

Adult clinical cases

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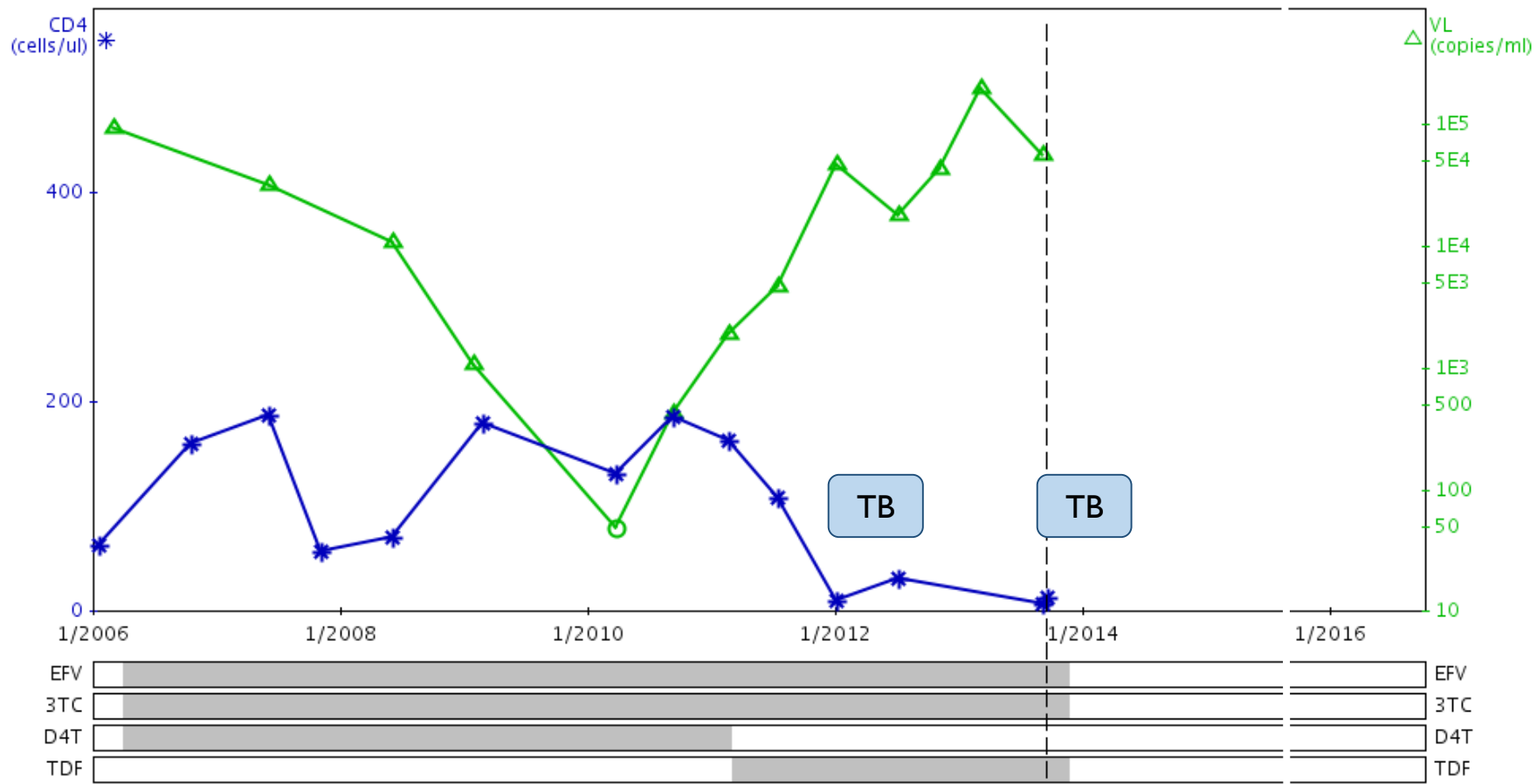


ANNUAL WORKSHOP ON ADVANCED CLINICAL CARE - AIDS

Disclosure

- In relation to this presentation, I have no actual or potential conflict of interest

Adult clinical case I



Hyperlactataemia

In the absence of resistance testing, which second-line regimen would you use?

- A. TDF/FTC/LPV_r
- B. AZT/3TC/LPV_r
- C. ABC/3TC/LPV_r
- D. AZT/3TC/TDF/LPV_r
- E. AZT/3TC/ATV/r

Genotypic resistance test report

Antiretroviral experience: d4T, 3TC, TDF, EFV
Subtype: HIV-1 Subtype C
Resistance interpretations: HIVdb 8.1.1

| Drug | Mutations | Description | Level | Score |
|---------------|-------------------------------|--------------------------------|-------|-------|
| Zidovudine | M41L, A62V, K65R, V75I, M184V | Susceptible | 1 | 0 |
| Didanosine | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 90 |
| Lamivudine | M41L, K65R, V75I, M184V | High-level resistance | 5 | 100 |
| Stavudine | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 75 |
| Abacavir | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 75 |
| Emtricitabine | M41L, K65R, V75I, M184V | High-level resistance | 5 | 100 |
| Tenofovir | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 65 |
| Nevirapine | K013N, V106M, E138G | High-level resistance | 5 | 130 |
| Efavirenz | K013N, V106M, E138G | High-level resistance | 5 | 130 |
| Etravirine | K013N, V106M, E138G | Potential low-level resistance | 2 | 10 |
| Lopinavir/r | - | Susceptible | 1 | 0 |
| Atazanavir/r | - | Susceptible | 1 | 0 |
| Darunavir/r | - | Susceptible | 1 | 0 |

Genotypic resistance test report

Mutations

Individual mutations associated with resistance/susceptibility for each drug

Level 1-5

Higher score – higher level of resistance

Corresponds to description, e.g. 1=Susceptible, 5=High-level resistance

Score

Higher score - higher level of resistance (0 = susceptible)

| Drug | Mutations | Description | Level | Score |
|---------------|-------------------------------|--------------------------------|-------|-------|
| Zidovudine | M41L, A62V, K65R, V75I, M184V | Susceptible | 1 | 0 |
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| Lamivudine | M41L, K65R, V75I, M184V | High-level resistance | 5 | 100 |
| Stavudine | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 75 |
| Abacavir | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 75 |
| Emtricitabine | M41L, K65R, V75I, M184V | High-level resistance | 5 | 100 |
| Tenofovir | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 65 |
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| Etravirine | K013N, V106M, E138G | Potential low-level resistance | 2 | 10 |
| Lopinavir/r | - | Susceptible | 1 | 0 |
| Atazanavir/r | - | Susceptible | 1 | 0 |
| Darunavir/r | - | Susceptible | 1 | 0 |

Genotypic resistance test report

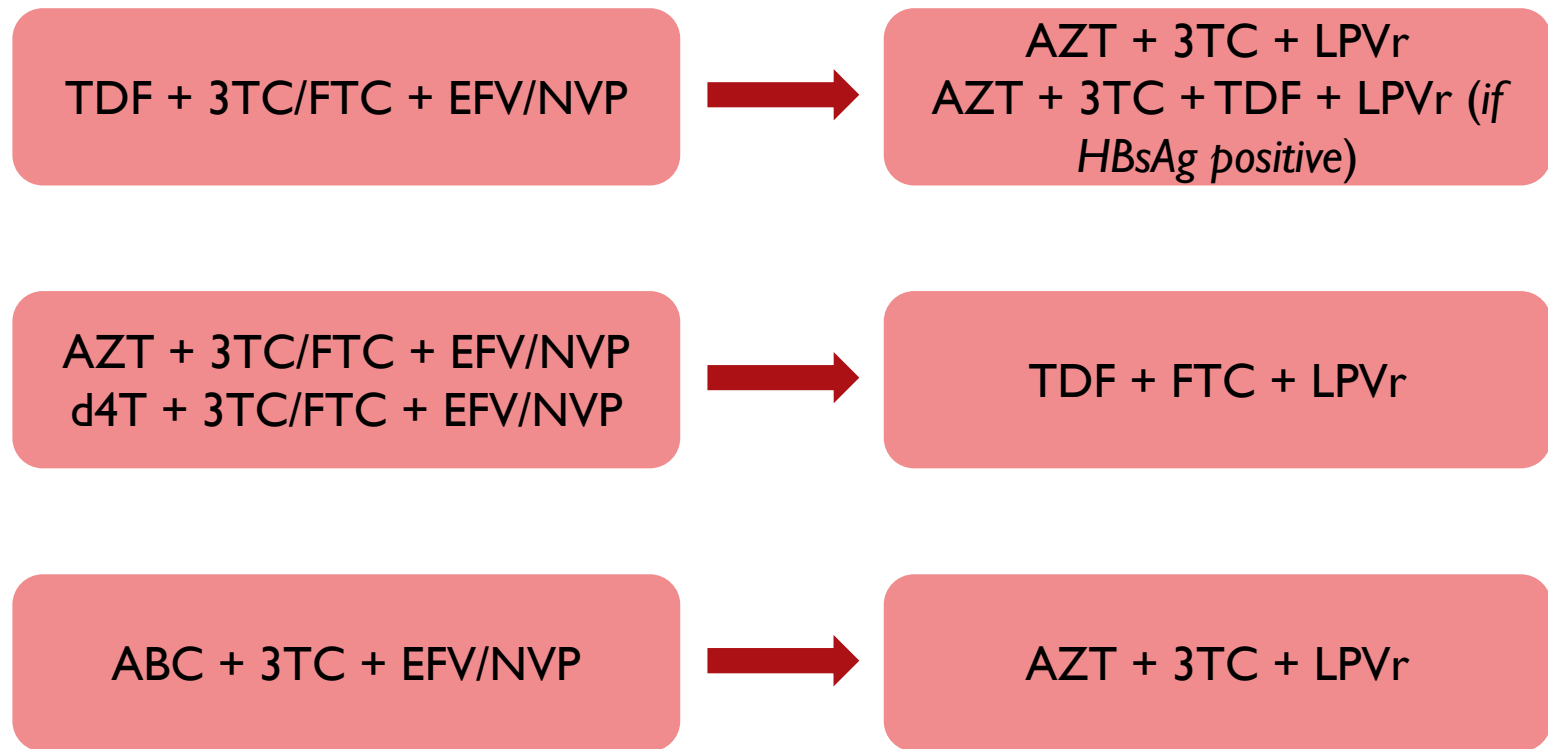
Antiretroviral experience: d4T, 3TC, TDF, EFV
Subtype: HIV-1 Subtype C
Resistance interpretations: HIVdb 8.1.1

