

CLINICAL CASE

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Virologic failure even at low levels of viremia can be associated to integrase strand-transfer inhibitors resistance in HIV-1 infected patients

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Clinical history

DEMOGRAPHICS:

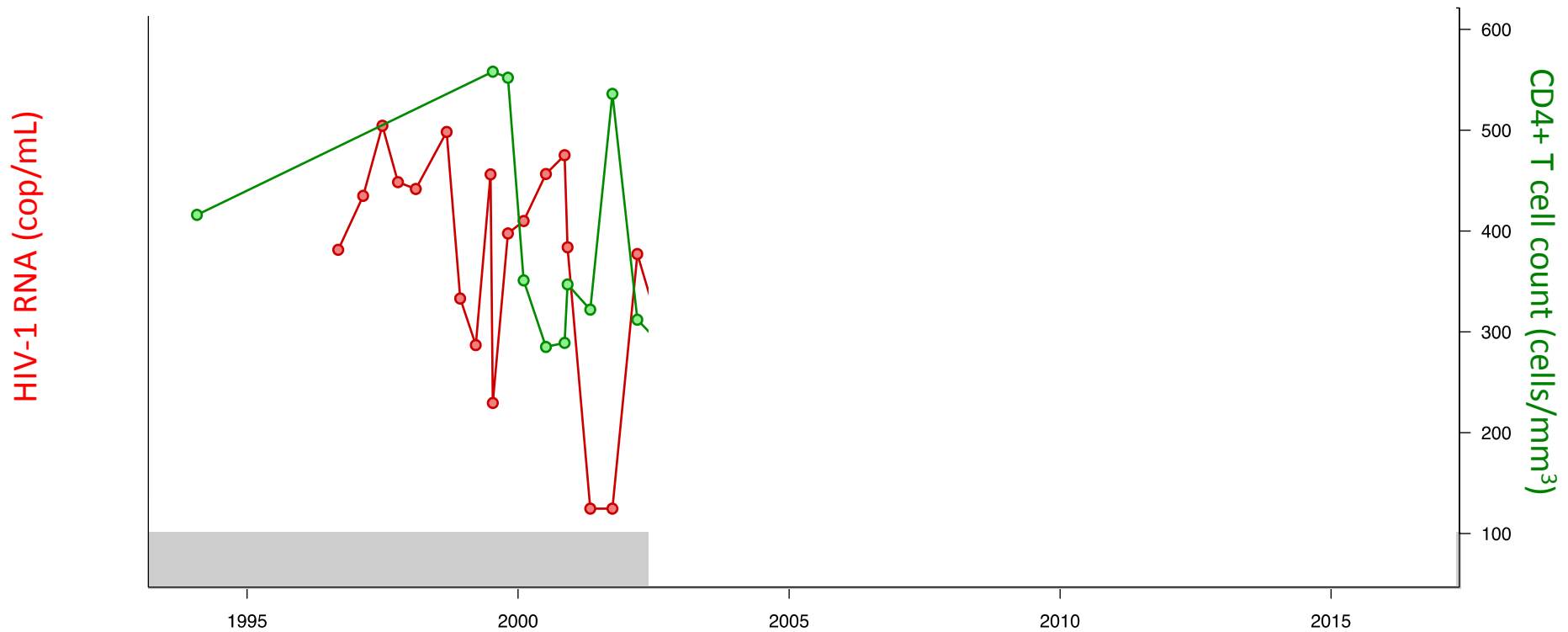
- Men, MSM
- Born in 1954

HIV HISTORY:

- HIV-1 infection category C diagnosed at 33 years old (1987): cutaneous Kaposi sarcoma

Clinical evolution

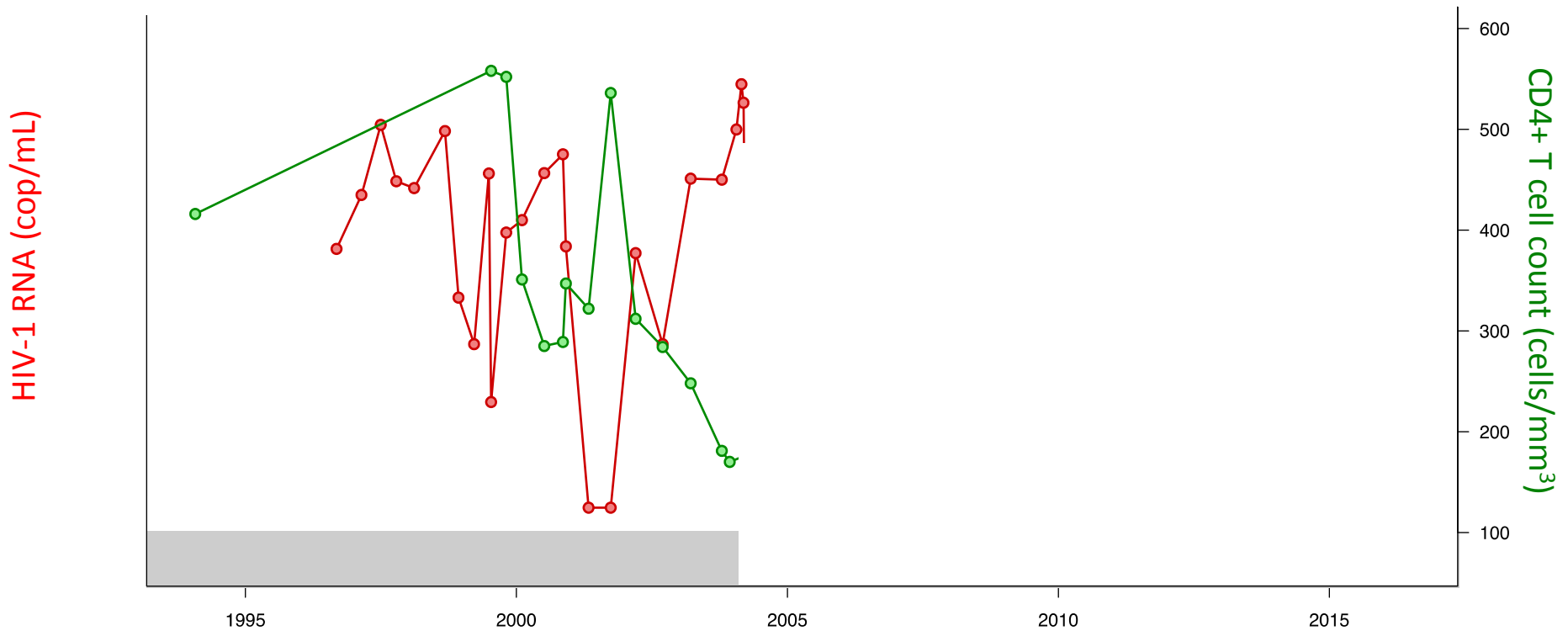
	ddI + EFV + LPV + SQV/r
AZT	3TC/FTC + ABV + LPV/r
AZT + RTV	d4T + 3TC/FTC + SQV/r
+ ddI + 3TC/FTC	ddI + 3TC/FTC + TDF + APV/r



