

Management of NRTI Resistance

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Disclosures

Dr. Spach has no disclosures.

NRTI Resistance: Outline

- M184V Mutation

- K65R Mutation

- Thymidine Analog Mutations (TAMs)

Managing the M184V

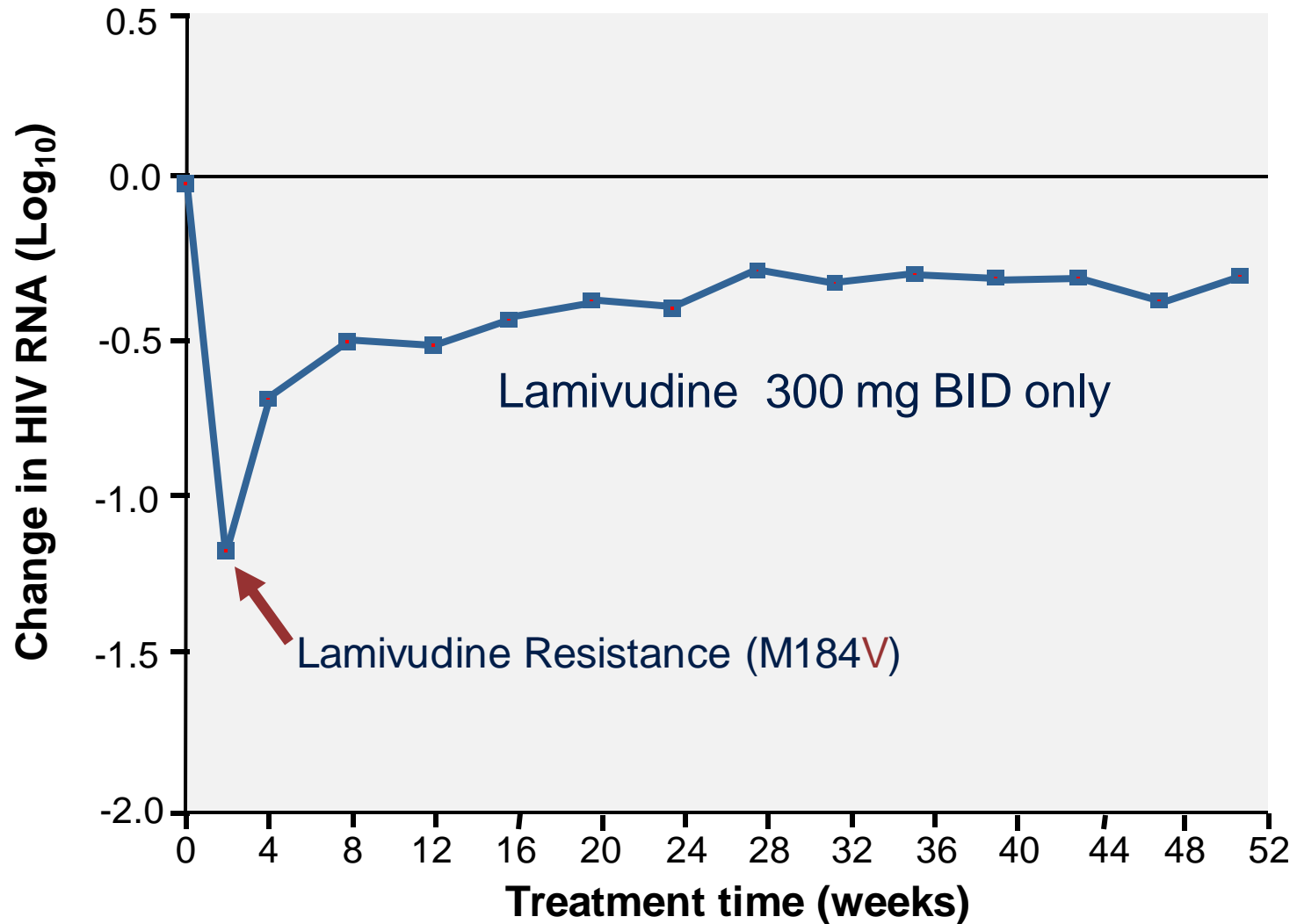
Case History

- A 27-year-old woman develops virologic failure while taking rilpivirine- tenofovir DF-emtricitabine (*Complera*). The most recent HIV RNA level was 2,340 copies/mL. A drug resistance genotype shows M184V and E138Q mutations.
- **In constructing a new antiretroviral regimen, what would you recommend?**
 - One that maintains the M184V?
 - Switch backbone to Abacavir-Lamivudine?
 - 3-drug regimen? or 4-drug regimen?