| Drug | Mutations | Description | Level | Score |
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| Zidovudine | M41L, A62V, K65R, V75I, M184V | Susceptible | 1 | 0 |
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| Lamivudine | M41L, K65R, V75I, M184V | High-level resistance | 5 | 100 |
| Stavudine | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 75 |
| Abacavir | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 75 |
| Emtricitabine | M41L, K65R, V75I, M184V | High-level resistance | 5 | 100 |
| Tenofovir | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 65 |
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| Etravirine | K013N, V106M, E138G | Potential low-level resistance | 2 | 10 |
| Lopinavir/r | - | Susceptible | 1 | 0 |
| Atazanavir/r | - | Susceptible | 1 | 0 |
| Darunavir/r | - | Susceptible | 1 | 0 |

With the results of the resistance test, which second-line regimen would you use?

- A. TDF/FTC/LPV_r
- B. AZT/3TC/LPV_r
- C. ABC/3TC/LPV_r
- D. AZT/3TC/TDF/LPV_r
- E. AZT/3TC/ATV/r

Choice of second-line ART regimens



The guidelines do not explicitly cover what to do for people exposed to both TDF and thymidine analogue (AZT or d4T)

Genotypic resistance test report

Antiretroviral experience: d4T, 3TC, TDF, EFV
Subtype: HIV-1 Subtype C
Resistance interpretations: HIVdb 8.1.1

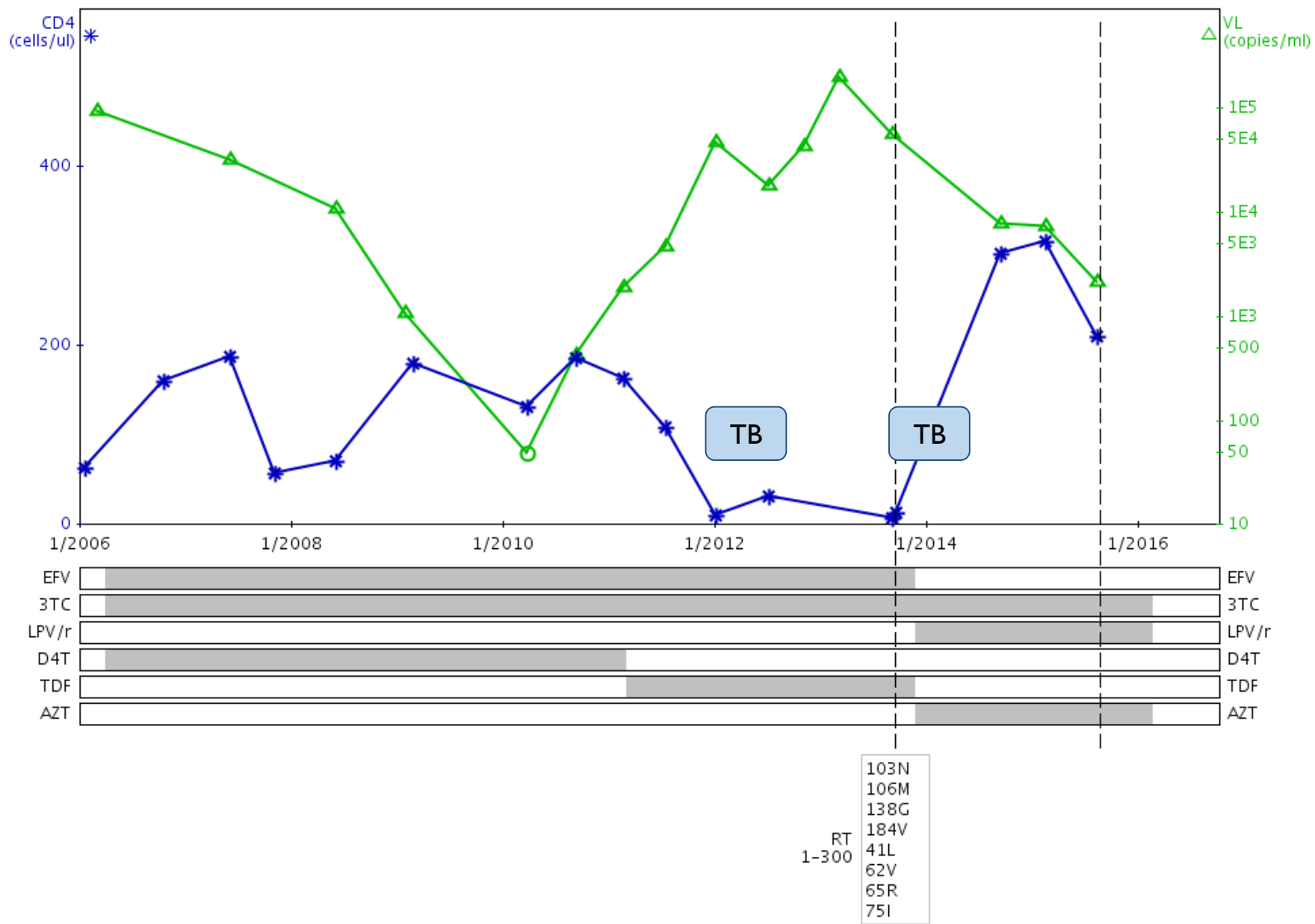
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| Lamivudine | M41L, K65R, V75I, M184V | High-level resistance | 5 | 100 |
| Stavudine | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 75 |
| Abacavir | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 75 |
| Emtricitabine | M41L, K65R, V75I, M184V | High-level resistance | 5 | 100 |
| Tenofovir | M41L, A62V, K65R, V75I, M184V | High-level resistance | 5 | 65 |
| Nevirapine | K013N, V106M, E138G | High-level resistance | 5 | 130 |
| Efavirenz | K013N, V106M, E138G | High-level resistance | 5 | 130 |
| Etravirine | K013N, V106M, E138G | Potential low-level resistance | 2 | 10 |
| Lopinavir/r | - | Susceptible | 1 | 0 |
| Atazanavir/r | - | Susceptible | 1 | 0 |
| Darunavir/r | - | Susceptible | 1 | 0 |

Which of the following mutations increase susceptibility to AZT?

- A. M184V
- B. K65R
- C. M41L
- D. M184V & K65R
- E. None of the above

Hypersusceptibility

- The presence of certain mutations render the virus more susceptible to specific drugs
- e.g. K65R and M184V lead to AZT hypersusceptibility by partially preventing the excision of incorporated AZT
- Hypersusceptibility may be associated with improved virological response, but not clear how this should be incorporated into treatment strategies



What is the recommended dose of lopinavir/ritonavir for adults taking rifampicin?