Clinical evolution

	ddI + EFV + LPV + SQV/r	TDF
AZT	3TC/FTC + ABV + LPV/r	EFV
AZT + RTV	d4T + 3TC/FTC + SQV/r	LPV/r
+ ddI + 3TC/FTC	ddI + 3TC/FTC + TDF + APV/r	SQV

G

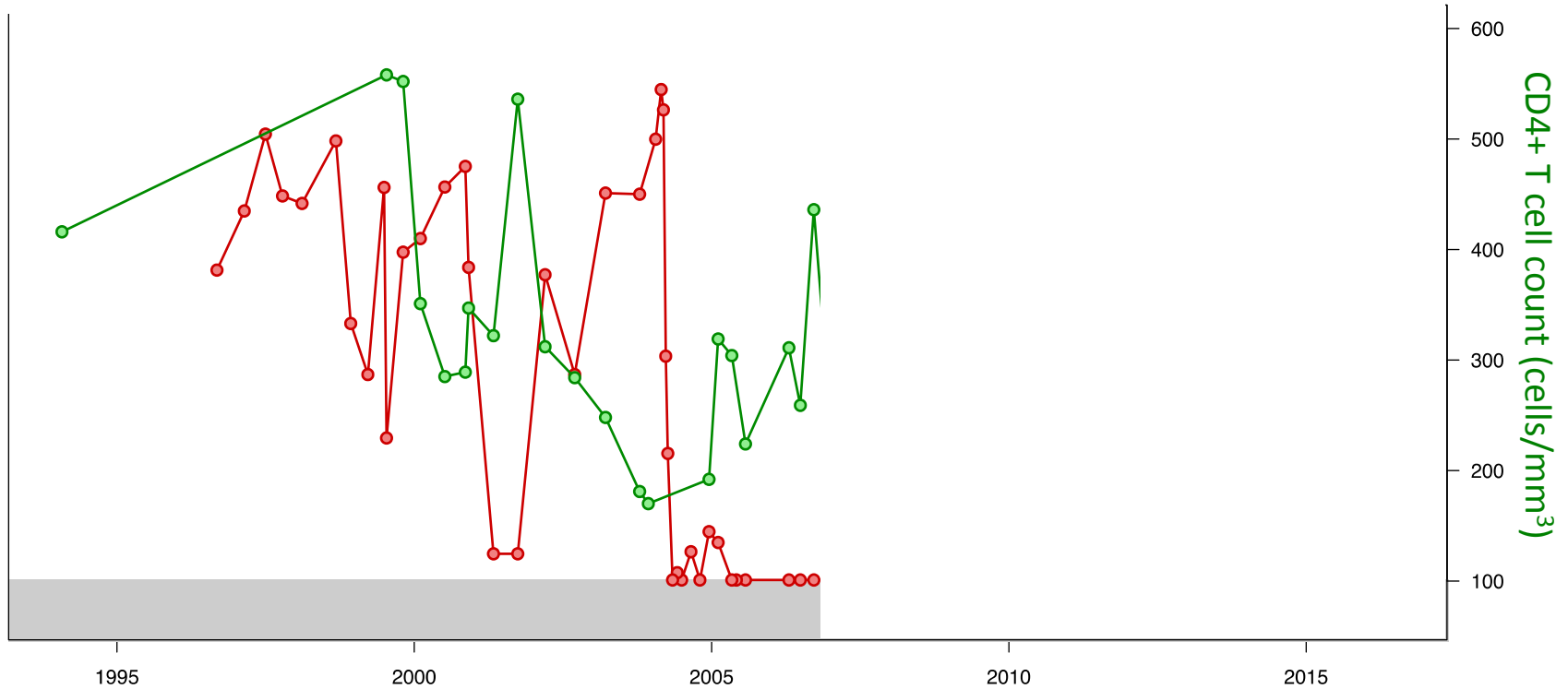


Clinical evolution

	ddl + EFV + LPV + SQV/r	TDF	ddl
AZT	3TC/FTC + ABV + LPV/r	EFV	ABV
AZT + RTV	d4T + 3TC/FTC + SQV/r	LPV/r	DRV/r
+ ddl + 3TC/FTC	ddl + 3TC/FTC + TDF + APV/r	SQV	T20
		G	G

HIV-1 RNA (cop/mL)

CD4+ T cell count (cells/mm³)