Maintaining M184V?

Response to Lamivudine Monotherapy

HIV RNA Levels Before and After M184V Mutation



Source: Eron JJ, et al. N Engl J Med 1995;333:1662-9.



Impact of M184V/I Mutation on NRTIs

Stanford HIV Drug Resistance Database Mutation Scoring: RT

| NRTI | ABC | AZT | FTC | 3TC | TAF/TDF |
|----------------|-----------|------------|-----------|-----------|------------|
| M184V/I | 15 | -10 | 60 | 60 | -10 |
| Total | 15 | -10 | 60 | 60 | -10 |

Wild-Type HIV-1: NRTIs

Wild-Type HIV-1

Tenofovir

Zidovudine

Abacavir

Lamivudine

Emtricitabine

Increased
Susceptibility

Wild-Type HIV-1

Low-Level
Resistance

High-Level
Resistance

Impact of M184V/I Mutation on NRTIs

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Switch Backbone to Abacavir-Lamivudine?

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Low-Level
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Use 3- or 4-Drug Regimen?

Switching to Bictegravir-TAF-FTC with Archived M184V Studies 1844 and 1878: Design

Gilead: Analysis of Switch Studies

- **Background:** Preexisting resistance data were assessed from 2 studies that switched adult with suppressed HIV RNA levels for ≥ 6 months to bictegravir-tenofovir alafenamide-emtricitabine (BIC-TAF-FTC) versus continuing regimen
- **Analysis for Resistance Criteria**
 - Historical genotypes
 - Retrospective proviral archived DNA genotype
 - Resistance data obtained for 95% (543/570) of participants who switched to BIC-TAF-FTC

Switch
Bictegravir-TAF-FTC

Maintain Initial Regimen
1844: Dolutegravir + ABC-3TC
1878: Boosted PI* + 2NRTIs

*56% boosted Darunavir

Switching to Bictegravir-TAF-FTC with Archived M184V Studies 1844 and 1878: Key Points

- Baseline M184V/I in 10% of switch group (BIC-TAF-FTC)
- 96% (52/54) with archived M184V had HIV RNA <50 copies/mL for up to 48 weeks ON BIC-TAF-FTC

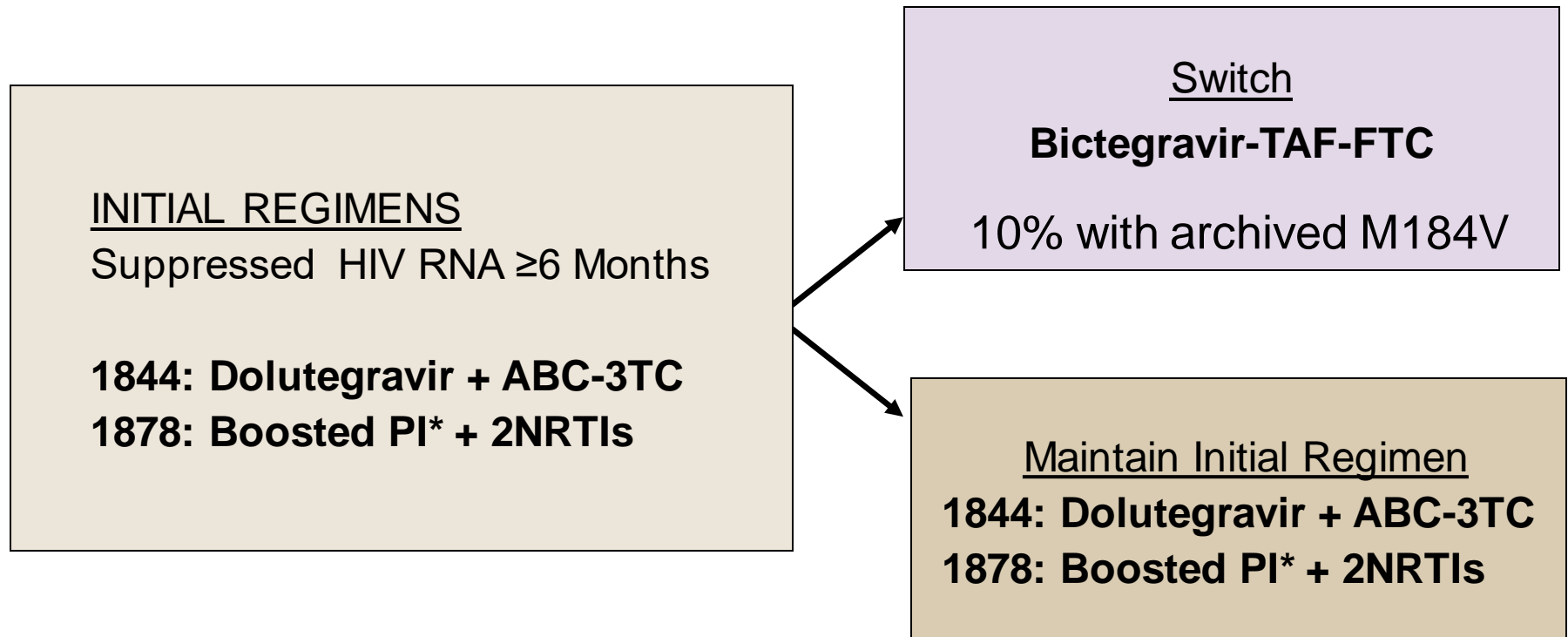
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- **CONCLUSION**