- A. 400/100mg bd
- B. 400/200mg bd
- C. 800/100mg bd
- D. 800/200mg bd
- E. 400/400mg bd

Genotypic resistance test report

Antiretroviral experience: d4T, 3TC, TDF, AZT, EFV, LPVr
Subtype: HIV-1 Subtype C
Resistance interpretations: HIVdb 8.1.1

| Drug | Mutations | Description | Level | Score |
|---------------|------------------------------------|-------------------------|-------|-------|
| Zidovudine | M41L, A62V, V75I, M184V, T215Y | High-level resistance | 5 | 65 |
| Didanosine | M41L, A62V, V75I, M184V, T215Y | Intermediate resistance | 4 | 55 |
| Lamivudine | M41L, V75I, M184V, T215Y | High-level resistance | 5 | 75 |
| Stavudine | M41L, A62V, V75I, M184V, T215Y | High-level resistance | 5 | 65 |
| Abacavir | M41L, A62V, V75I, M184V, T215Y | Intermediate resistance | 4 | 50 |
| Emtricitabine | M41L, V75I, M184V, T215Y | High-level resistance | 5 | 75 |
| Tenofovir | M41L, A62V, V75I, M184V, T215Y | Low-level resistance | 3 | 25 |
| Nevirapine | K013N | High-level resistance | 5 | 60 |
| Efavirenz | K013N | High-level resistance | 5 | 60 |
| Etravirine | K013N | Susceptible | 1 | 0 |
| Lopinavir/r | L10F, M46I, I54V, A71V, L76V, V82A | High-level resistance | 5 | 120 |
| Atazanavir/r | L10F, M46I, I54V, A71V, L76V, V82A | High-level resistance | 5 | 60 |
| Darunavir/r | L10F, M46I, I54V, A71V, V82A | Low-level resistance | 3 | 25 |

Cumulative resistance test results

Combined results from two genotypic resistance tests

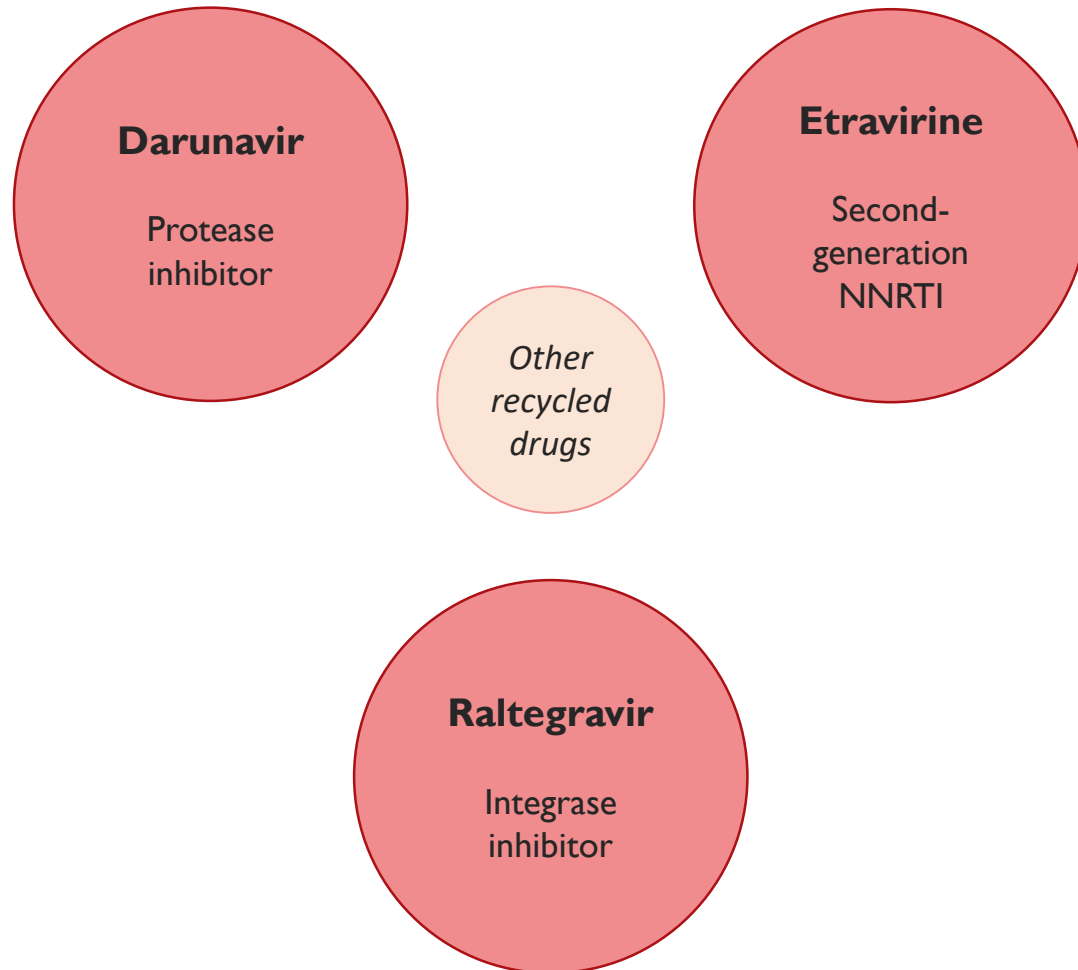
Antiretroviral experience: d4T, 3TC, TDF, AZT, EFV, LPVr
 Subtype: HIV-1 Subtype C
 Resistance interpretations: HIVdb 8.1.1

| Drug | Mutations | Description | Level | Score |
|-------------------|---|---------------------------------------|----------|-----------|
| Zidovudine | M41L, A62V, K65R, V75I, M184V, T215Y | Intermediate resistance | 4 | 50 |
| Didanosine | M41L, A62V, K65R, V75I, M184V, T215Y | High-level resistance | 5 | 115 |
| Lamivudine | M41L, K65R, V75I, M184V, T215Y | High-level resistance | 5 | 105 |
| Stavudine | M41L, A62V, K65R, V75I, M184V, T215Y | High-level resistance | 5 | 125 |
| Abacavir | M41L, A62V, K65R, V75I, M184V, T215Y | High-level resistance | 5 | 95 |
| Emtricitabine | M41L, K65R, V75I, M184V, T215Y | High-level resistance | 5 | 105 |
| Tenofovir | M41L, A62V, K65R, V75I, M184V, T215Y | High-level resistance | 5 | 85 |
| Nevirapine | K013N, V106M, E138G | High-level resistance | 5 | 130 |
| Efavirenz | K013N, V106M, E138G | High-level resistance | 5 | 130 |
| Etravirine | K013N, V106M, E138G | Potential low-level resistance | 2 | 10 |
| Lopinavir/r | L10F, M46I, I54V, A71V, L76V, V82A | High-level resistance | 5 | 120 |
| Atazanavir/r | L10F, M46I, I54V, A71V, L76V, V82A | High-level resistance | 5 | 60 |
| Darunavir/r | L10F, M46I, I54V, A71V, V82A | Low-level resistance | 3 | 25 |

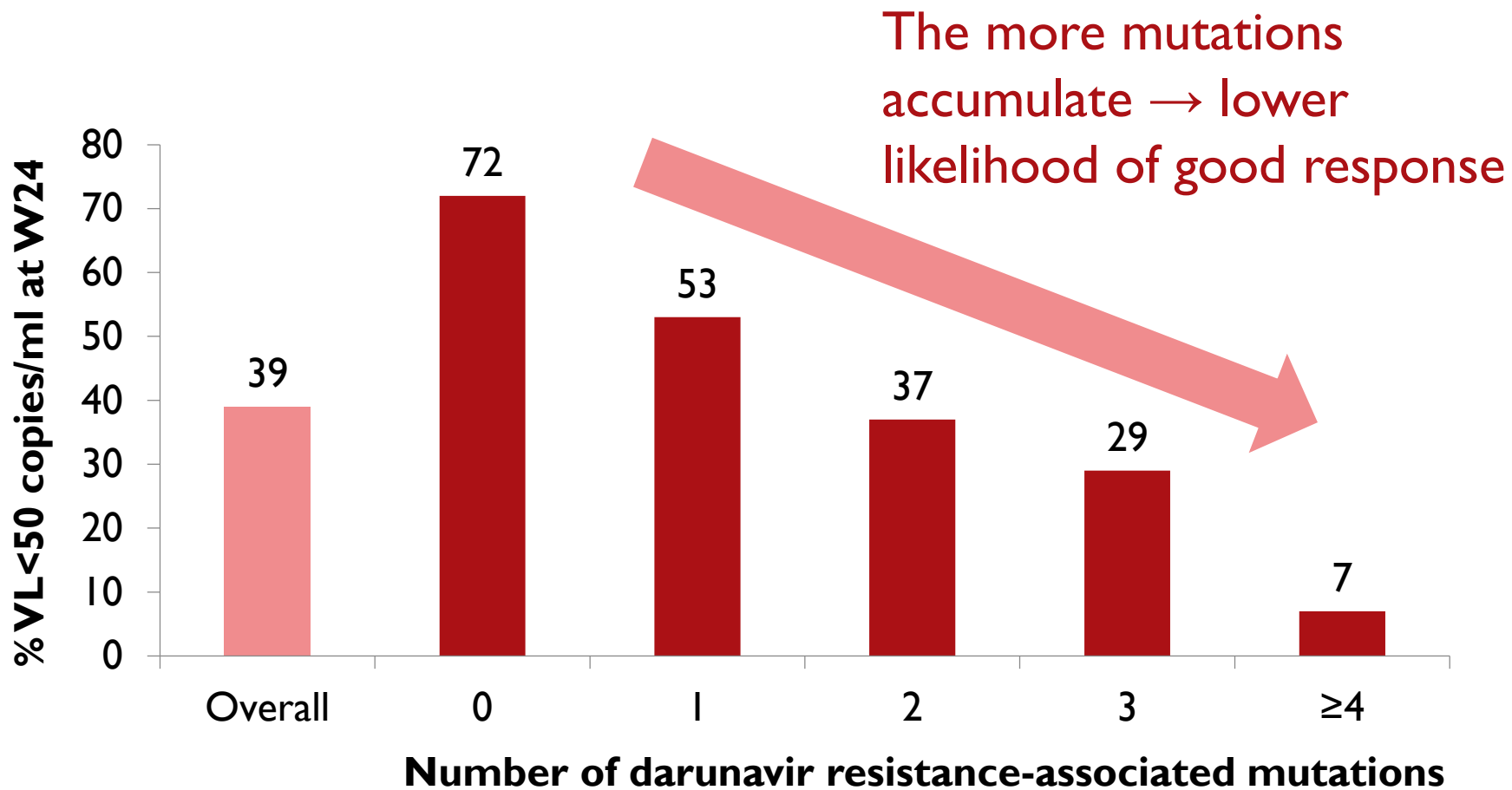
Which third-line regimen would you request?

