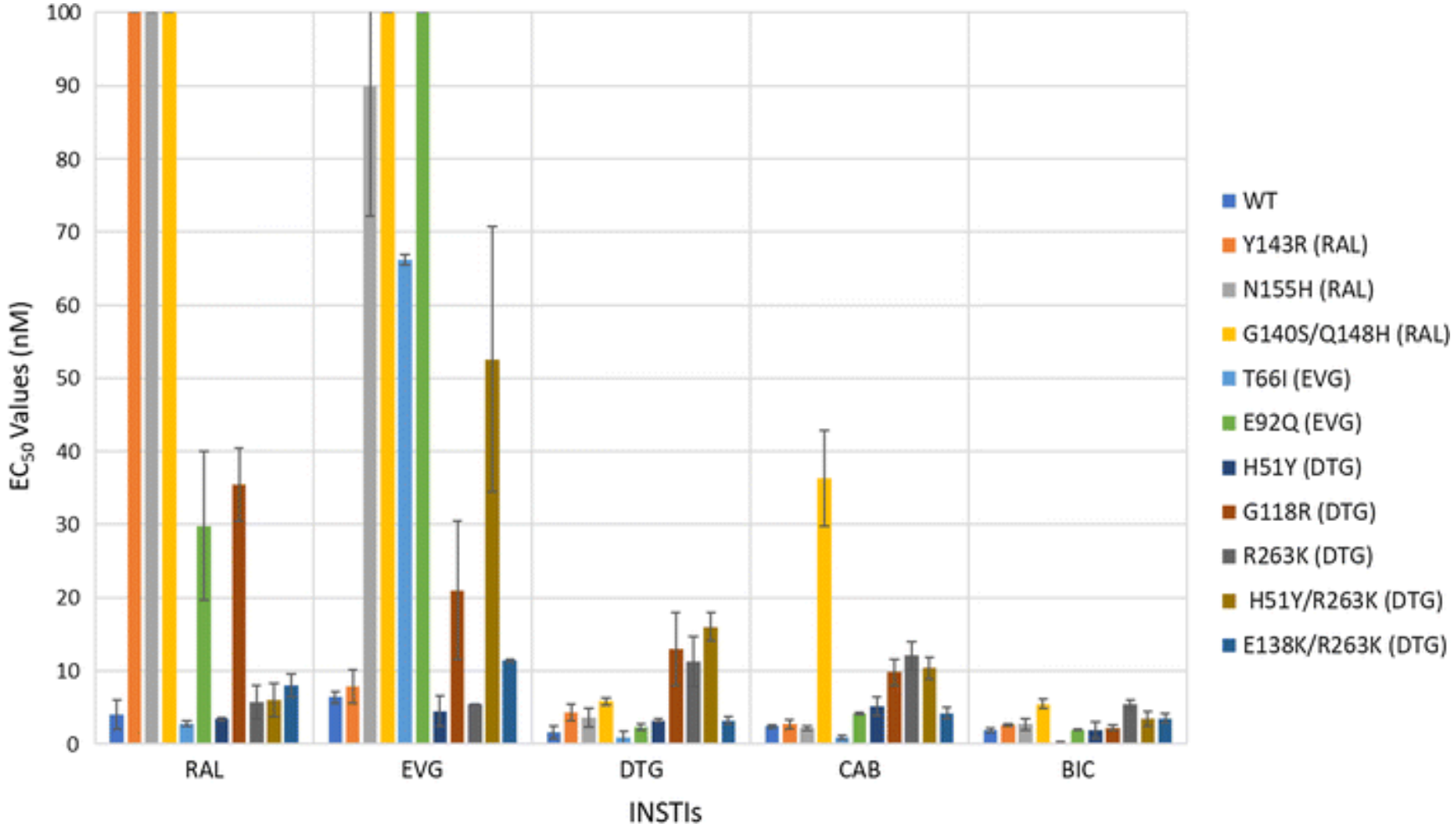
- He has been on this new regimen for a month:
  - His GI side effects have resolved
  - His blood sugar is better controlled
  - He feels better, his VL decreased to 30 copies/mL, and CD4 increased to 560

What does the future look like for treatment-experienced patients with HIV?

Cabotegravir

- INSTI in phase III development for treatment and prevention
- Potentially will be available in both oral and injection formulations
- In vitro data suggests it may not be susceptible to common INSTI resistance mutations/pathways
- ATLAS and FLAIR are the ongoing trials

Cabotegravir



Smith et al Retrovirology 2018

Doravirine

- FDA Approved in 2018
- Metabolized by CYP(3A)
- Available as single tablet or combination
- Has activity against other common NNRTI resistance mutations

TABLE 1

Resistance selection with DOR, EFV, and RPV in subtype B virus using MT4-GFP cells in the presence 10% FBS

NNRTI	Pathway	Evolution of mutants as NNRTI concn increases[a]
DOR	1	V106A → V106A/F227L
		(9.6 ± 1.8) (>2,000)
	2	V106A → V106A/L234I → V106A/L234I/F227L
		(9.6 ± 1.8) (173 ± 17.5) (>2,000)
EFV	1	L100I → L100I/K103N
		(16 ± 0.6) (>2,000)
	2	L100I → L100I/V179D → L100I/V179D/P225H or M230L
		(16 ± 0.6) (76 ± 15) (465 ± 127)
	3	K103N → K103N/L100I
		(58 ± 13) (>2,000)
RPV	1	E138K → E138K/L100I → E138K/L100I/V179I
		(3.8 ± 0.6) (2.0 ± 0.01) (8.7 ± 3.8)
	2	E138K → E138K/V106A
		(3.8 ± 0.6) (8.1 ± 2.1)
	3	K101P → K101P/V179I
		(40 ± 18) (199 ± 40)

Adventures in the Therapeutic Alliance

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