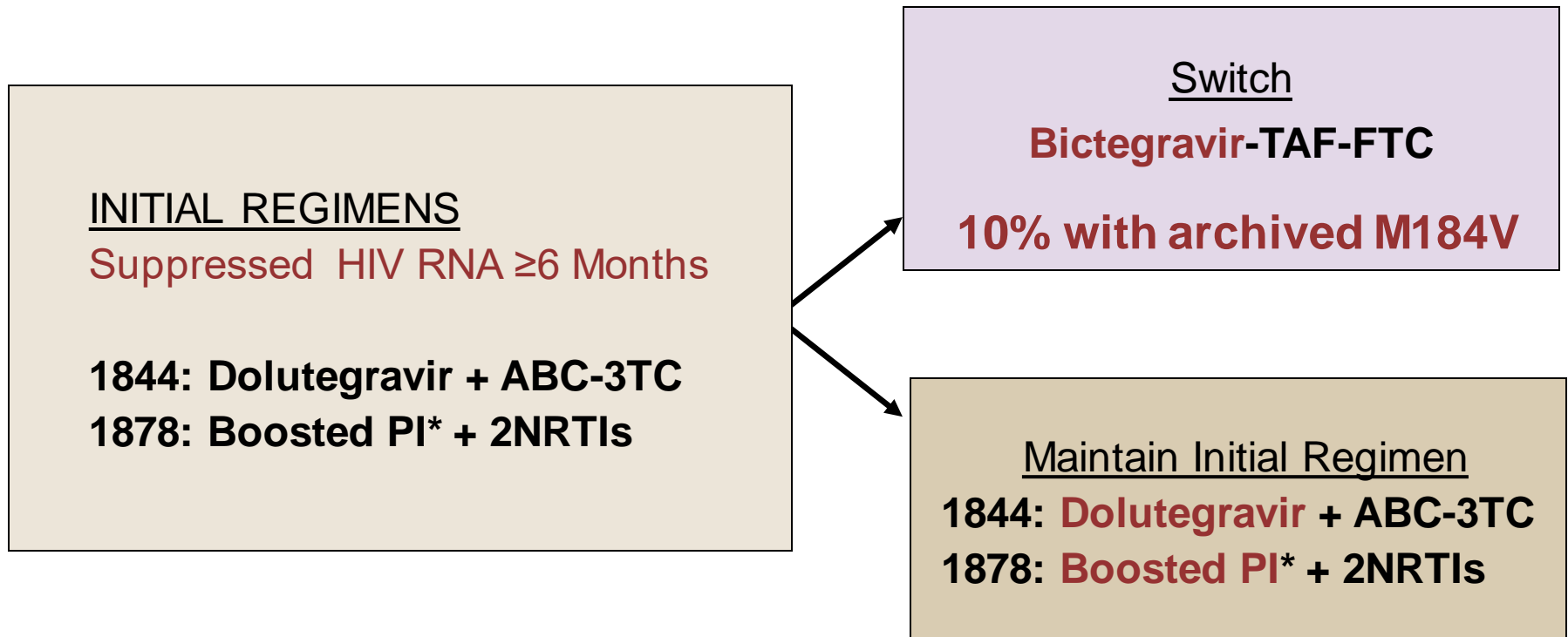
BIC/TAF/FTC is an effective treatment option for suppressed patients with evidence of archived M184V

Switching to Bictegravir-TAF-FTC with Archived M184V Studies 1844 and 1878: Design



