Review of clinical experiences: Long Acting

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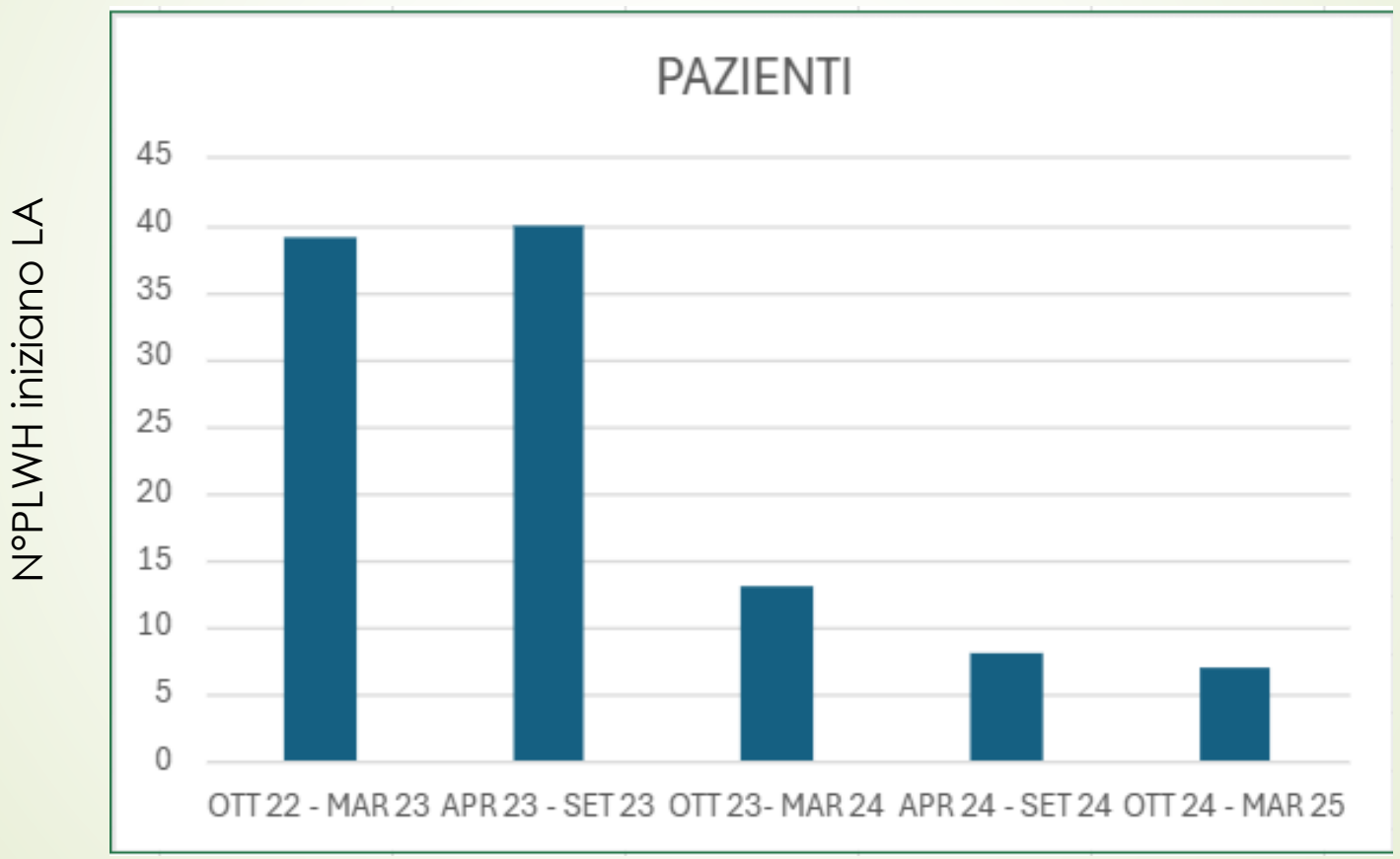
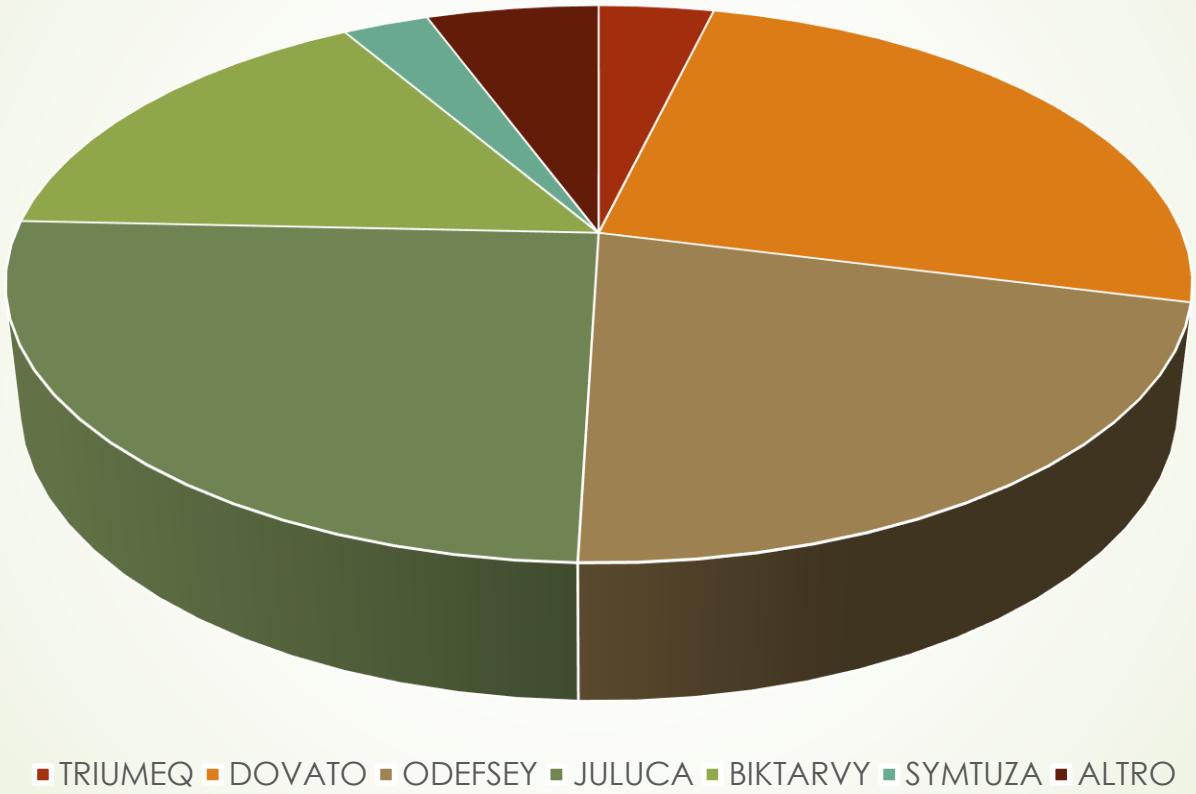
Caratteristiche di popolazione