- A. TDF/FTC/DRV/r
- B. TDF/FTC/RAL/DRV/r
- C. AZT/3TC/RAL/DRV/r
- D. RAL/ETR/DRV/r
- E. TDF/FTC/RAL/ETR/DRV/r

Third-line ART regimens

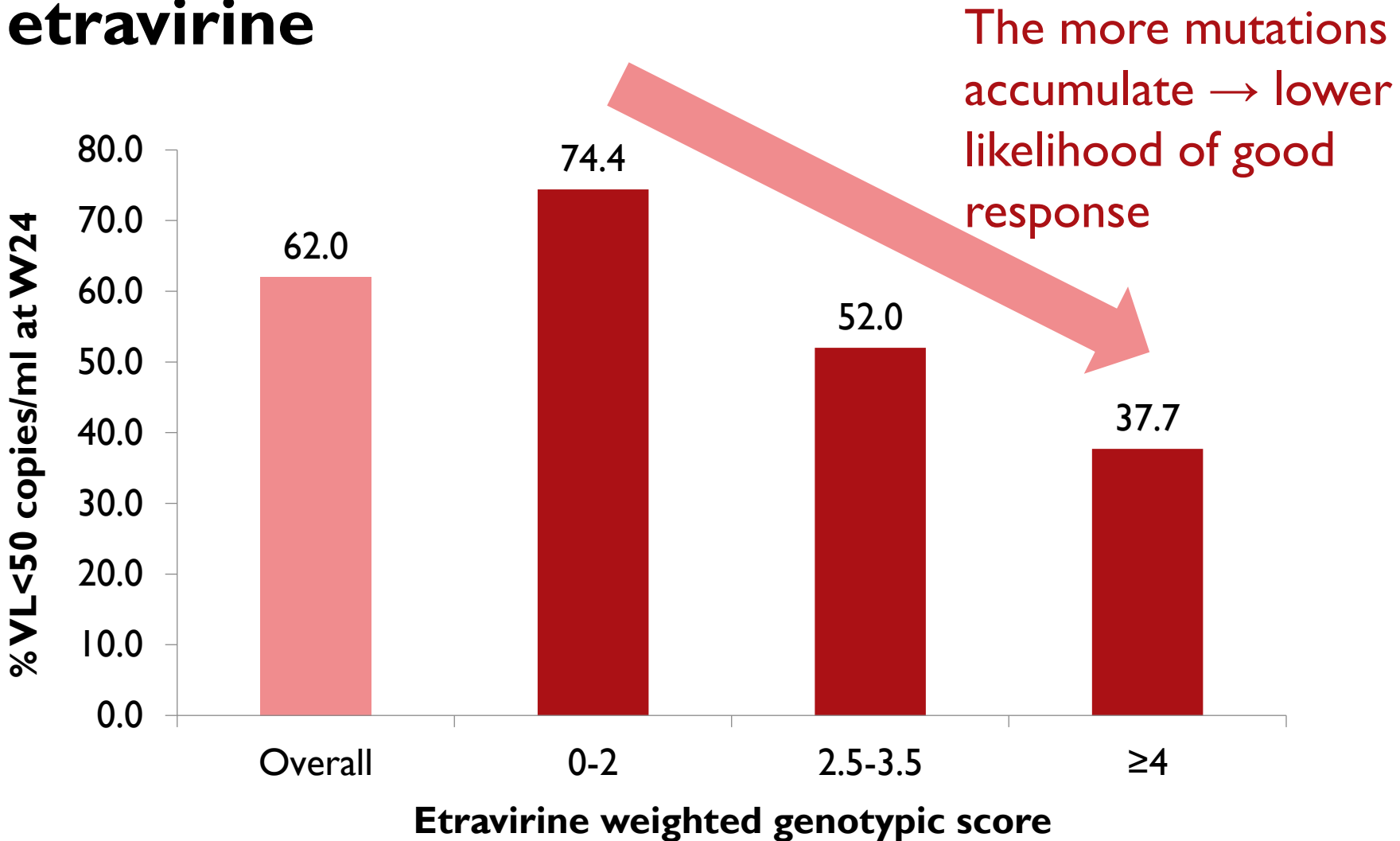


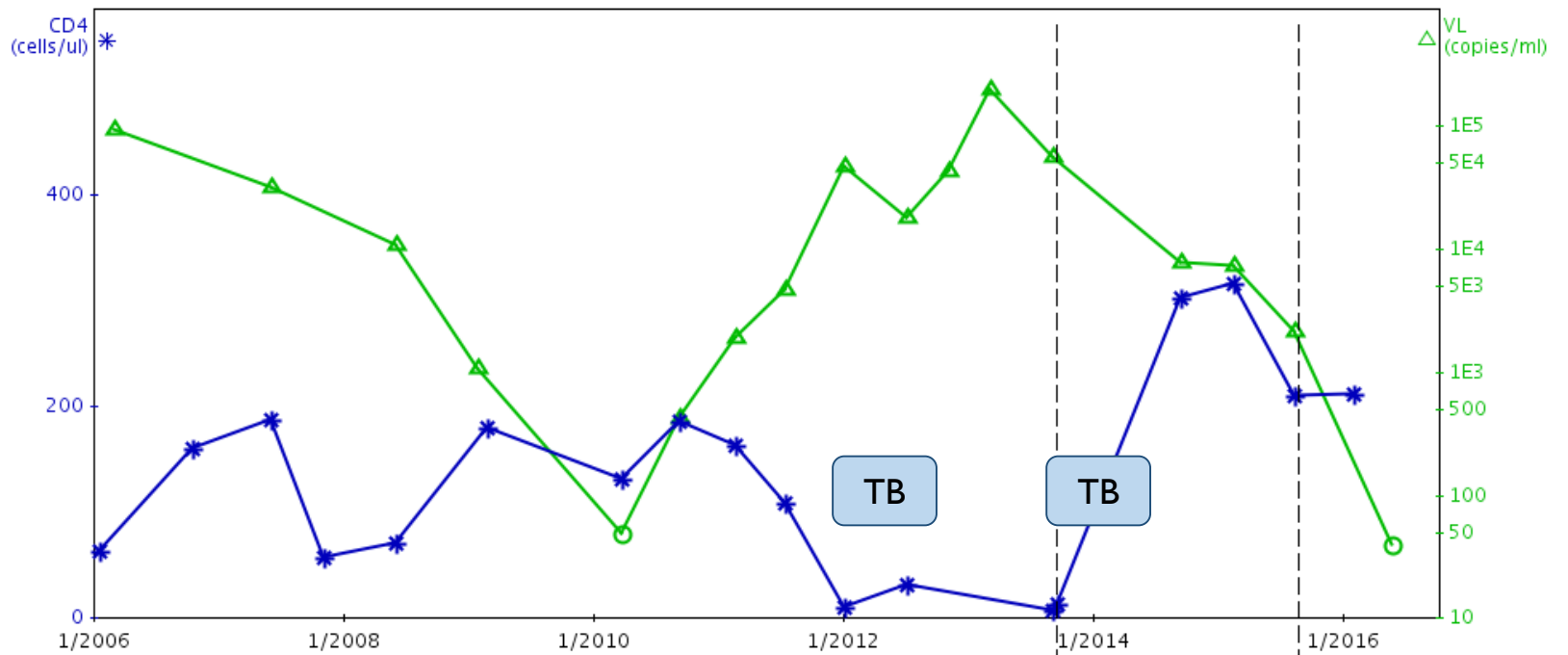
Impact of mutations on response to darunavir



DRV mutations: V11I, V32I, L33F, I47V, I50V, I54L, I54M, G73S, L76V, I84V, and L89V