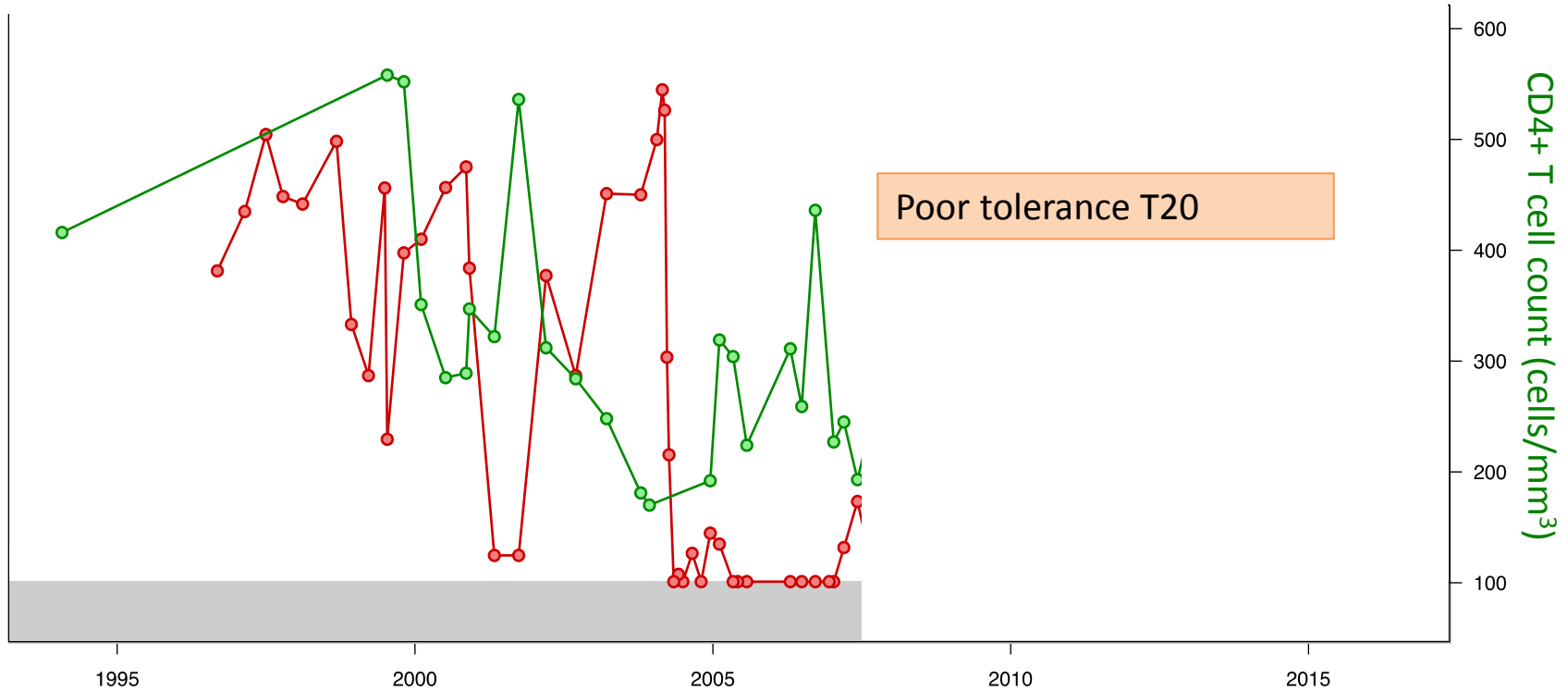
Clinical evolution

	ddl + EFV + LPV + SQV/r	TDF	ddl
AZT	3TC/FTC + ABV + LPV/r	EFV	ABV
AZT + RTV	d4T + 3TC/FTC + SQV/r	LPV/r	DRV/r
+ ddl + 3TC/FTC	ddl + 3TC/FTC + TDF + APV/r	SQV	T20



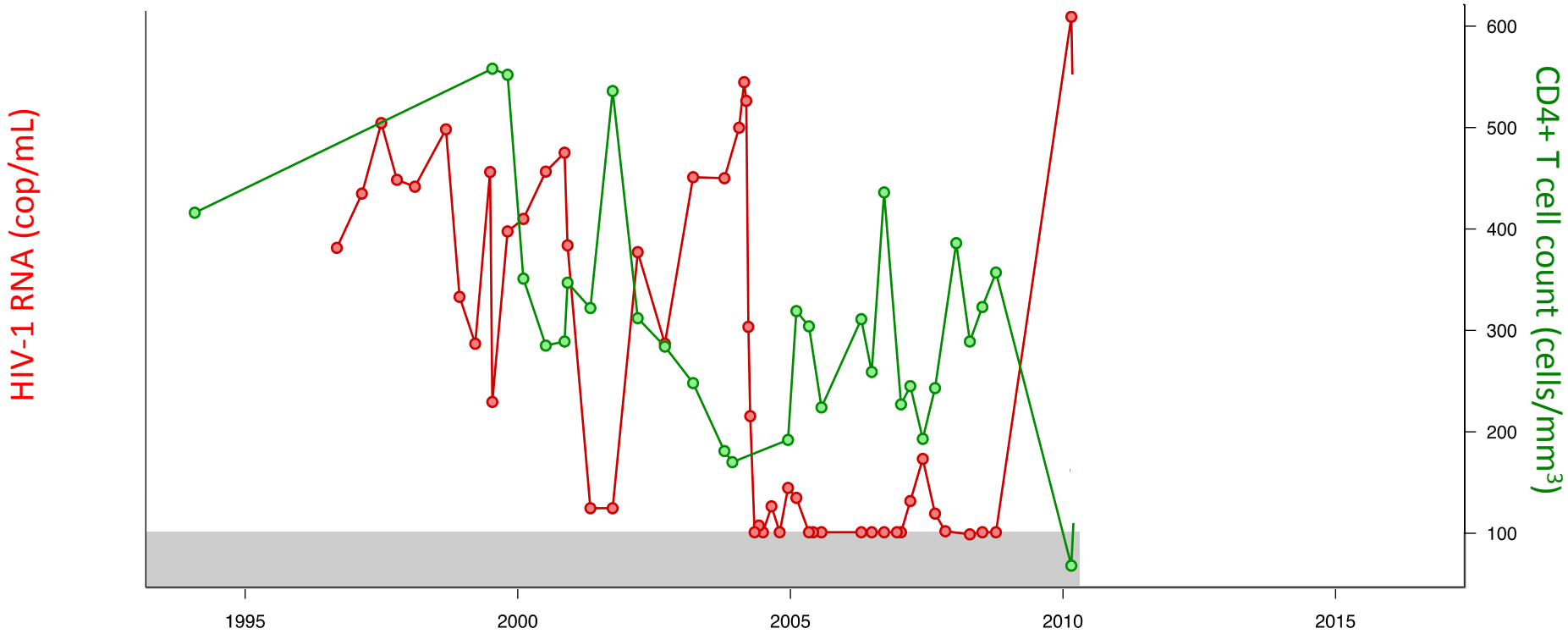
HIV-1 RNA (cop/mL)

CD4+ T cell count (cells/mm³)



Clinical evolution

	ddl + EFV + LPV + SQV/r	TDF	ddl	ddl
AZT	3TC/FTC + ABV + LPV/r	EFV	ABV	ABV
AZT + RTV	d4T + 3TC/FTC + SQV/r	LPV/r	DRV/r	DRV/r
+ ddl + 3TC/FTC	ddl + 3TC/FTC + TDF + APV/r	SQV	T20	RAL
		G	G	G



Cumulative resistance test results

Protease

L63P, L10I, L24I, L33F, **M46L**, **I54V**, A71V, V77I, **V82A**, **I84V**, T91S

High level resistance: ATV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r

Low level resistance: DRV/r

Reverse transcriptase

V118I/V, **M184V/M**, T200T/A, Q207Q/E, L210W/L, R211K/R, T215N/S, M41L, D67N, V75M, **K103N**, V118I, **Y188L**, L210W, T215Y, E138S/P, V178I/M, **K238T**