Caratteristiche di popolazione	Totale: 107 PLWH
Male, n (%)	91/107 (85%)
Age at switch, years, median	49 (42-56)
Country of origin (Italy)	69/107 (64.5%)
Epidemiology MSM Eterosex IDU	 44/107 (41%) 20/107 (18.6%) 1/107 (0.9%)
At least one comorbidity, n (%)	16/107 (15%)
HBcAb positive, n (%)	26/107 (24%)
HCV Ab positive, n (%)	12/107 (11.2%)
Previous AIDS, n (%)	10/107 (9%)
CD4 nadir, median (cell/mm3)	748 (248-540)
BMI>30	4/107 (3.7%)
Number of previous therapies, median	3 (2-5)
GRT available	64/107 (59%)
OLI	49/107 (45.7%)

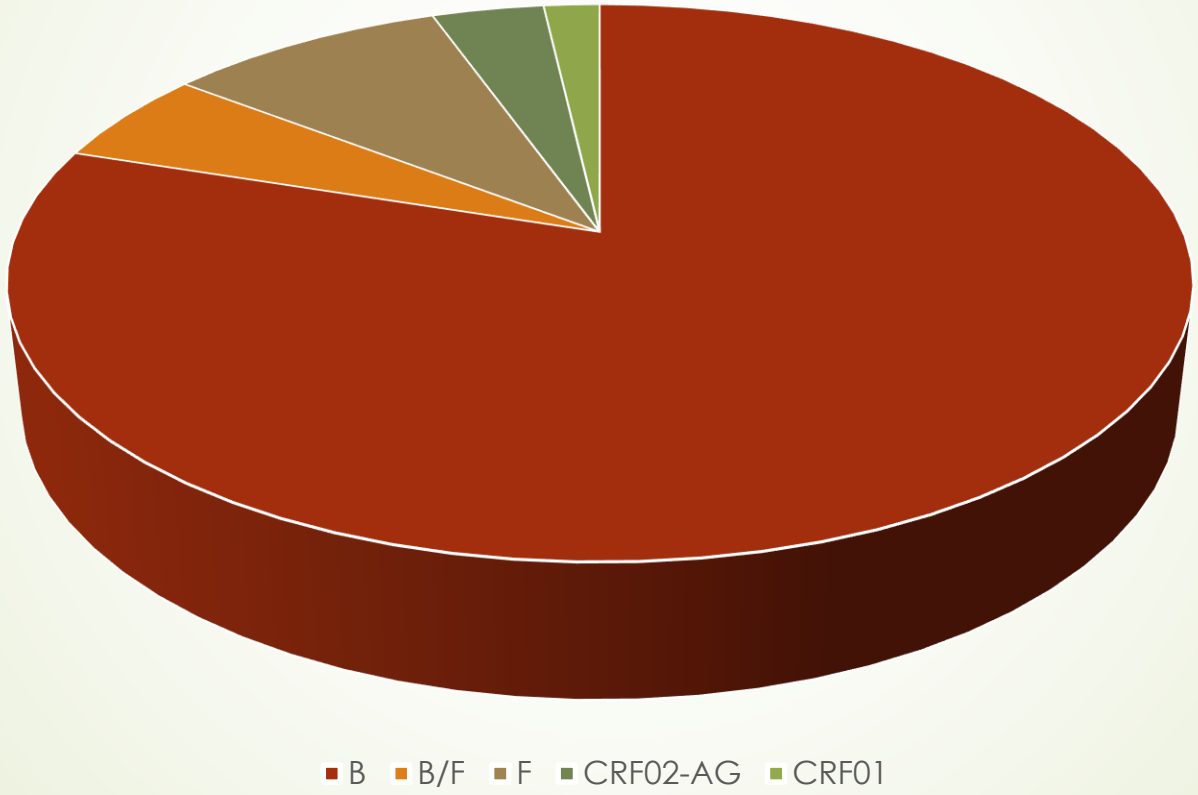
PLWH che hanno iniziato la terapia LA



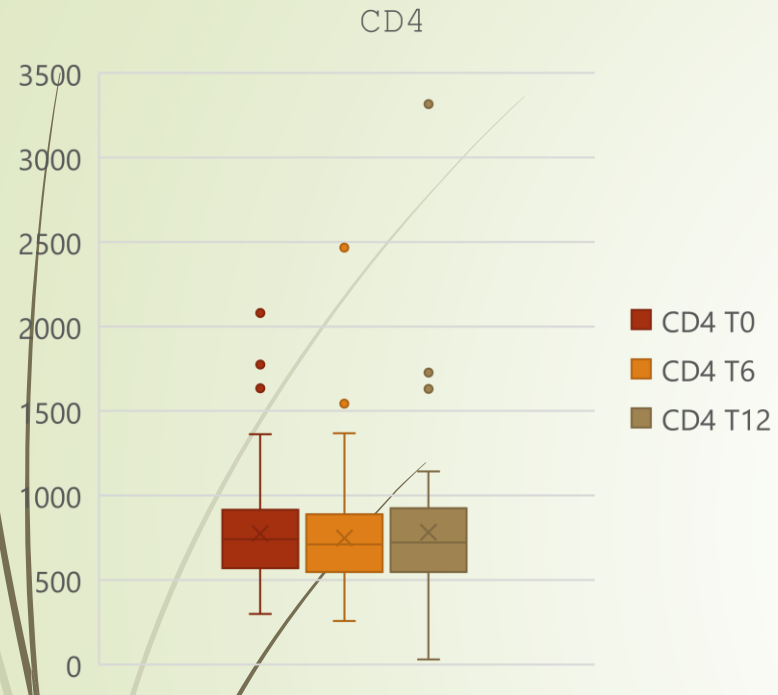
HAART allo switch

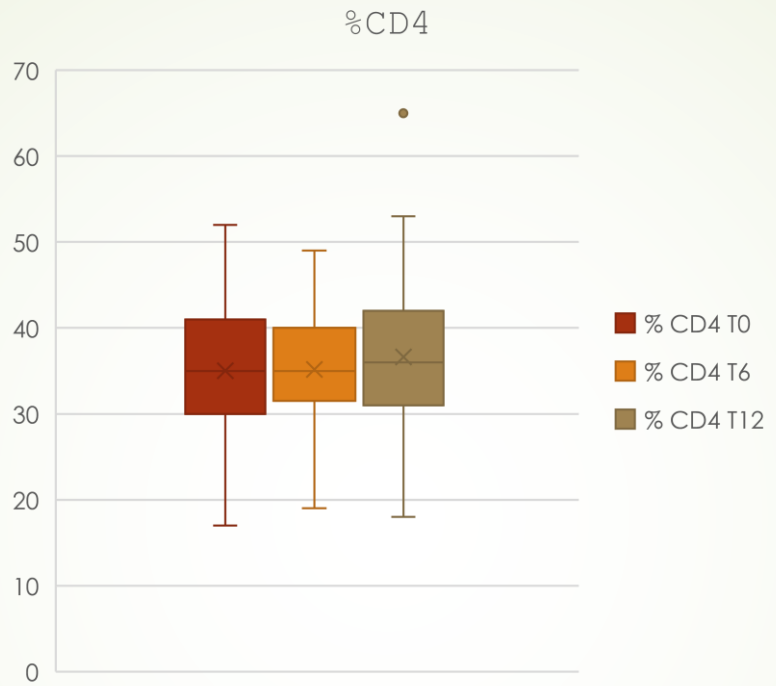


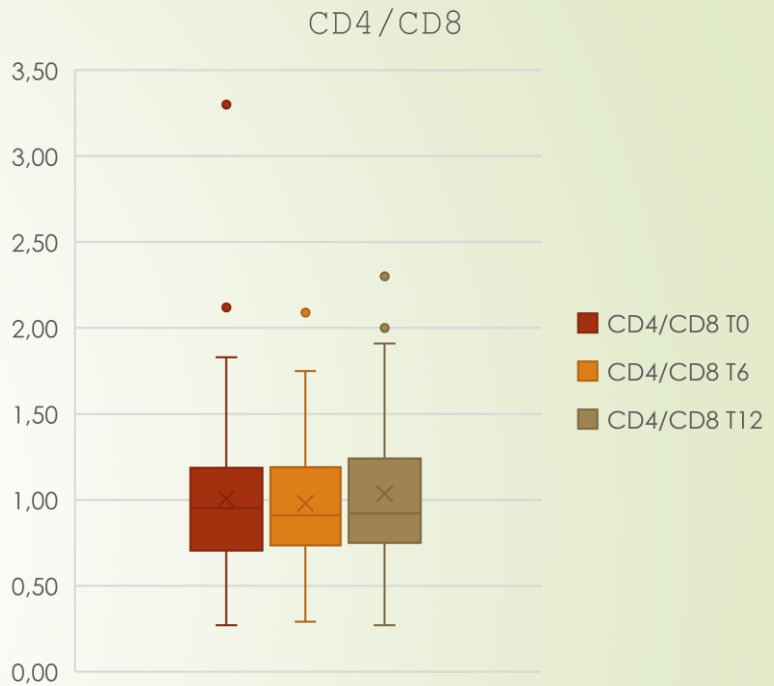
HIV Sottotipo



Parametri immunologici

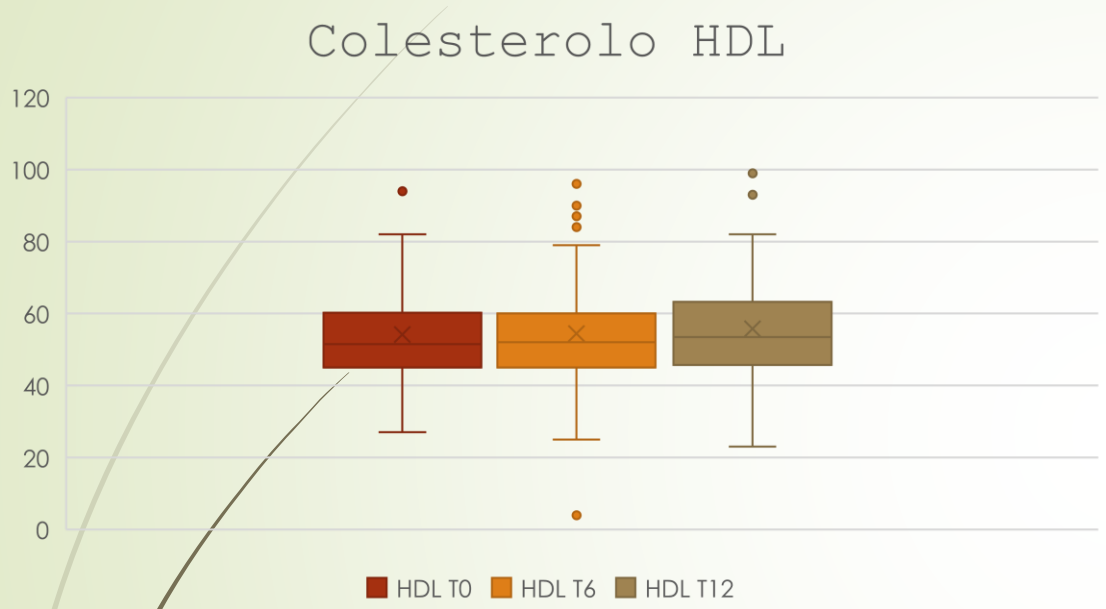


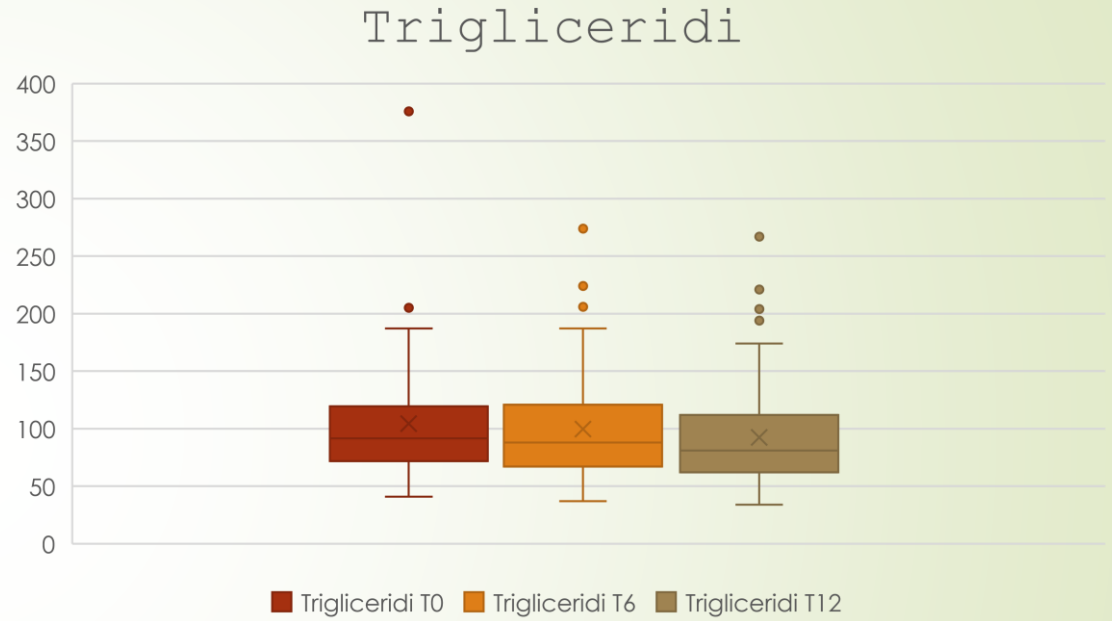




Mediana (IQR)	T0	T6	T12	p
CD4	741 (581-901)	710 (559-881)	721 (548-925)	**0,04**