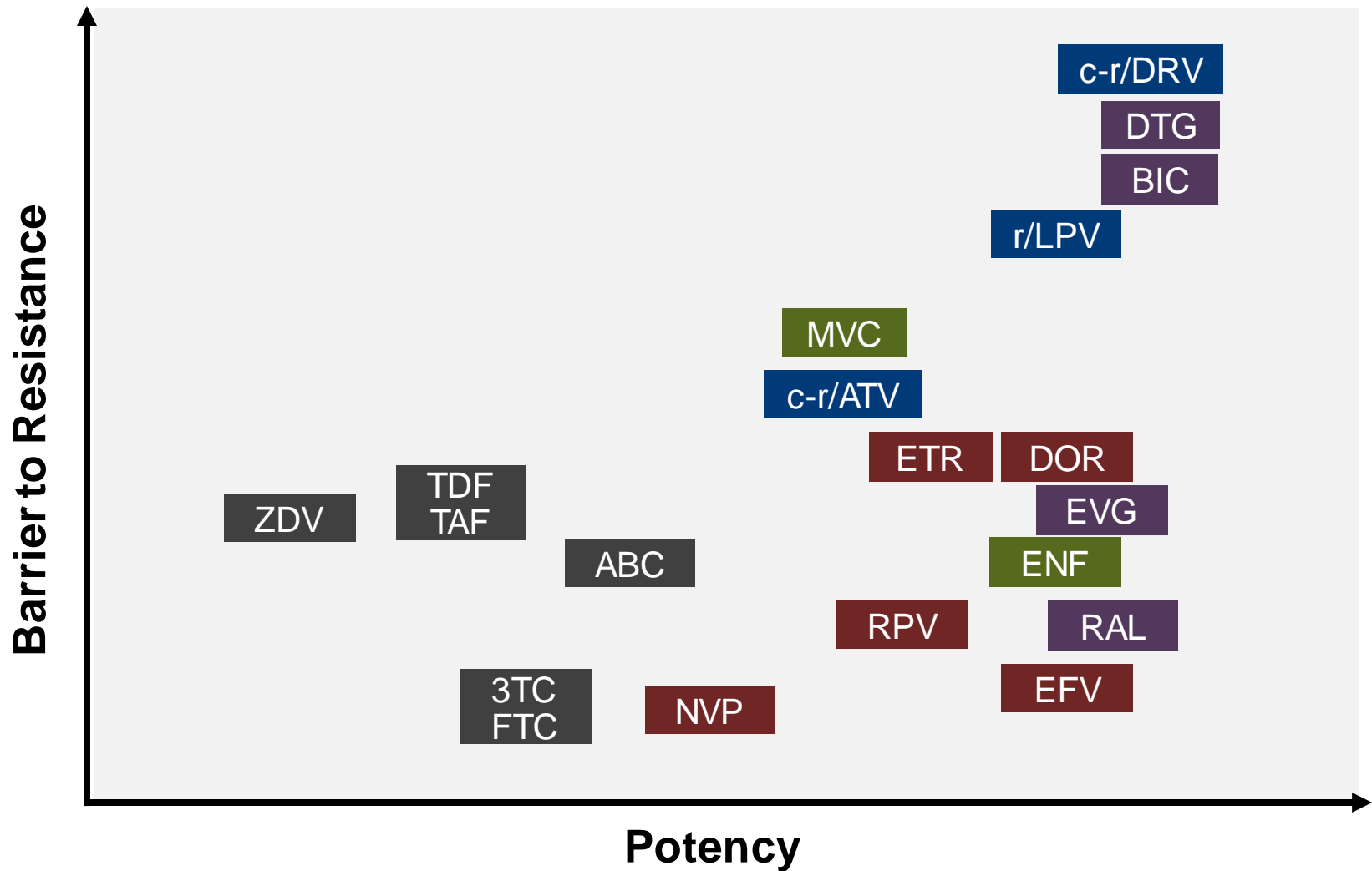
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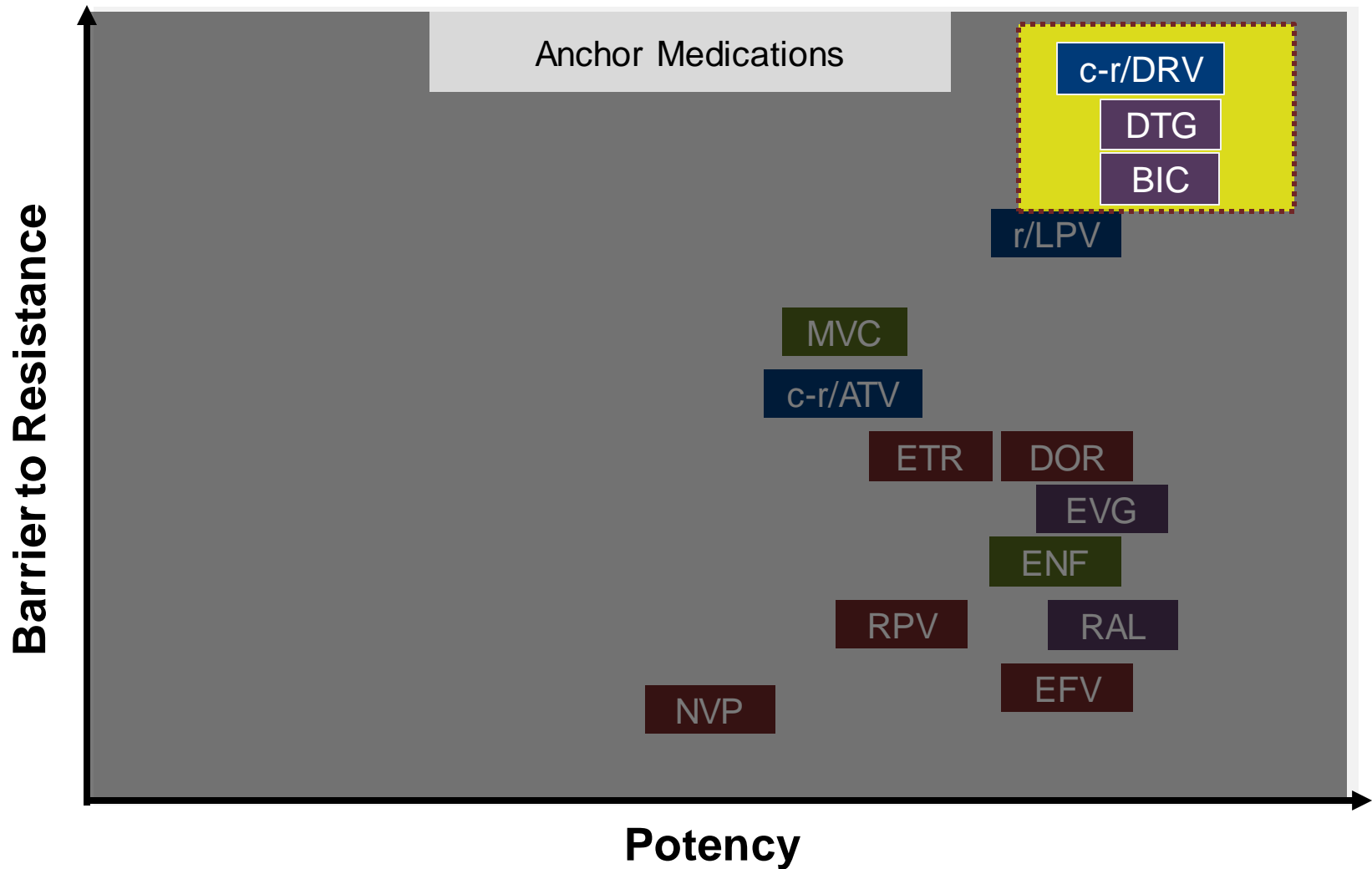
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Potency and Genetic Barrier to Resistance