Impact of mutations on response to etravirine





RT
1-300

103N
106M
138G
184V
41L
62V
65R
75I

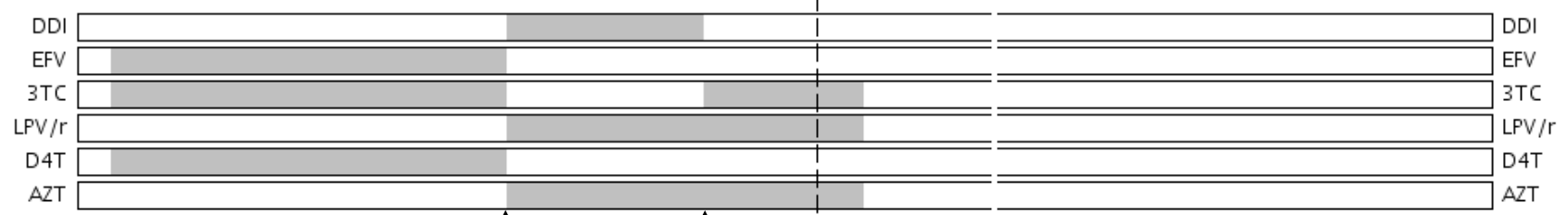
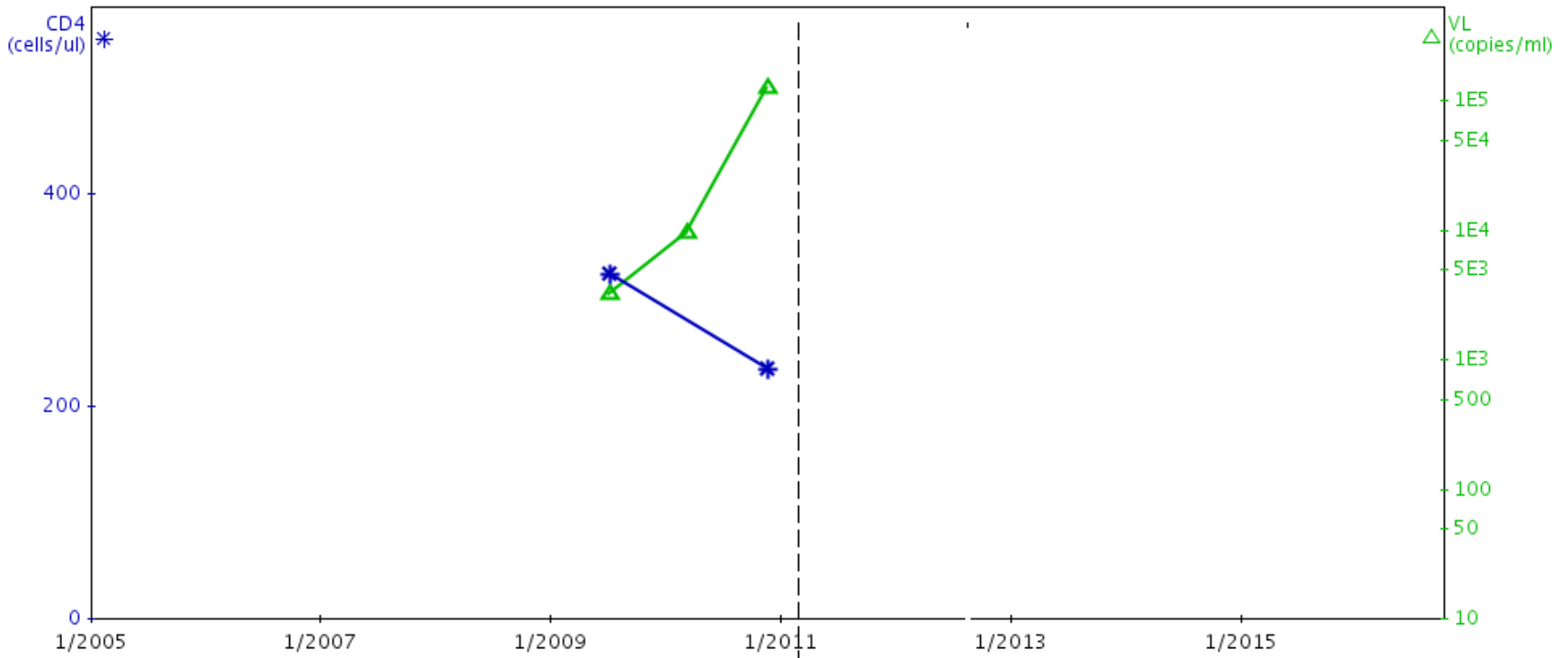
PR
1-99