% CD4	35 (30-41)	35 (32-40)	36 (31-42)	0,16
CD4/CD8	0,95 (0,72-1,16)	0,91 (0,74-1,19)	0,92 (0,75-1,24)	0,36

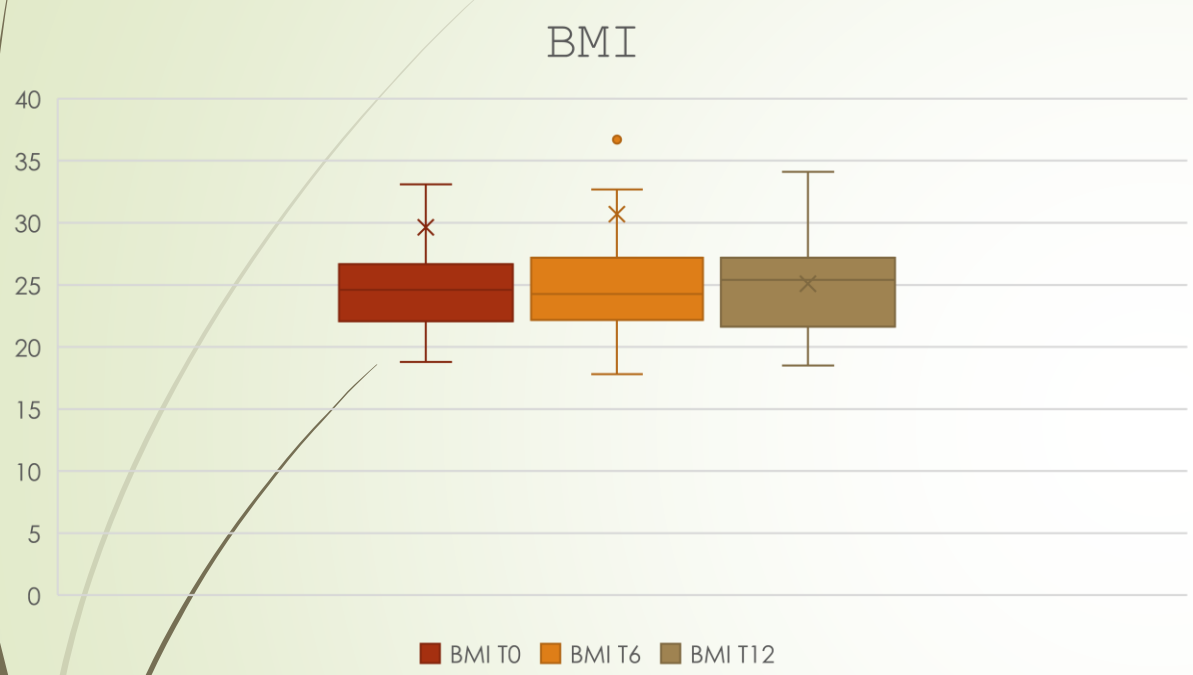
Parametri metabolici

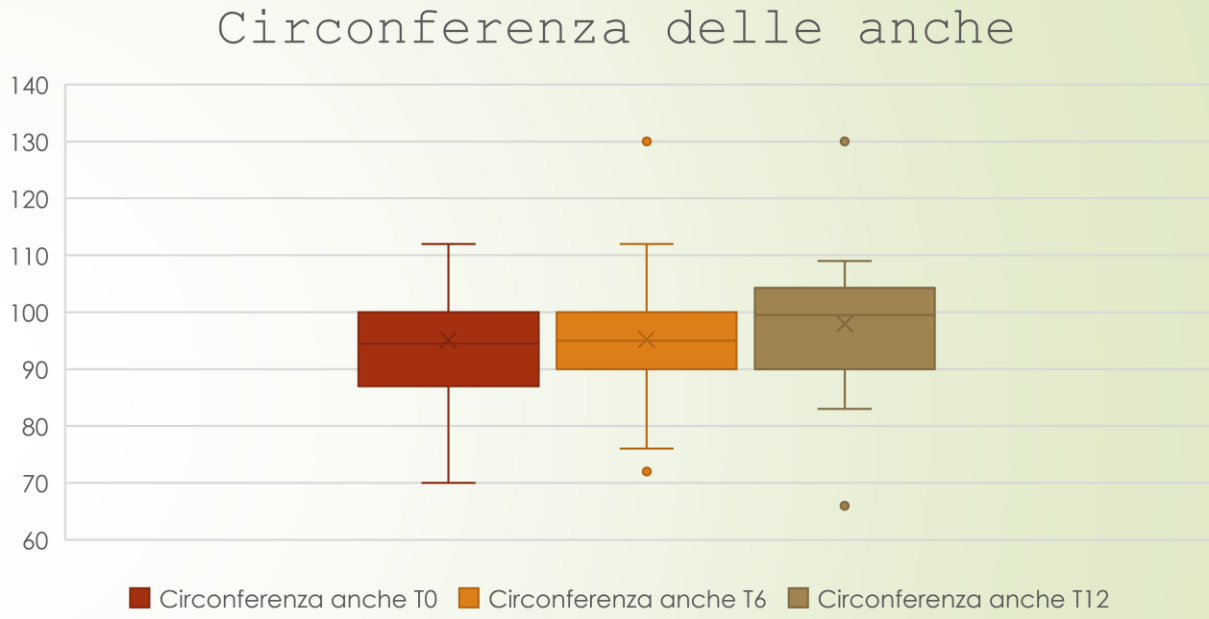




Mediana (IQR)	T0	T6	T12	p
Colesterolo totale	182 (167-204)	183 (161-205)	183 (157-210)	0,29
HDL	52 (45-60)	52 (45-60)	54 (47-63)	**<0,01**
LDL	114 (96-135)	109 (94-129)	111 (88-138)	0,62
Trigliceridi	92 (73-117)	88 (67-119)	81 (63-110)	**0,02**