Modified from: Tang MW, Shafer RW. *Drugs*. 2012;72:e1-e25.

Potency and Genetic Barrier to Resistance



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K65R

Case History

- A 32-year-old man presents after acquiring HIV while on PrEP (Tenofovir DF-Emtricitabine). An initial genotype shows K65R and M184V mutations.
- **How would you manage this?**

K65R Mutation Score

Stanford HIV Drug Resistance Database Mutation Scoring: RT

| RT | ABC | AZT | FTC | 3TC | TAF/TDF |
|--------------|-----------|------------|-----------|-----------|-----------|
| K65R | 45 | -15 | 30 | 30 | 60 |
| Total | 45 | -15 | 30 | 30 | 60 |

K65R

K65R

Zidovudine

Tenofovir

Abacavir

Lamivudine

Emtricitabine

Increased
Susceptibility

Wild-Type HIV-1

Low-Level
Resistance

High-Level
Resistance

M184V/I + K65R Mutation Score

Stanford HIV Drug Resistance Database Mutation Scoring: RT

| RT | ABC | AZT | FTC | 3TC | TAF/TDF |
|--------------|-----------|------------|-----------|-----------|-----------|
| K65R | 45 | -15 | 30 | 30 | 60 |
| M184V | 15 | -10 | 60 | 60 | -10 |
| Total | 60 | -25 | 90 | 90 | 50 |