10F
46I
54V
71V
76V
82A

RT
1-301

103N
184V
215Y
41L
62V
75I

Adult clinical case 2



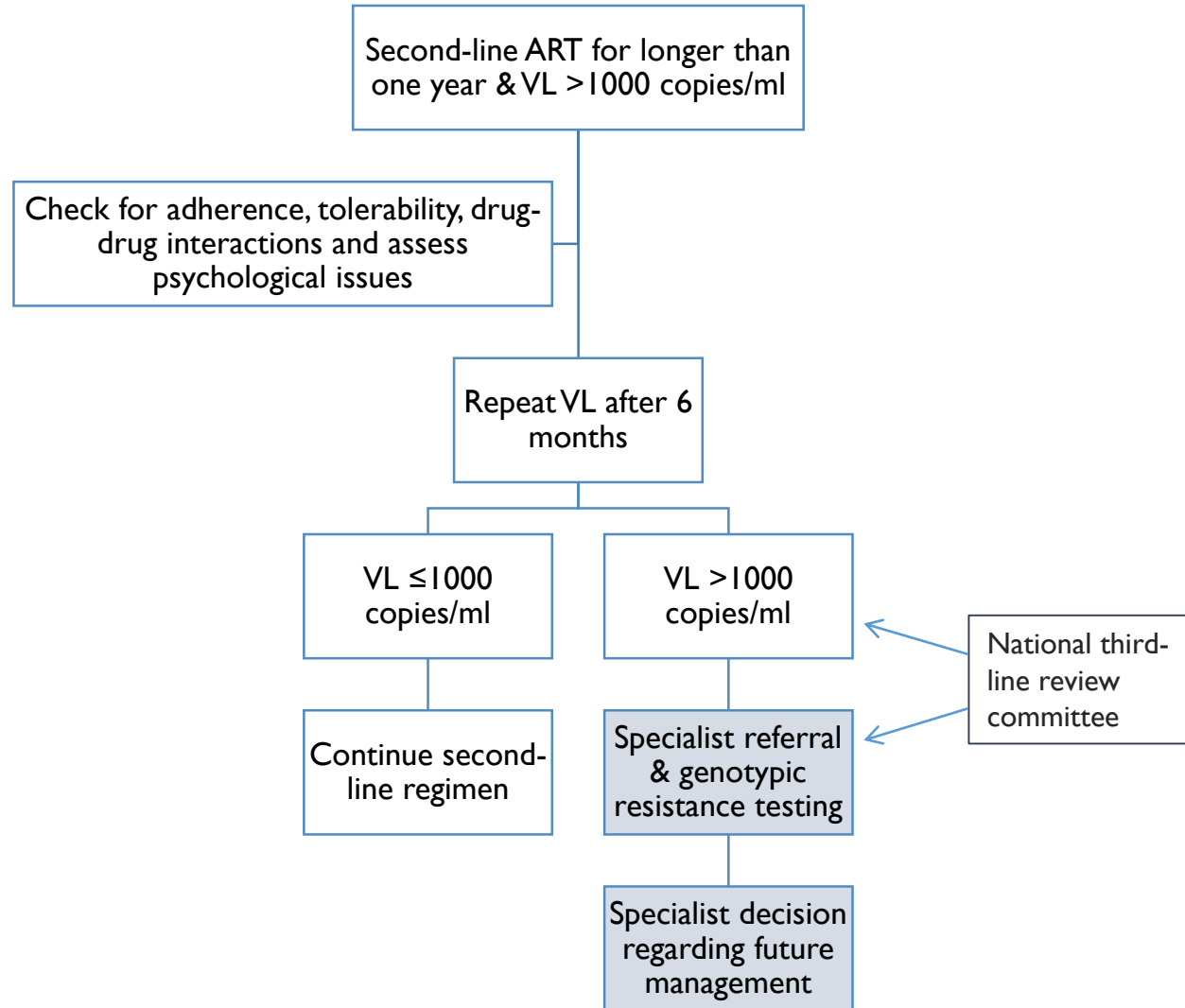
↑
**First-line
 treatment
 failure**

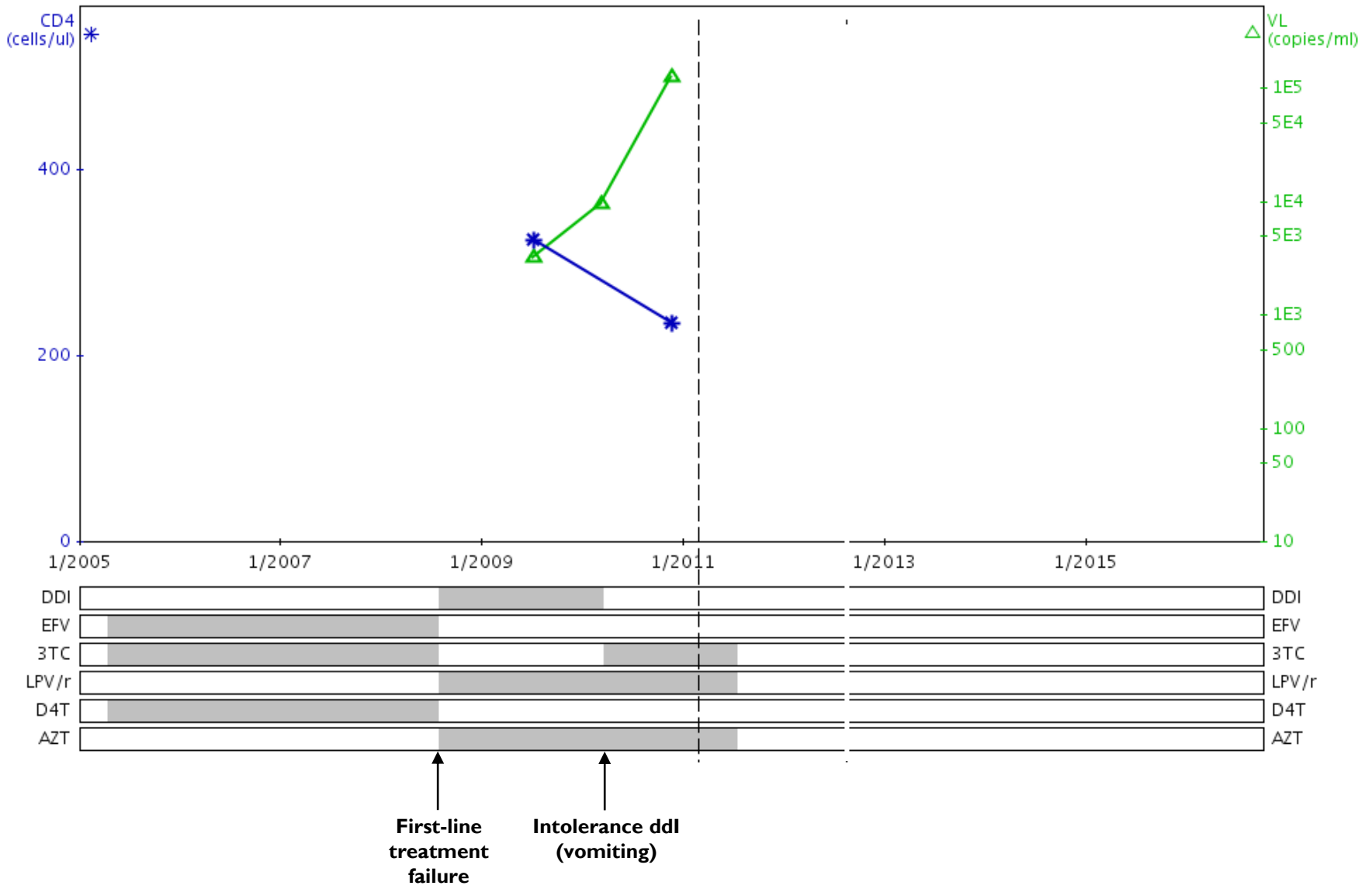
↑
**Intolerance ddl
 (vomiting)**

What would you do in this situation?

- A. Order genotypic resistance test
- B. Continue adherence support & repeat VL 6 months
- C. Switch back to AZT/ddI/LPVr
- D. Switch to AZT/3TC/ATV/r
- E. Stop all ART

Algorithm for management of second-line ART failure





Do you expect there to be drug resistance?

A. Yes

B. No

C. Don't know

Resistance at second-line ART failure in South Africa

| Study author | N | Criteria for genotype | Duration on second-line ART (median) | Drug resistance |
|--------------|----|----------------------------------|--------------------------------------|--|
| Wallis | 75 | 2 x VL >5000 | 16 months | 39% no major DRAM 7% major PI mutations |
| El-Khatib | 35 | 1 x VL >400 | - | 6% major PI mutations |
| van Zyl | 33 | 1 x VL >5000 | - | 85% no major DRAM 6% major PI mutations |
| Levison | 33 | 2 x VL >1000 | 10 months | 67% no major DRAM No major PI mutations |
| Sigaloff | 15 | 1 x VL >1000 | >12 months | 40% no major DRAM 7% major PI mutations |
| Berhanu | 65 | 1 x VL >400 then 1 x VL >1000 | - | 18% no major DRAM 26% PI mutations |

Sources: *AIDS Res Treat* 2011; 769627. *AIDS* 2010; 24: 1679. *JAIDS* 2011; 56: 333. *PLoS ONE* 2012; 3: e32144. *JID* 2012; 205: 1739-44. *CROI* 2016 [abstract 1049]

Resistance at second-line ART failure

- The published evidence suggests that resistance to protease inhibitors in adults failing second-line ART is rare
- Need to interpret cautiously given short duration of second-line ART and inherent bias (many individuals switched early to second-line ART will have had adherence problems with first-line ART)
- Increasing number of people exposed to second-line regimens for longer durations – protease resistance will increase

Genotypic resistance test report

Antiretroviral experience: d4T, 3TC,AZT, ddi, EFV, LPVr
Subtype: HIV-1 Subtype C
Resistance interpretations: HIVdb 8.1.1

| Drug | Mutations | Description | Level | Score |
|---------------|------------|--------------------------------|-------|-------|
| Zidovudine | M184V | Susceptible | 1 | -10 |
| Didanosine | M184V | Potential low-level resistance | 2 | 10 |
| Lamivudine | M184V | High-level resistance | 5 | 60 |
| Stavudine | M184V | Susceptible | 1 | -10 |
| Abacavir | M184V | Low-level resistance | 3 | 15 |
| Emtricitabine | M184V | High-level resistance | 5 | 60 |
| Tenofovir | M184V | Susceptible | 1 | -10 |
| Nevirapine | | Susceptible | 1 | 0 |
| Efavirenz | | Susceptible | 1 | 0 |
| Etravirine | | Susceptible | 1 | 0 |
| Lopinavir/r | I47A, I84V | High-level resistance | 5 | 95 |
| Atazanavir/r | I47A, I84V | High-level resistance | 5 | 60 |
| Darunavir/r | I47A, I84V | Intermediate resistance | 4 | 30 |

How many PI mutations are typically required for high-level resistance to LPVr?

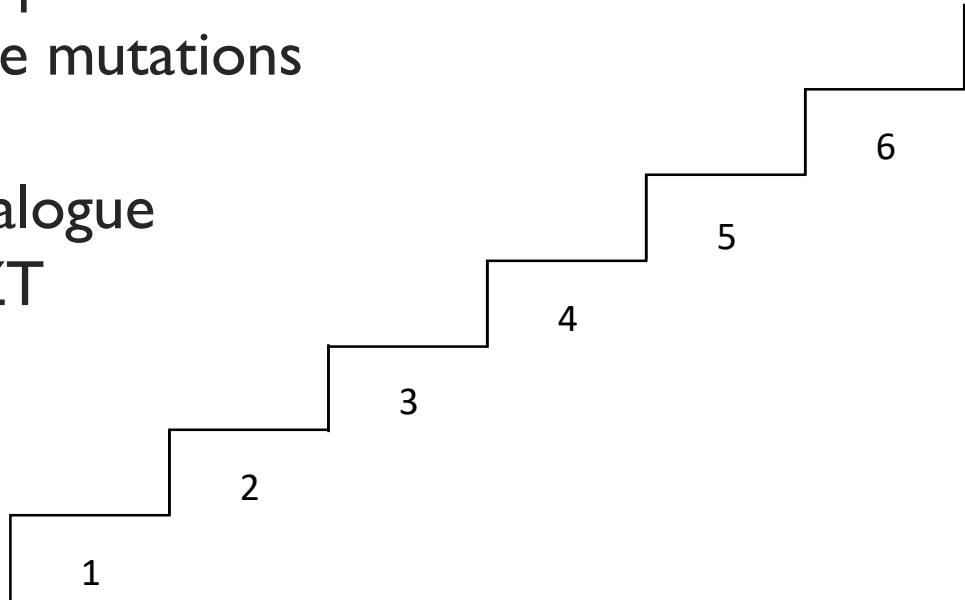
- A. 1 mutation
- B. 2-3 mutations
- C. 4-5 mutations
- D. 6 or more mutations

Resistance to protease inhibitors

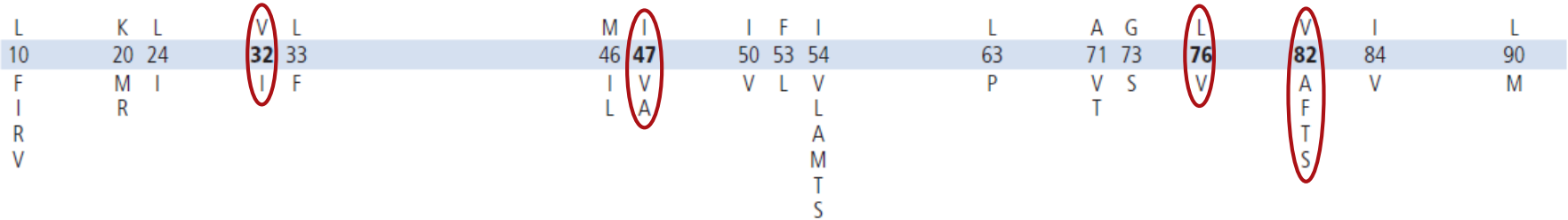
Classically occurs in an ordered stepwise process

High-level resistance requires accumulation of multiple mutations

Similar to thymidine analogue mutations with d4T/AZT



Resistance to protease inhibitors



Major PI mutations – mutations occurring within the active binding site of protease enzyme which disrupt PI binding; have the greatest impact on PI susceptibility

Minor PI mutations – mutations outside the active binding site; can enhance resistance and can be compensatory, i.e. restore enzyme activity or reverse viral fitness defects

Resistance to lopinavir/ritonavir

| | | | | | | | | | | | | | | | | |
|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| L | K | L | V | L | M | I | I | F | I | L | A | G | L | V | I | L |
| 10 | 20 | 24 | 32 | 33 | 46 | 47 | 50 | 53 | 54 | 63 | 71 | 73 | 76 | 82 | 84 | 90 |
| F | M | I | I | F | I | V | V | L | V | P | V | S | V | A | V | M |
| I | R | | | | L | A | | | L | | T | | | F | | |
| R | | | | | | | | | A | | | | | T | | |
| V | | | | | | | | | M | | | | | S | | |
| | | | | | | | | | T | | | | | | | |
| | | | | | | | | | S | | | | | | | |