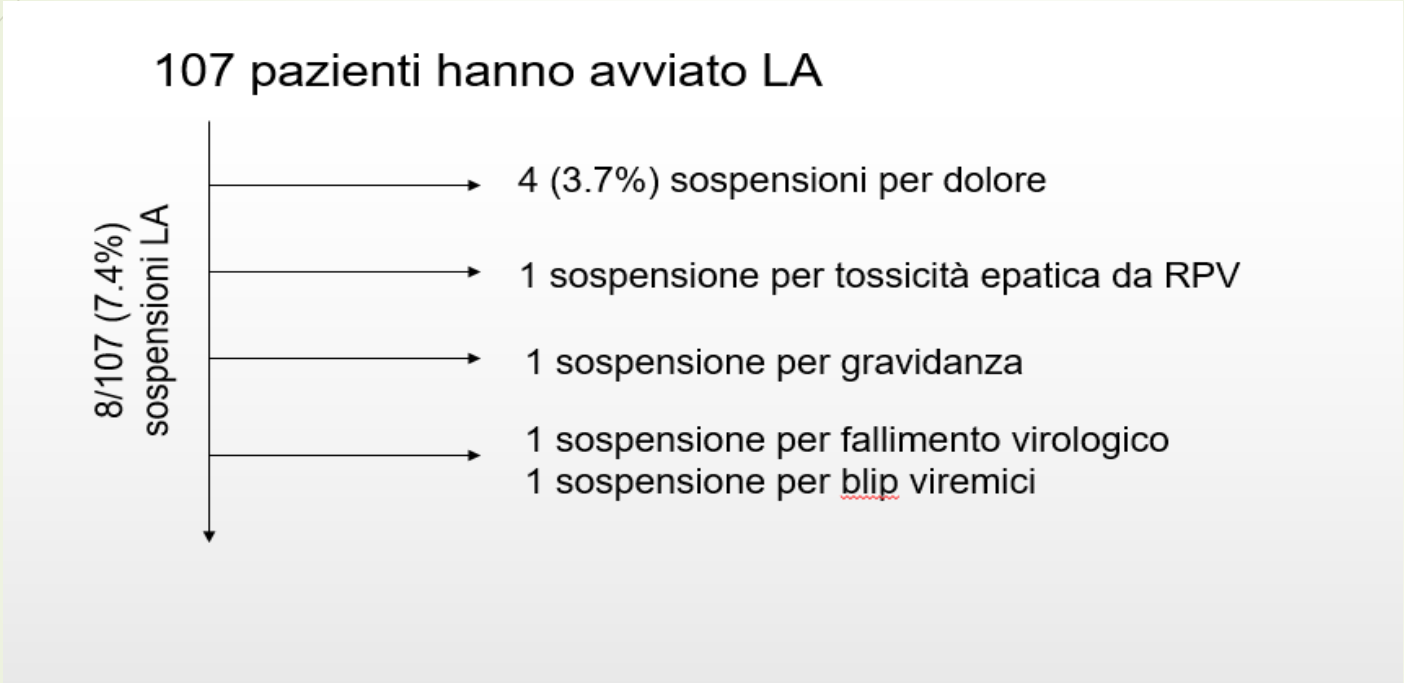
Parametri metabolici





Mediana (IQR)	T0	T6	T12	p
BMI	24,6 (22,1-26,7)	24,3 (22,1-27,2)	25,2 (21,6-27,2)	0,36
Circonferenza vita	88 (83-96)	89 (84-97)	90 (83-99)	0,52
Circonferenza anche	94,5 (87-100)	95 (90-100)	99,5 (90-104)	**<0,01**

Sospensioni LA



99 pazienti attualmente in LA

19-21 GIUGNO ROMA UNIVERSITA' CATTOLICA DEL SACRO CUORE CENTRO CONGRESSI EUROPA
RESEARCH and CARE: FROM BENCH, TO BEDSIDE, TO COMMUNITY
16° CONGRESSO NAZIONALE CAR Italian Conference on AIDS and Antiviral Research
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Idiosyncratic drug liver injury during long-acting HIV treatment: A Case Report

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Background

Transaminase elevation is a recognized, yet usually transient and rare adverse effect of long-acting injectable antiretroviral therapy (ART) drugs like cabotegravir and rilpivirine in people living with HIV (PLWH)[1,2]. We report a case of hepatopathy in a patient transitioning to long-acting injectable (LAI) ART and subsequently returning to oral therapy due to liver toxicity.

Case Presentation

We describe a 68-year-old man diagnosed with HIV since 2015, with a nadir CD4 count of 122 cells/mm³ and peak HIV-RNA of 302174 cp/mL (CDC stage A3). Virologically suppressed for years, he had been on combination ART since diagnosis with 3TC/DTG since 2019.