K65R + M184V

K65R + M184V/I

Zidovudine

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Resistance

High-Level
Resistance

Treatment Options with K65R + M184V

- Dolutegravir-Rilpivirine
- Dolutegravir + Boosted-PI
- 4-Drug Regimen (2NRTIs + INSTI + boosted-PI)
- Regimen that includes zidovudine (AZT)

TAMs

Case History

- A 58-year-old man presents as a new patient to the clinic after recently moving. He has a long history of taking antiretroviral therapy, beginning in the early 1990s. He has been off antiretroviral therapy for 6 months.
- The most recent genotype shows the following mutations:
RT: M41L, K103N, Y181C, M184V, L210W, T215Y
Protease: D30N, I54L, and L90M
- **What is the significance of the RT mutations M41L, L210W, and T215?**

Thymidine Analog Mutations (TAMs)

Thymidine Analogs

Zidovudine

Stavudine

Thymidine Analog Mutations

M41L

D67N

K70R

L210W

T215YF

K219QE

M184V/I and Multiple TAMs (M41L, L210W, T215Y)

Stanford HIV Drug Resistance Database Mutation Scoring: RT

| RT | ABC | AZT | FTC | 3TC | TAF/DF |
|----------------------|-----------|-----------|-----------|-----------|-----------|
| M41L | 5 | 15 | 0 | 0 | 5 |
| M184V | 15 | -10 | 60 | 60 | -10 |
| L210W | 5 | 15 | 0 | 0 | 5 |
| T215Y | 10 | 40 | 0 | 0 | 10 |
| M41L + T210W | 10 | 10 | 0 | 0 | 10 |
| M41L + T215Y | 15 | 10 | 5 | 5 | 10 |
| T210W + T215Y | 10 | 10 | 5 | 5 | 10 |
| M41L + T210W + T215Y | 5 | 0 | 5 | 5 | 5 |
| Total | 75 | 90 | 75 | 75 | 45 |

Source: Stanford University: HIV Drug Resistance Database



M184V/I and Multiple TAMs

M184V/I + 3TAMs (M41L, L210W, T215Y)