High level resistance: **ABC**, AZT, D4T, DDI, FTC, 3TC
EFV, **NVP**, **RPV**

Intermediate resistance: **TDF**

Potential low level resistance: **ETR**

New regimen proposed

ETR

Low level resistance: 0,5 p

DRV/r

Low level resistance: 0,5 p

RAL

Fully active: 1 p

MVC

Fully active: 1 p

GSS: 3p

Subtype: B

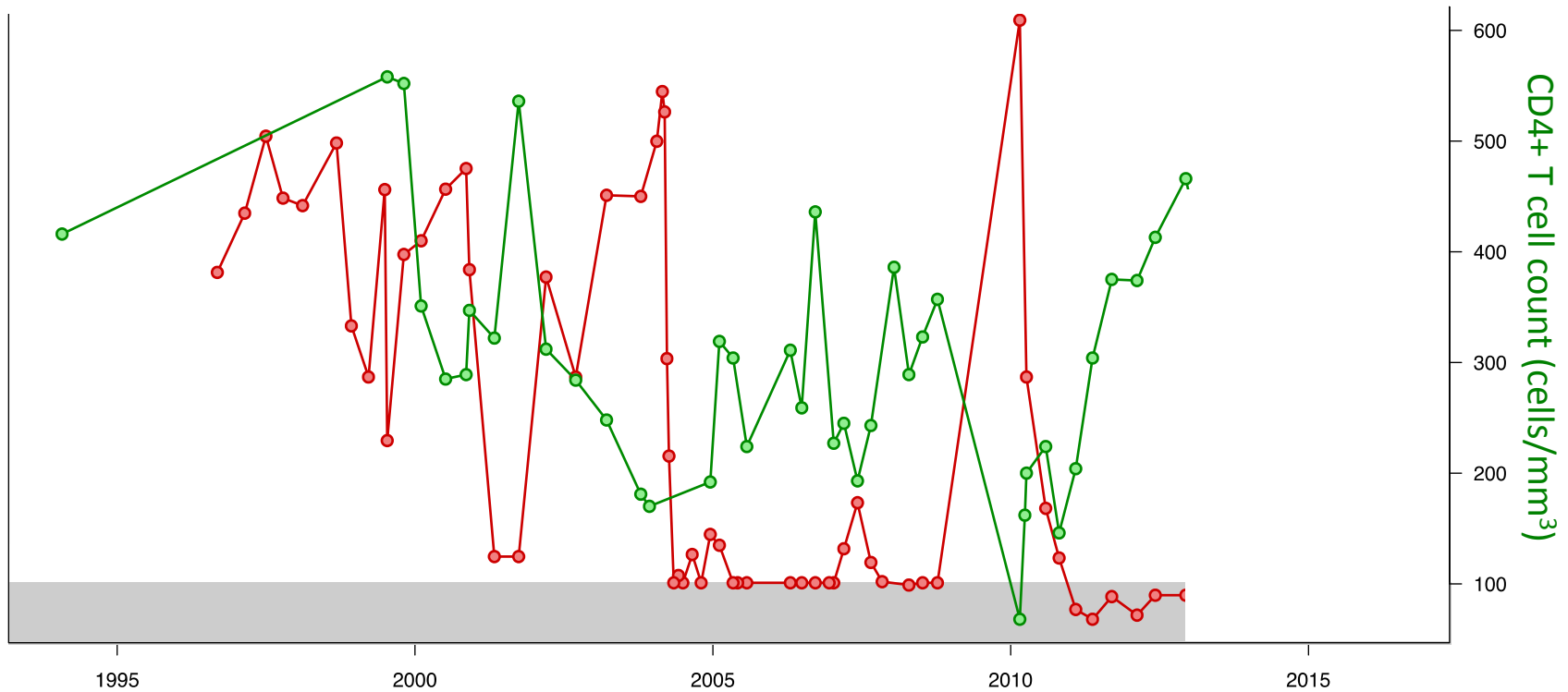
Viral tropism: CCR5

Clinical evolution

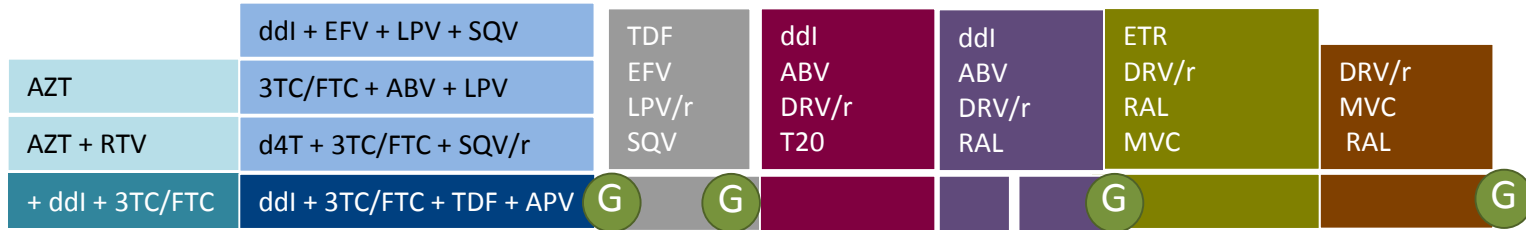
	ddi + EFV + LPV + SQV	TDF EFV LPV/r SQV	ddl ABV DRV/r T20	ddl ABV DRV/r RAL	ETR DRV/r RAL MVC
AZT	3TC/FTC + ABV + LPV				
AZT + RTV	d4T + 3TC/FTC + SQV/r				
+ ddi + 3TC/FTC	ddi + 3TC/FTC + TDF + APV	G	G		G

HIV-1 RNA (cop/mL)

CD4+ T cell count (cells/mm³)