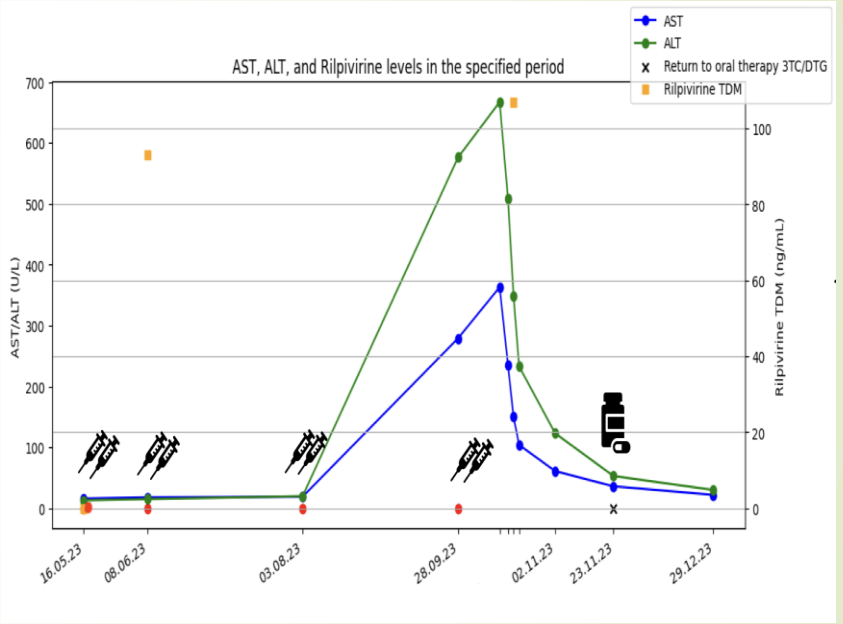
In May '23, he switched to LAI with intramuscular cabotegravir 600 mg/3mL and rilpivirine 900mg/3mL without oral bridging. The patient weighed 59 kg and was 170 cm tall (BMI 20.4 kg/m²). He received the second injection after 21 days due to personal reasons, but was still within the suggested time window of injection. Rilpivirine therapeutic drug monitoring (TDM) showed a trough concentration of 93 ng/mL (target >48 ng/mL) after the first injection. TDM for cabotegravir was not performed. The third and fourth injections followed at 8-week intervals. Asymptomatic transaminase elevation (AST 279 U/L, ALT 578 U/L) with stable immunovirological parameters occurred at the fourth injection.

Repeated tests after 2 weeks confirmed elevated transaminases, prompting follow-up with supportive therapy and investigations. Rilpivirine TDM was rechecked, resulting in 107 ng/mL. Transaminases gradually decreased. **Figure 1** shows AST and ALT levels, rilpivirine concentration, and dates of cabotegravir and rilpivirine injections. Hepatic stasis indices and bilirubin were always within normal limits. The patient was vaccinated against HAV and HBV while HCV antibodies were negative. Serologies for T. pallidum, HEV, and Parvovirus B19 were negative, with negative HCV-RNA and CMV-DNA, and irrelevant EBV-DNA (42 cp/mL). Liver ultrasound was normal. Autoimmune disease investigations yielded inconclusive results.

In November '23, following a rapid decrease in transaminase levels, we proposed to continue LAI with a fifth dose, but the patient preferred to revert to oral 3TC/DTG regimen.

Discussion

This case highlights the importance of monitoring hepatic function during the transition to LAI. Rilpivirine TDM may be useful in assessing drug toxicity, but the lack of a universal reference range, particularly in the upper range, hinders dose adjustment in singular cases. Additionally, the patient received the second loading dose three weeks after the first, which, although clinically feasible, may have contributed to drug accumulation.



Efficacia virologica

- 17/107 (14%) BLIP virologici non confermati >50 e <400cp/mL
- 2/107 (1.9%) BLIP virologico confermato >50 e <400cp/mL
  (HIV-RNA: 55 cp/mL → 69cp/mL → NR)
  (HIV-RNA: 56cp/mL → 21cp/mL → 27cp/mL in 4 mesi; interruzione)
- 1/107 (0.9%) BLIP virologico non confermato >400cp/mL non confermato
- 1/107 (0.9%) Viremia >400 confermata
  (HIV-RNA: 438cp/mL → 1100cp/mL)

Test di Resistenza al fallimento :nessuna mutazione su RT e PR
INSTI non amplificabile. Interruzione.