Tenofovir

Zidovudine

Abacavir

Lamivudine

Emtricitabine

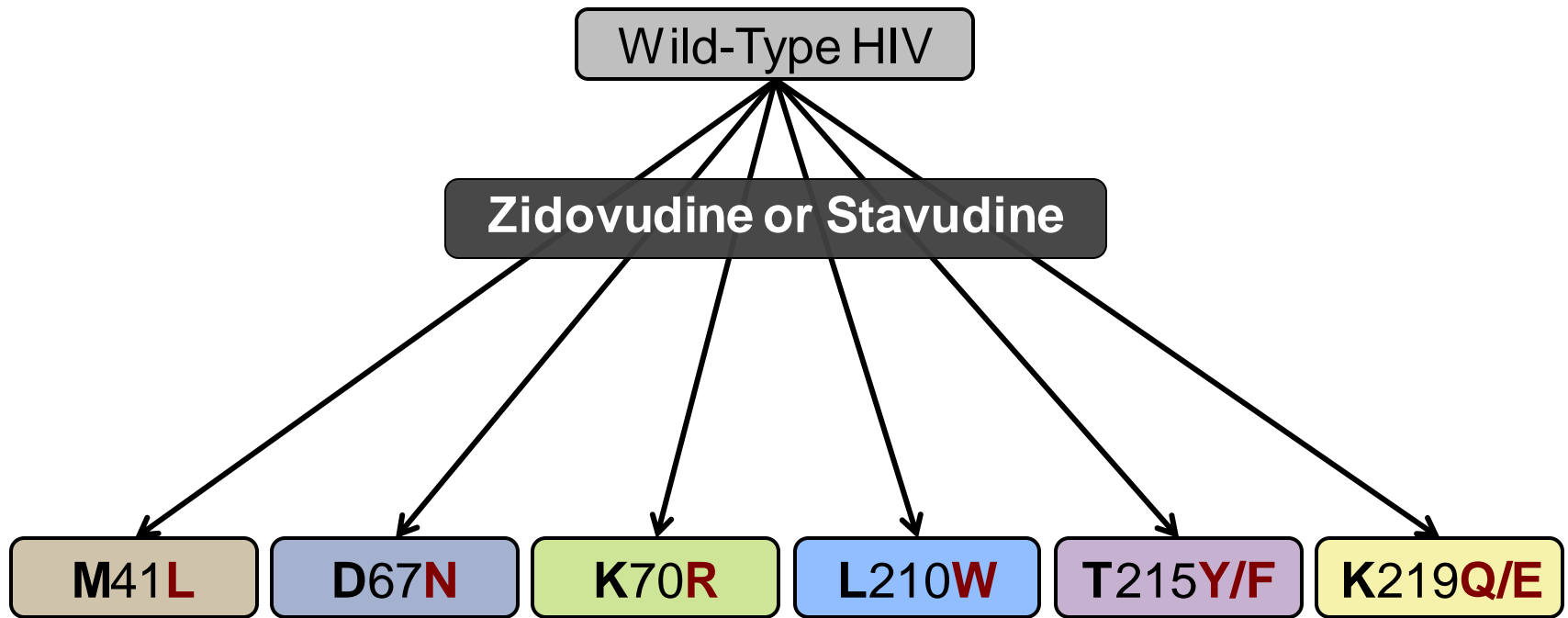
Increased
Susceptibility

Wild-Type HIV-1

Low-Level
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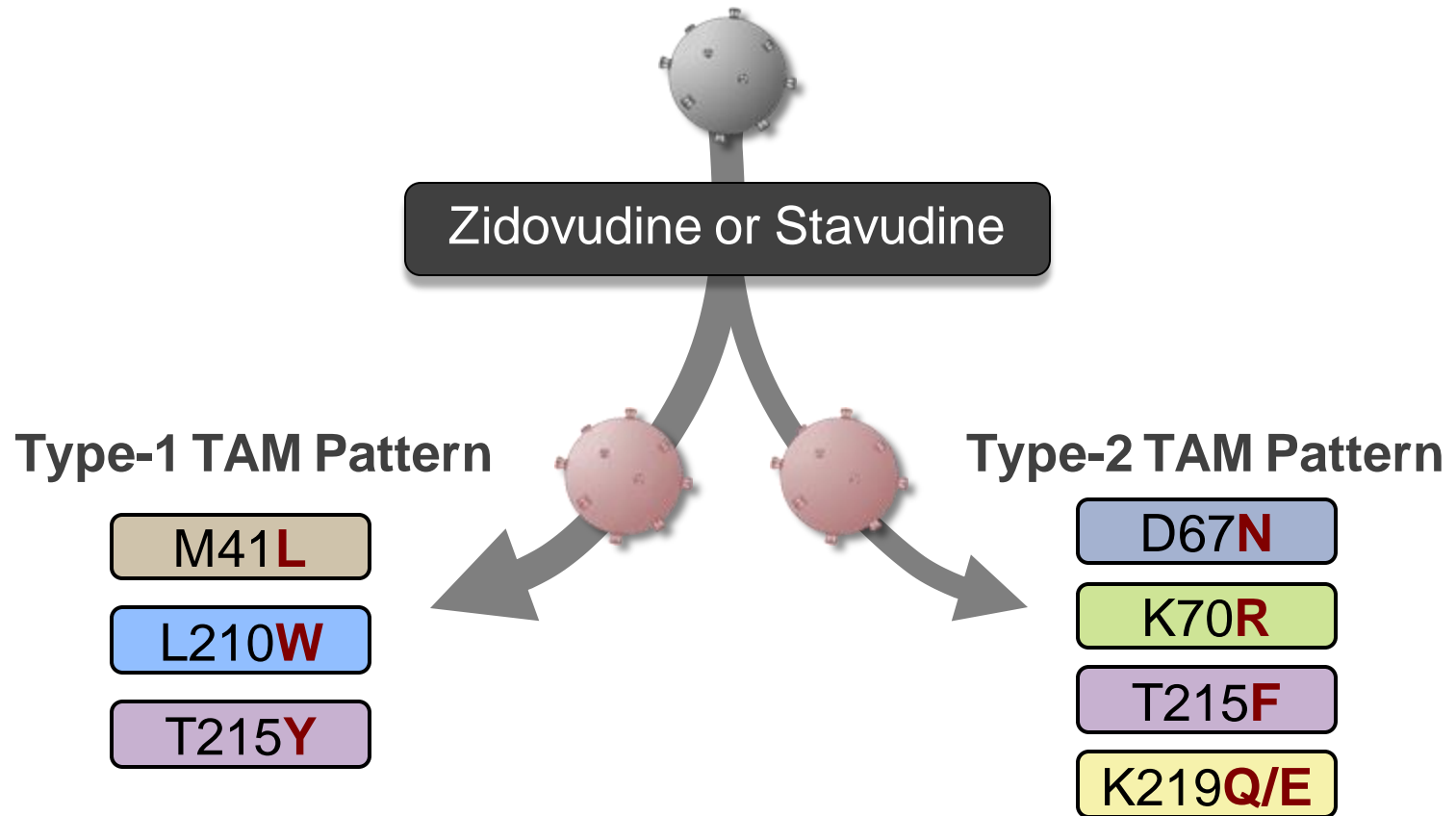
High-Level
Resistance