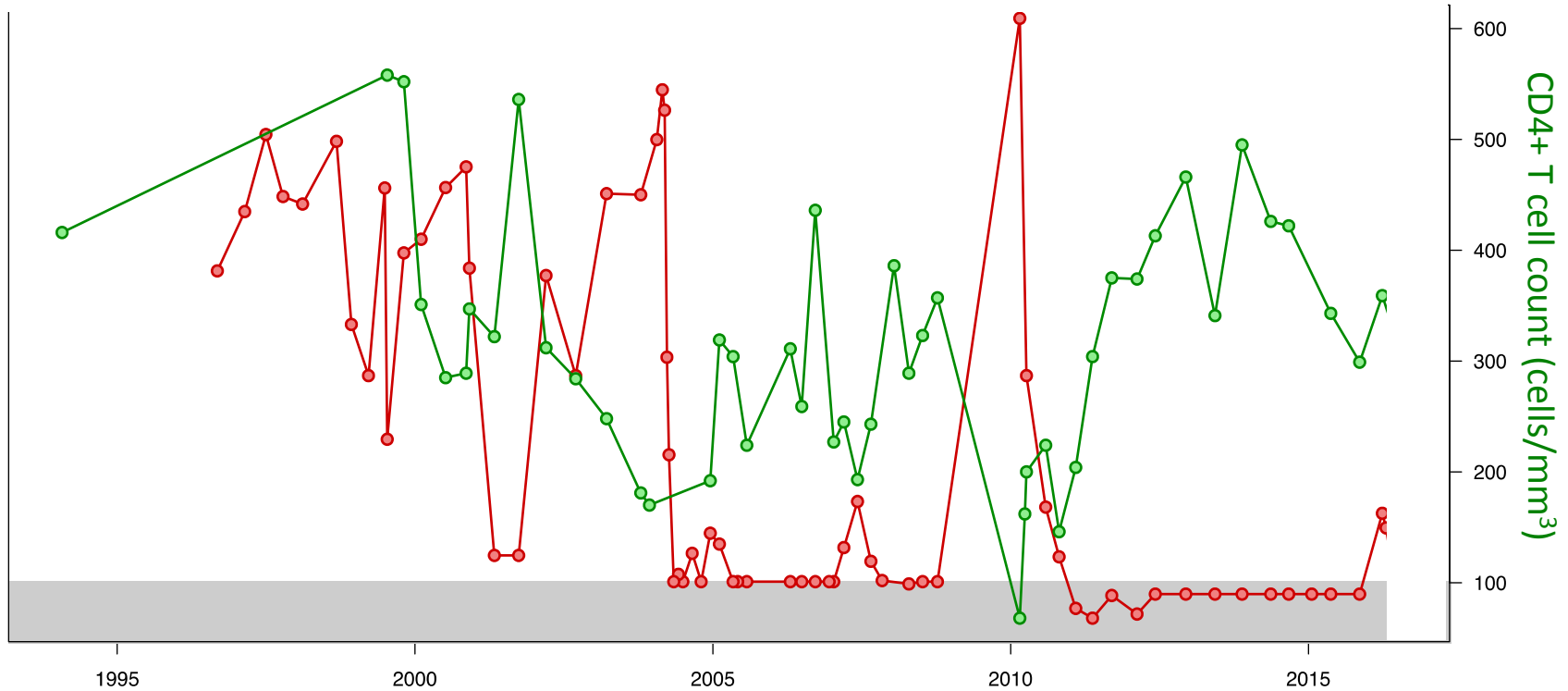


Clinical evolution



HIV-1 RNA (cop/mL)

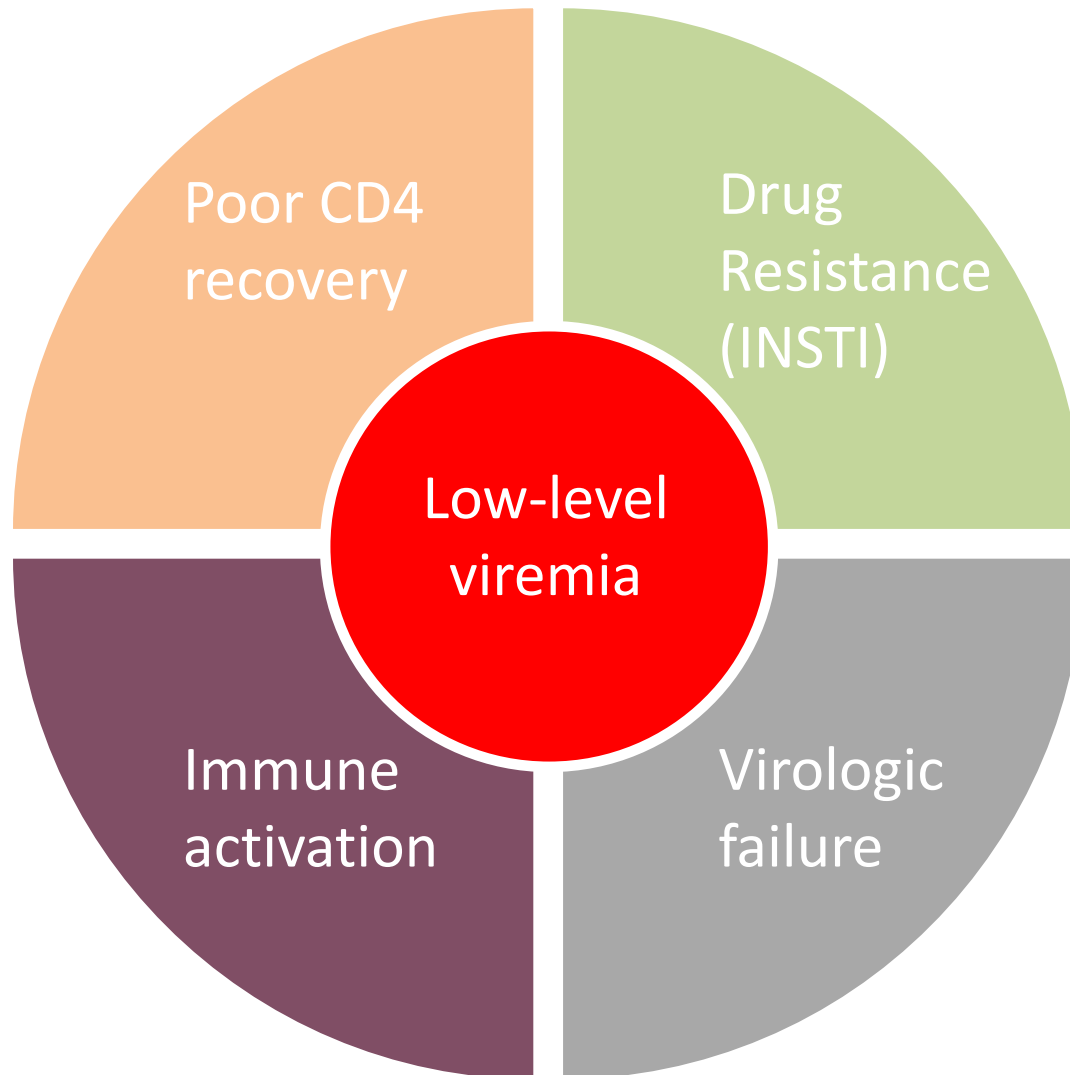
CD4+ T cell count (cells/mm³)