The accumulation of six or more mutations is associated with reduced virological response to LPVr

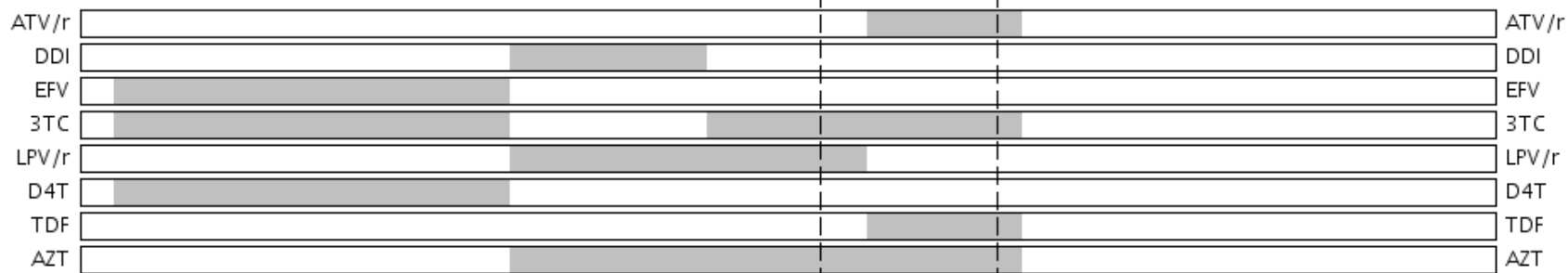
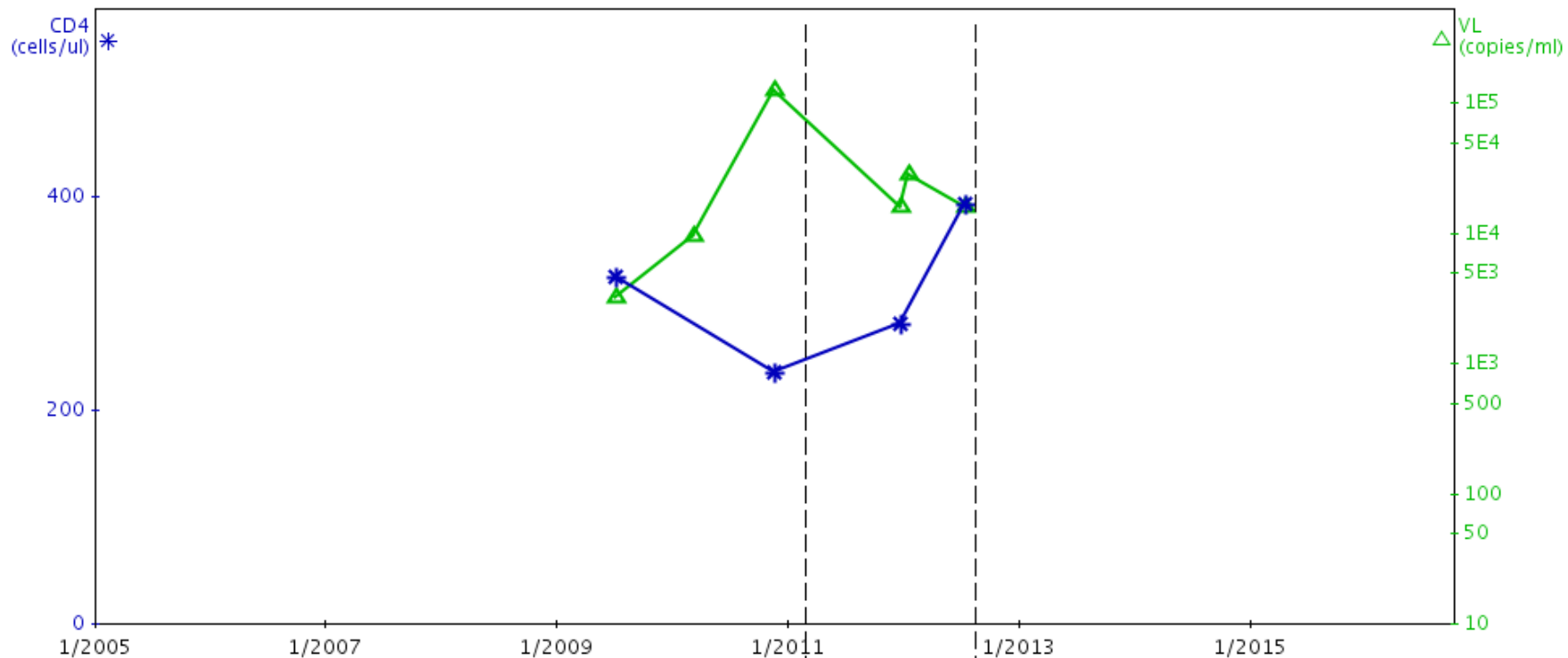
But there is evidence that specific mutations (I47A, V32I) alone are associated with high-level resistance

High-level resistance with I47A relates to significant decrease in the mutant PR–LPV binding energy

Genotypic resistance test report

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Subtype: HIV-1 Subtype C
Resistance interpretations: HIVdb 8.1.1

| Drug | Mutations | Description | Level | Score |
|---------------|------------|--------------------------------|-------|-------|
| Zidovudine | M184V | Susceptible | 1 | -10 |
| Didanosine | M184V | Potential low-level resistance | 2 | 10 |
| Lamivudine | M184V | High-level resistance | 5 | 60 |
| Stavudine | M184V | Susceptible | 1 | -10 |
| Abacavir | M184V | Low-level resistance | 3 | 15 |
| Emtricitabine | M184V | High-level resistance | 5 | 60 |
| Tenofovir | M184V | Susceptible | 1 | -10 |
| Nevirapine | | Susceptible | 1 | 0 |
| Efavirenz | | Susceptible | 1 | 0 |
| Etravirine | | Susceptible | 1 | 0 |
| Lopinavir/r | I47A, I84V | High-level resistance | 5 | 95 |
| Atazanavir/r | I47A, I84V | High-level resistance | 5 | 60 |
| Darunavir/r | I47A, I84V | Intermediate resistance | 4 | 30 |



↑
**HBsAg
 positive**

Which of these antiretrovirals are active against hepatitis B virus?

- A. 3TC
- B. FTC
- C. TDF
- D. 3TC & TDF
- E. 3TC & FTC & TDF

Genotypic resistance test report

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Subtype: HIV-1 Subtype C

Resistance interpretations: HIVdb 8.1.1

| Drug | Mutations | Description | Level | Score |
|---------------|------------------------------|-------------------------|-------|-------|
| Zidovudine | 67N, 70R, 184V, 215I, 219E | High-level resistance | 5 | 75 |
| Didanosine | 67N, 184V, 215I | Intermediate resistance | 4 | 50 |
| Lamivudine | 184V | High-level resistance | 5 | 70 |
| Stavudine | 67N, 70R, 184V, 215I, 219E | High-level resistance | 5 | 60 |
| Abacavir | 67N, 184V, 215I | Intermediate resistance | 4 | 45 |
| Emtricitabine | 184V | High-level resistance | 5 | 70 |
| Tenofovir | 67N, 70R, 184V, 215I | Low-level resistance | 3 | 20 |
| Nevirapine | 101E | Intermediate resistance | 4 | 30 |
| Efavirenz | 101E | Low-level resistance | 3 | 15 |
| Etravirine | 101E | Low-level resistance | 3 | 15 |
| Lopinavir/r | 46I, 47A, 50L, 71V, 73S, 84V | High-level resistance | 5 | 100 |
| Atazanavir/r | 46I, 47A, 50L, 71V, 73S, 84V | High-level resistance | 5 | 140 |
| Darunavir/r | 46I, 47A, 50L, 73S, 84V | Low-level resistance | 3 | 20 |

What would you do now?