Thymidine Analog Mutations (TAMs)

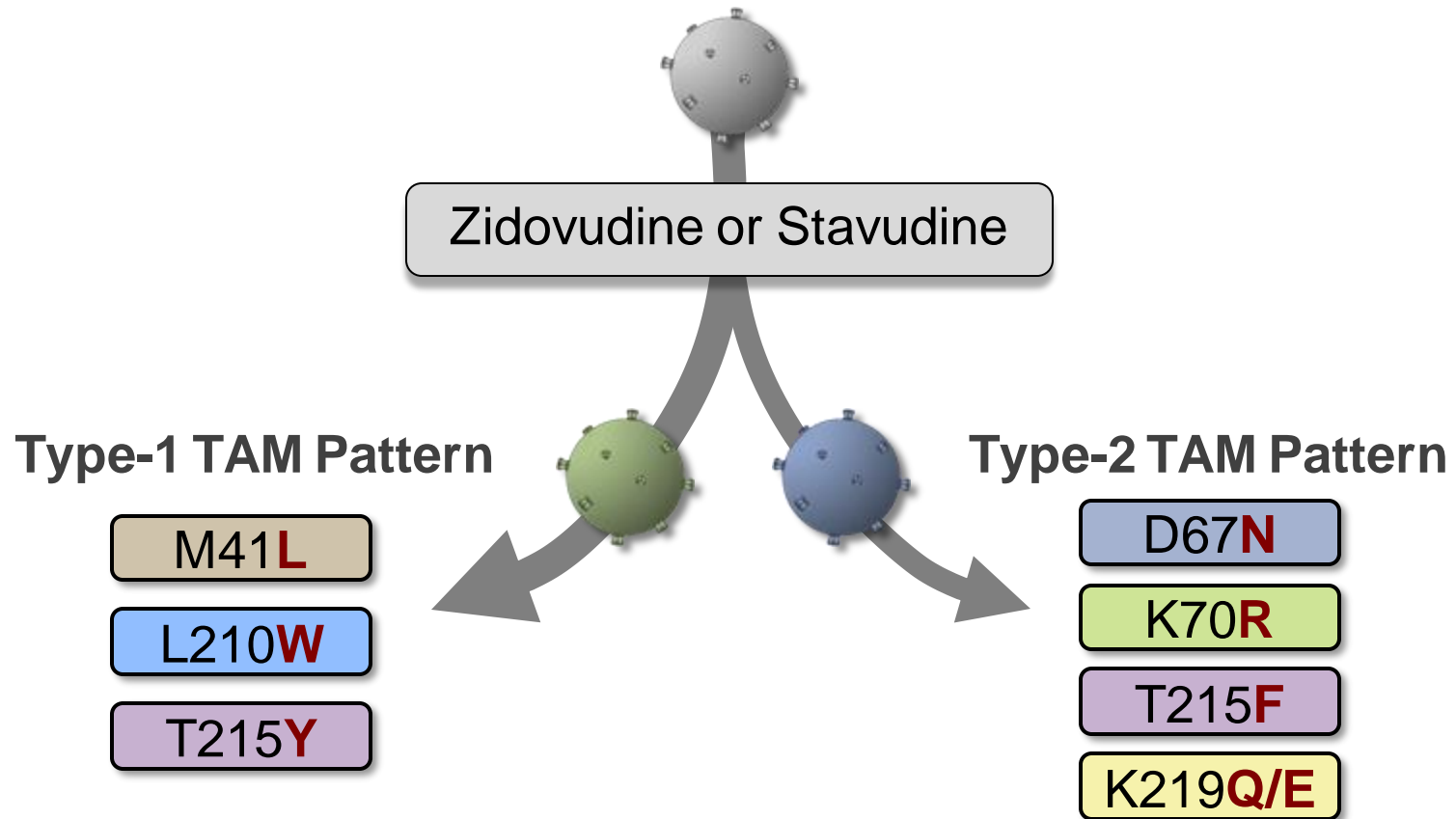


Thymidine Analog Mutations (TAMs)

Distinct TAM Pathways to Resistance



Distinct TAM Pathways to Resistance



Higher level of zidovudine resistance
Higher level NRTI cross-resistance
Less decrease in resistance with M184V

Lower level of zidovudine resistance
Lower level of NRTI cross-resistance
More decrease in resistance with M184V

Questions?

Acknowledgment

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