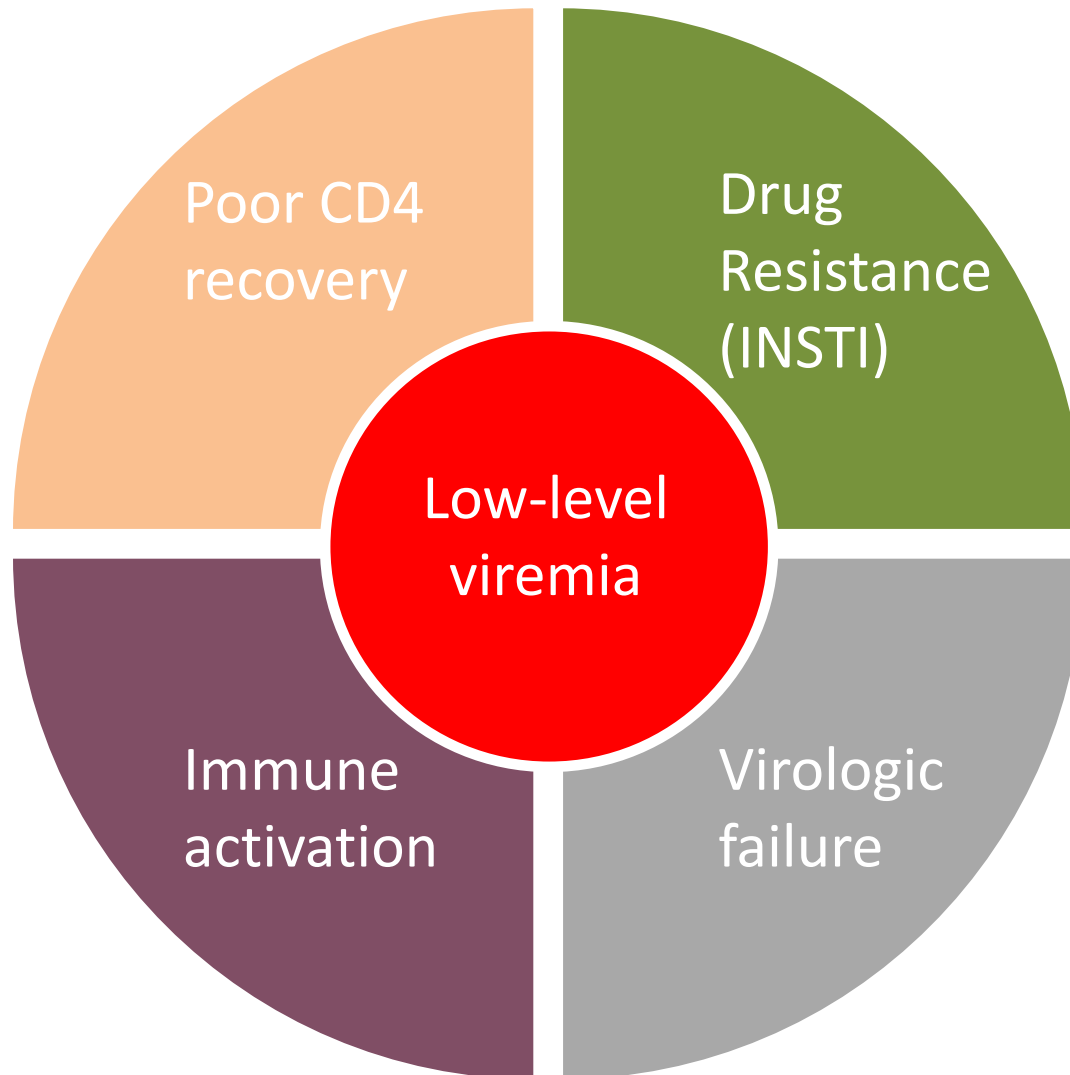
In summary

A highly ART- experienced patient with multidrug resistance who developed virologic failure at low-level viremia: <200 copies/mL

Impact of persistent low-level viremia



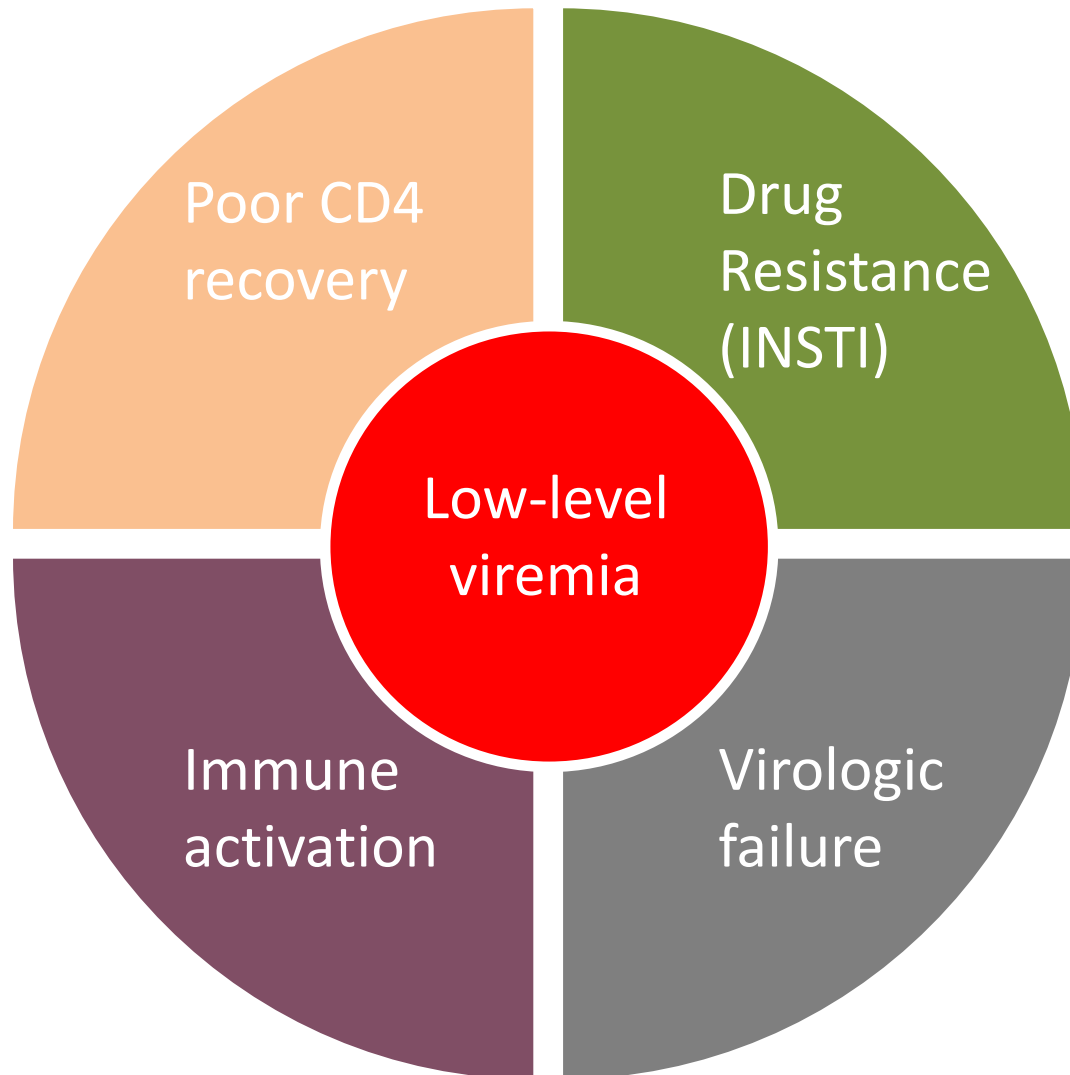
Impact of persistent low-level viremia



Gallien et al. AIDS, 2011.

Armenia et al. J Antimicrob Chemother, 2015.