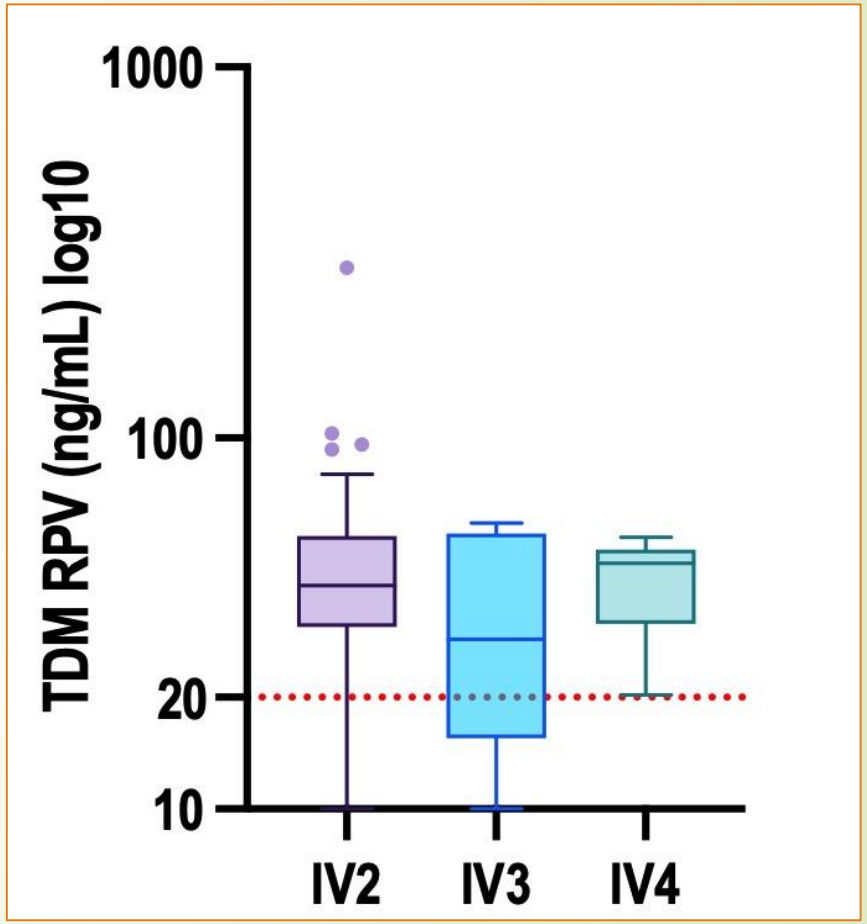
TDM RPV

TDM RPV assessed in 65 PLWH

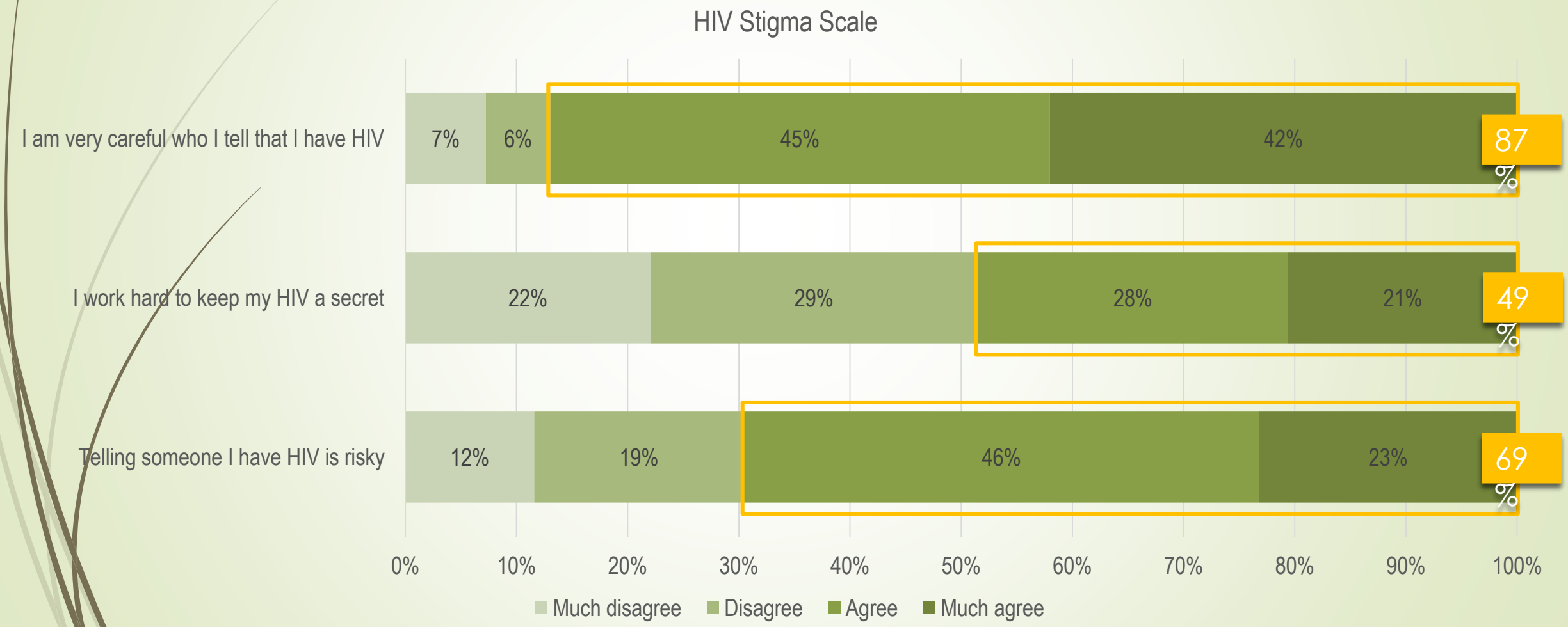
Prevalence of TDM RPV < 20ng/mL at IV2: **11** (**16.9%**)

- 5/11 (45.5%) reached the target at IV3
- 2/11 (18.2%) at IV4
- 4/11 (36.4%) did not furtherly assess TDM RPV

	Unadjusted OR TDM RPV <20 ng/mL	P
OLI, no	**8.23 (1.62-42.34)**	**0.011**
BMI, >30Kg/m2	2.18 (0.36-13.01)	0.393
Hip circumference, >100cm	3.07 (0.72-12.98)	0.127



Perception of Stigma (n=79)



Questionario sulla percezione del dolore

Appena prima dell'iniezione si è sentito ansioso di ricevere l'iniezione?

Per niente	Poco	Abbastanza	Molto	Moltissimo
O	O	O	O	O

Quanto fastidio Le ha dato il dolore durante l'iniezione?

Per niente	Poco	Abbastanza	Molto	Moltissimo
O	O	O	O	O

Da quando ha ricevuto l'iniezione:

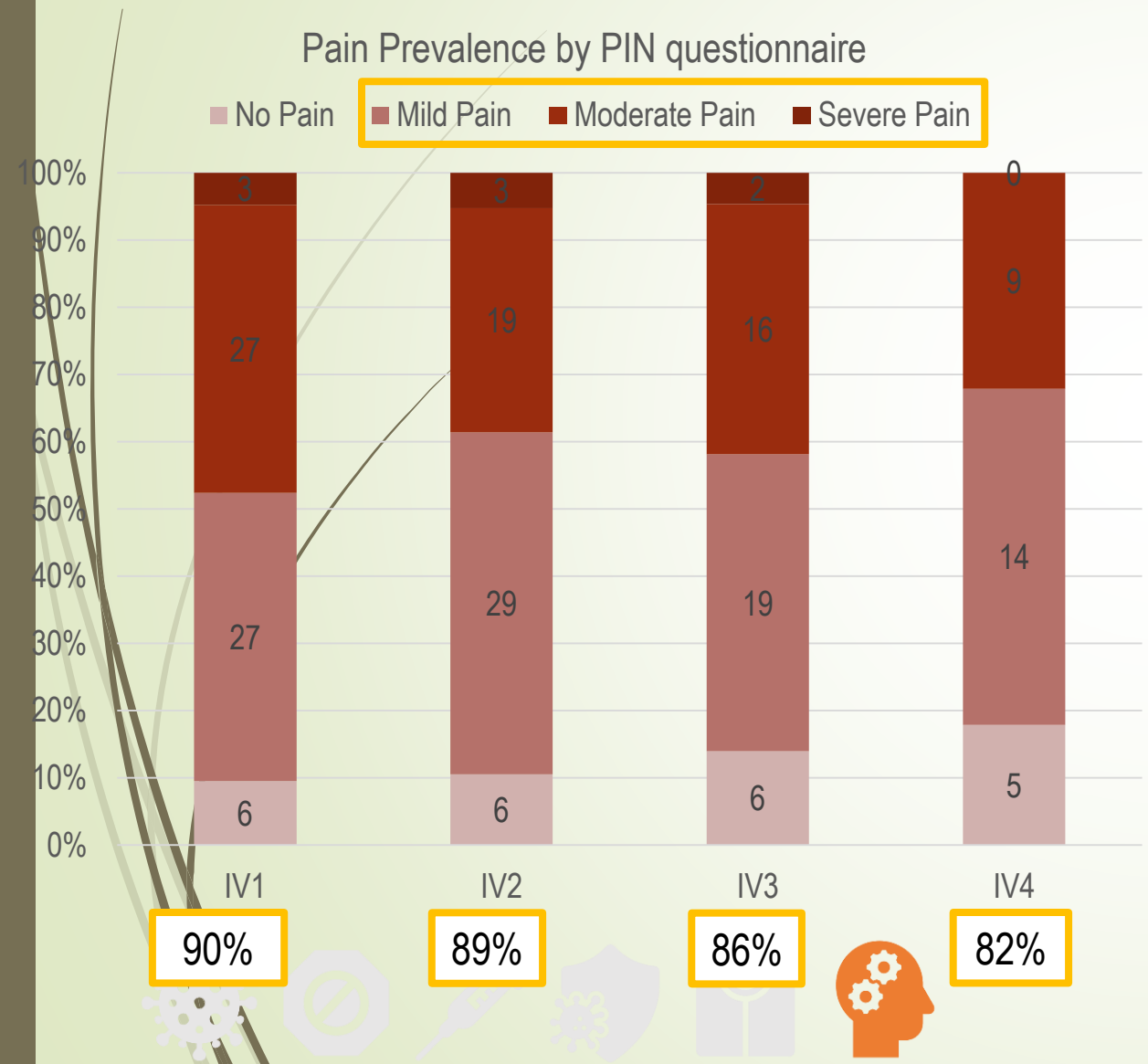
Quanto fastidio Le ha dato il dolore alla natica?