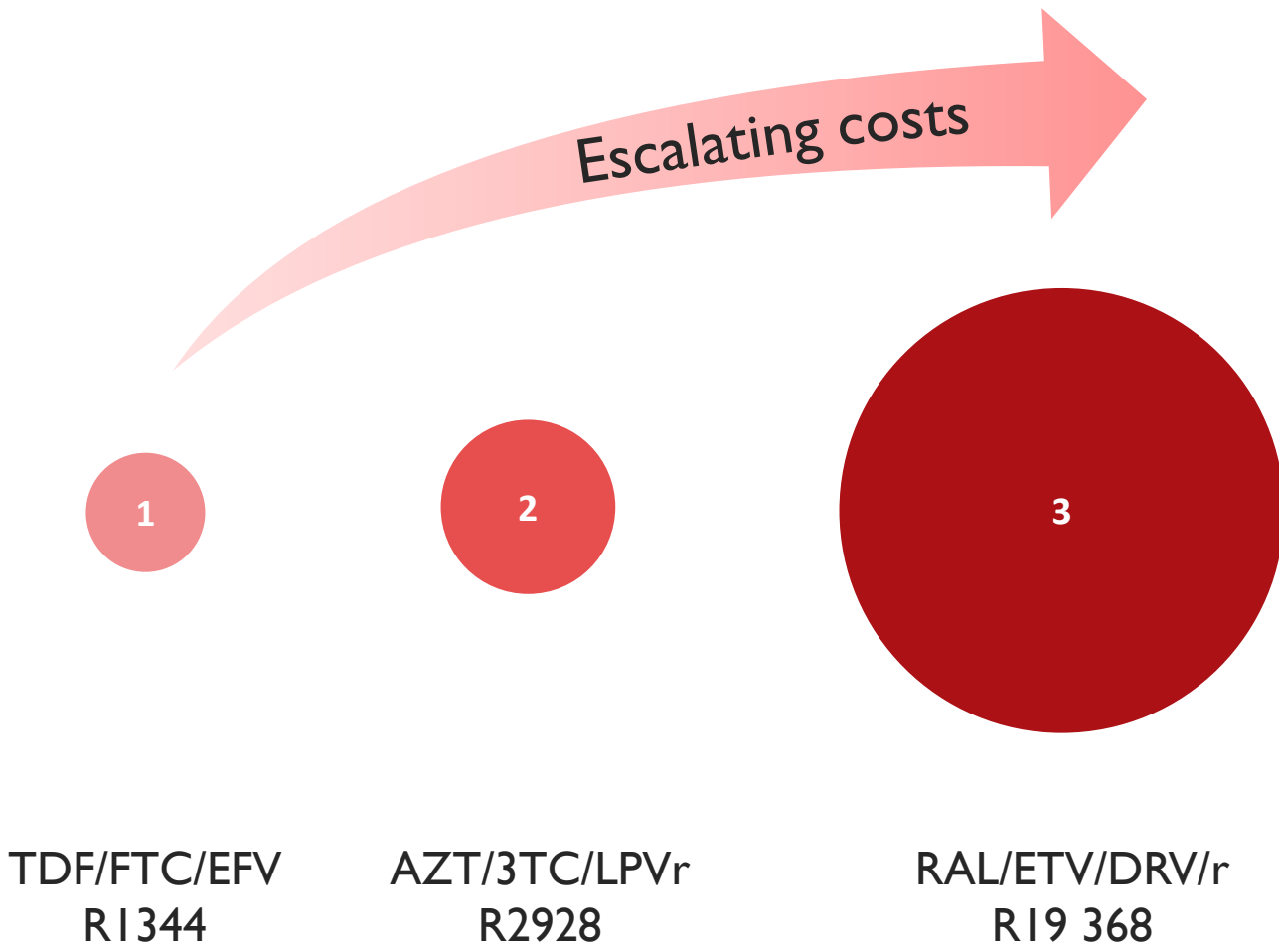
- A. Stop all ART
- B. Switch to TDF/FTC/EFV
- C. Switch to 3TC monotherapy
- D. Switch to TDF/FTC/RAL/DRV/r
- E. Switch to TDF/FTC/RAL/ETR/DRV/r

Genotypic resistance test report

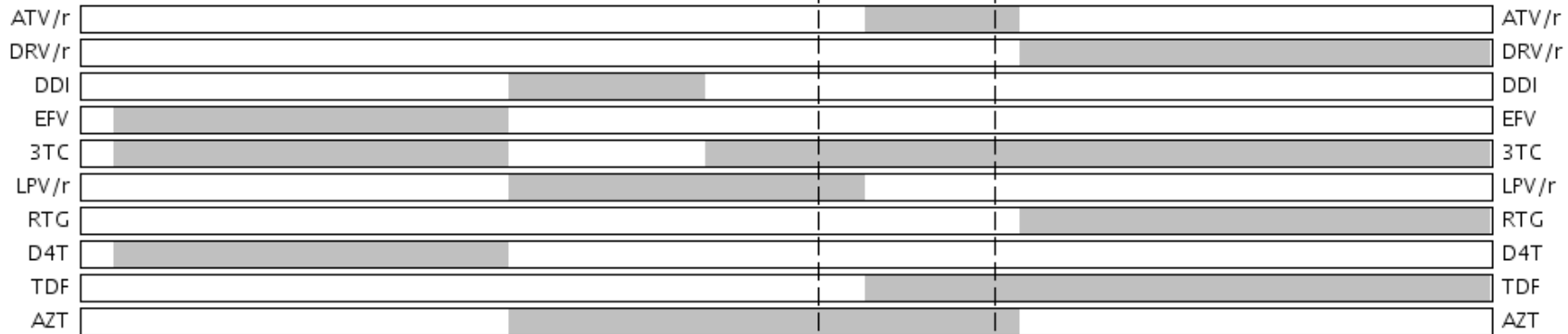
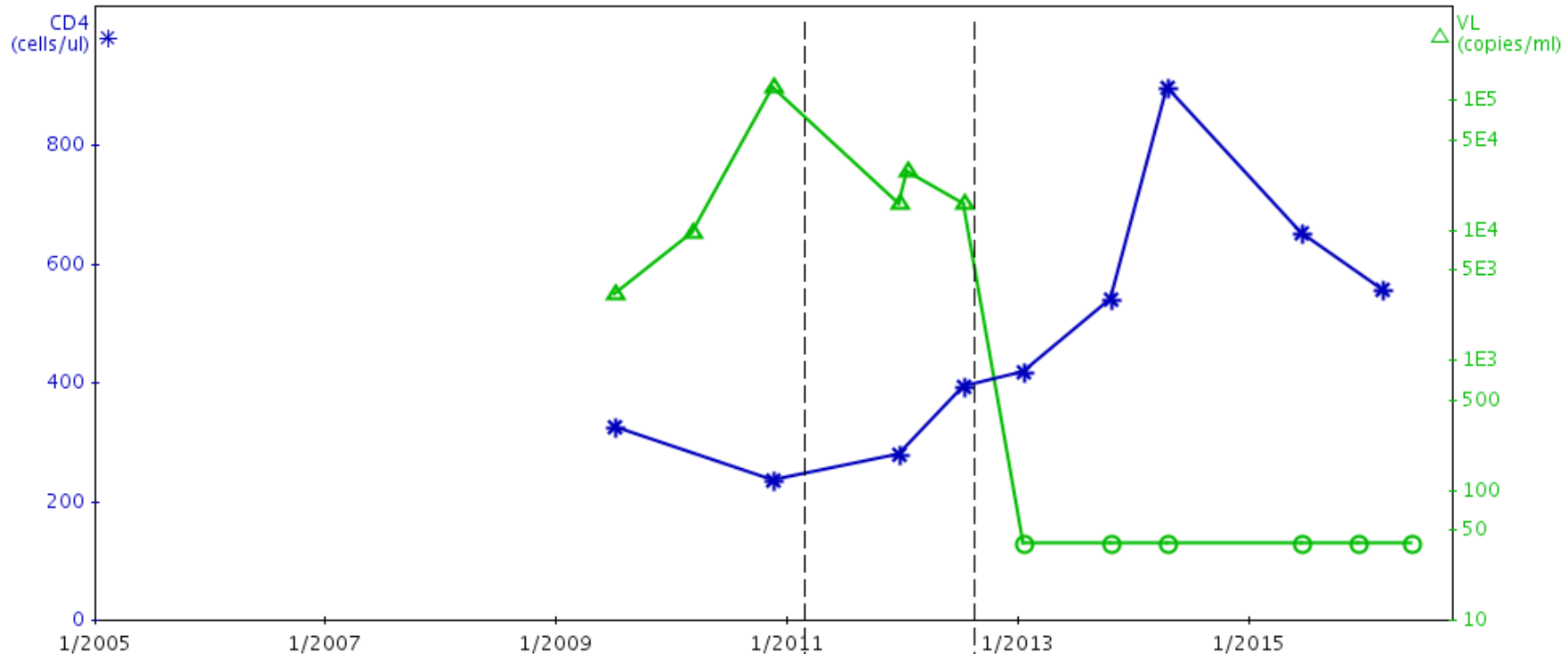
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| Stavudine | 67N, 70R, 184V, 215I, 219E | High-level resistance | 5 | 60 |
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| Emtricitabine | 184V | High-level resistance | 5 | 70 |
| Tenofovir | 67N, 70R, 184V, 215I | Low-level resistance | 3 | 20 |
| Nevirapine | 101E | Intermediate resistance | 4 | 30 |
| Efavirenz | 101E | Low-level resistance | 3 | 15 |
| Etravirine | 101E | Low-level resistance | 3 | 15 |
| Lopinavir/r | 46I, 47A, 50L, 71V, 73S, 84V | High-level resistance | 5 | 100 |
| Atazanavir/r | 46I, 47A, 50L, 71V, 73S, 84V | High-level resistance | 5 | 140 |
| Darunavir/r | 46I, 47A, 50L, 73S, 84V | Low-level resistance | 3 | 20 |

Hypersusceptibility also occurs
with PIs, e.g. I50L and DRV



Source: Department of Health ARV tender 2015-2018



Key learning points

- Genotypic resistance testing indicated if on second-line ART for >12 months and two viral loads >1000 copies/mL
- Certain single mutations confer high-level resistance to LPVr
- Always remember to check HBV status during work-up for any ART regimen change
- Response to key third-line drugs is influenced by number/type of mutations accumulated – avoid prolonged treatment failure on first-line and second-line regimens
- Well-designed third-line ART regimens are effective and can lead to durable virological suppression