Impact of persistent low-level viremia

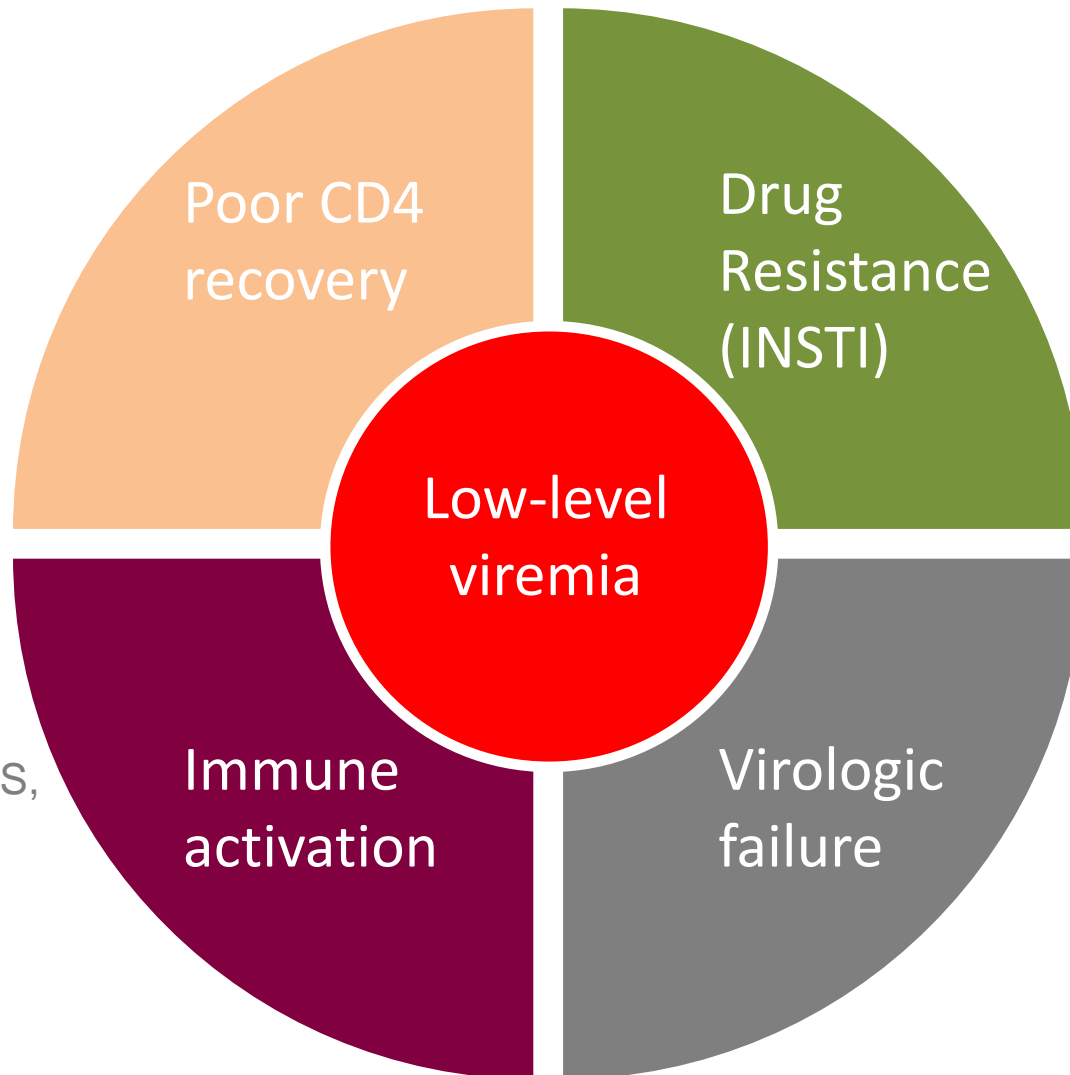


Laprise et al. Clin Infect Dis, 2013.

Santoro et al. Clin Infect Dis, 2014.

Swenson et al. AIDS, 2014.

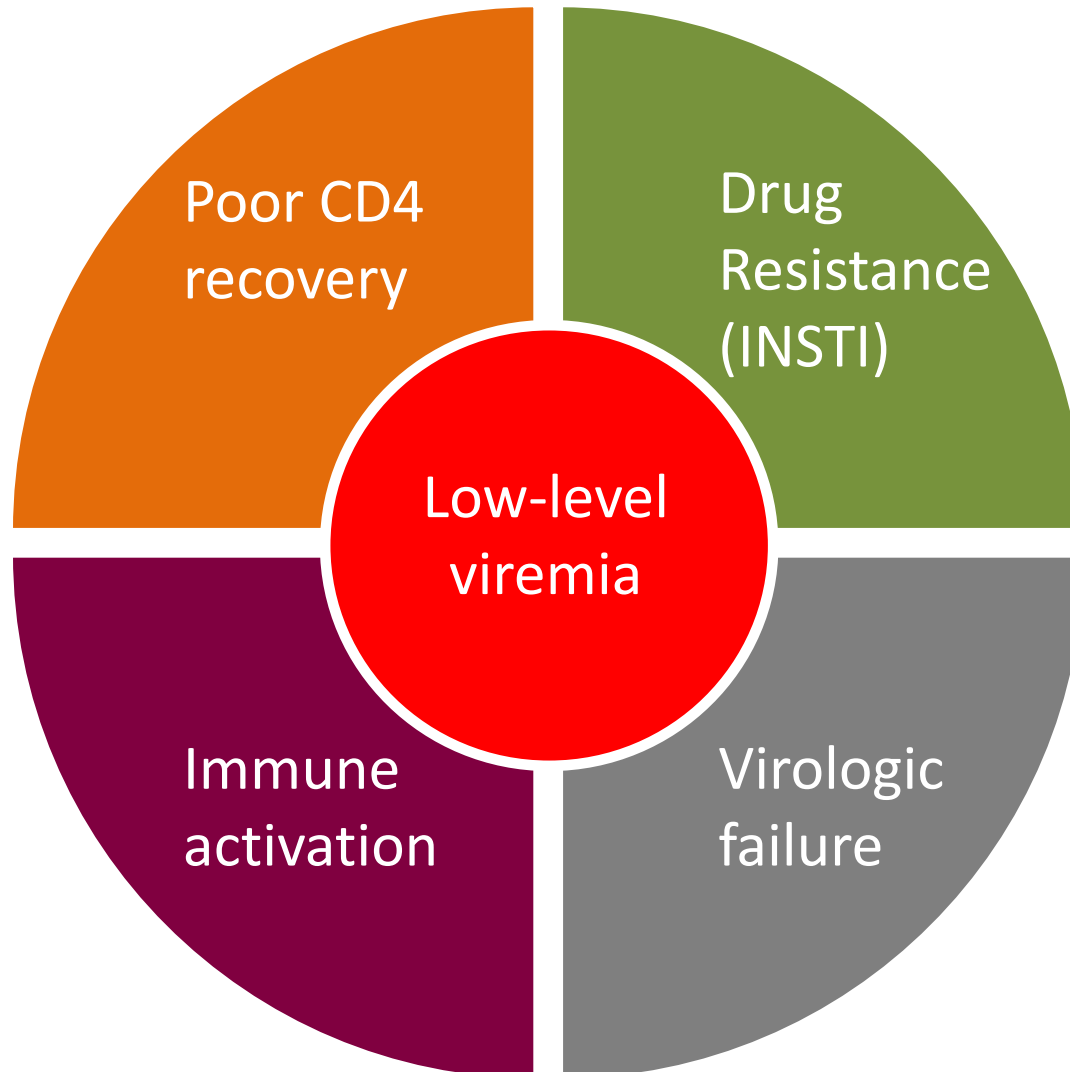
Impact of persistent low-level viremia



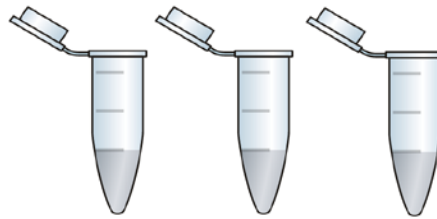
Karlsson et al. AIDS, 2004.

Impact of persistent low-level viremia

Steel et al. Antivir
Ther, 2007.



Genotypic resistance test: in-house system



15 mL plasma sample



Centrifuge 20.000 x rpm
90 minutes at room temperature

150 μ L \approx 100 x



RNA extraction



Amplification



Sequencing



Genotype

Genotypic resistance test

Protease

S37N

Reverse transcriptase

V35L, K70R, E138S,
V178M, K238T

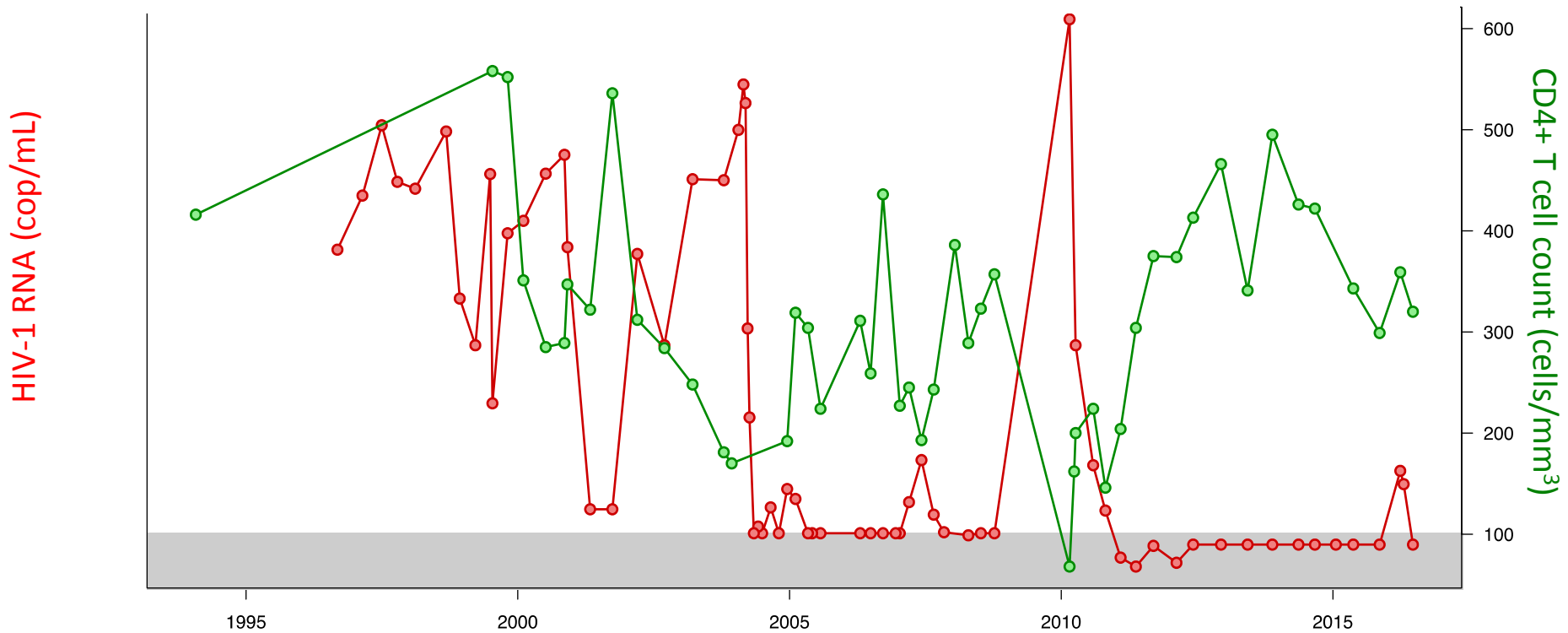
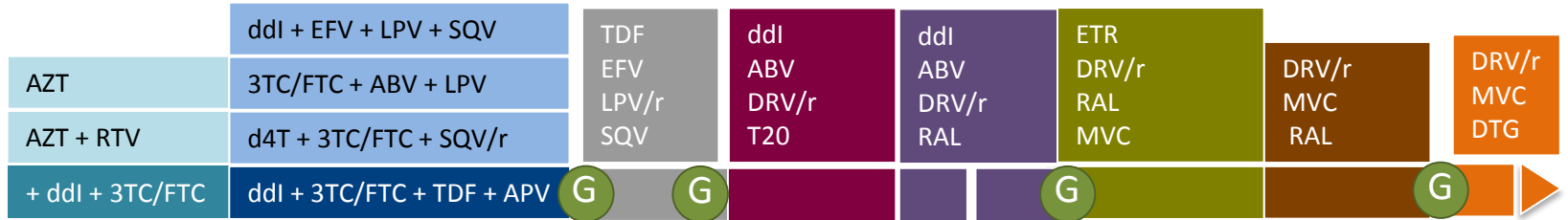
Viral tropism

CCR5

Integrase

D10E, E11D, V72I, **T97AT**,
L101I, S119P, T122I, G123S,
A124T, T125A, R127K, F181L,
201I, T206S, I220F, N232D,
K244R

Clinical evolution



Conclusions

- HIV-1 infected patients with virologic failure at low levels of viremia can also harbor resistance-associated mutations to integrase strand-transfer inhibitors
- Therefore, it is important to consider those cases for genotyping
- The use of plasma ultracentrifugation may be helpful in this clinical setting.

Acknowledgments



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