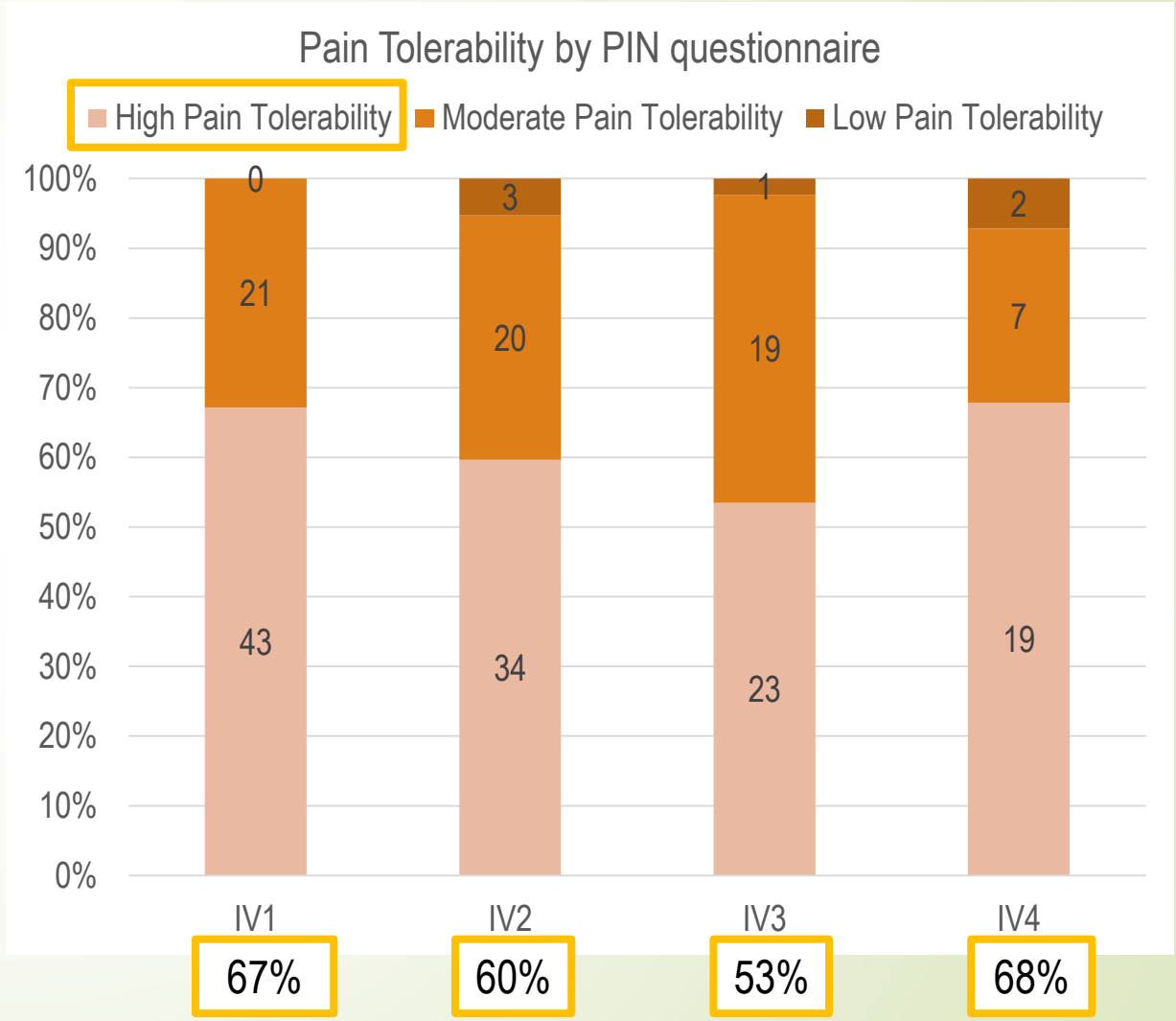
Per niente	Poco	Abbastanza	Molto	Moltissimo
O	O	O	O	O

Quanto fastidio Le ha dato l'arrossamento al sito di iniezione?

Per niente	Poco	Abbastanza	Molto	Moltissimo
O	O	O	O	O

PROs


Pain Prevalence by PIN questionnaire
No Pain
Mild Pain
Moderate Pain
Severe Pain
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
3
27
27
6
3
19
29
6
2
16
19
6
0
9
14
5
IV1
IV2
IV3
IV4
90%
89%
86%
82%


Pain Tolerability by PIN questionnaire
High Pain Tolerability
Moderate Pain Tolerability
Low Pain Tolerability
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
21
43
3
20
34
1
19
23
2
7
19
IV1
IV2
IV3
IV4
67%
60%
53%
68%

Questionario sulla percezione dell'iniezione

Quanto fastidio Le ha dato il gonfiore al sito di iniezione?

Per niente	Poco	Abbastanza	Molto	Moltissimo
O	O	O	O	O

Quanto fastidio Le ha dato il prurito al sito di iniezione?

Per niente	Poco	Abbastanza	Molto	Moltissimo
O	O	O	O	O

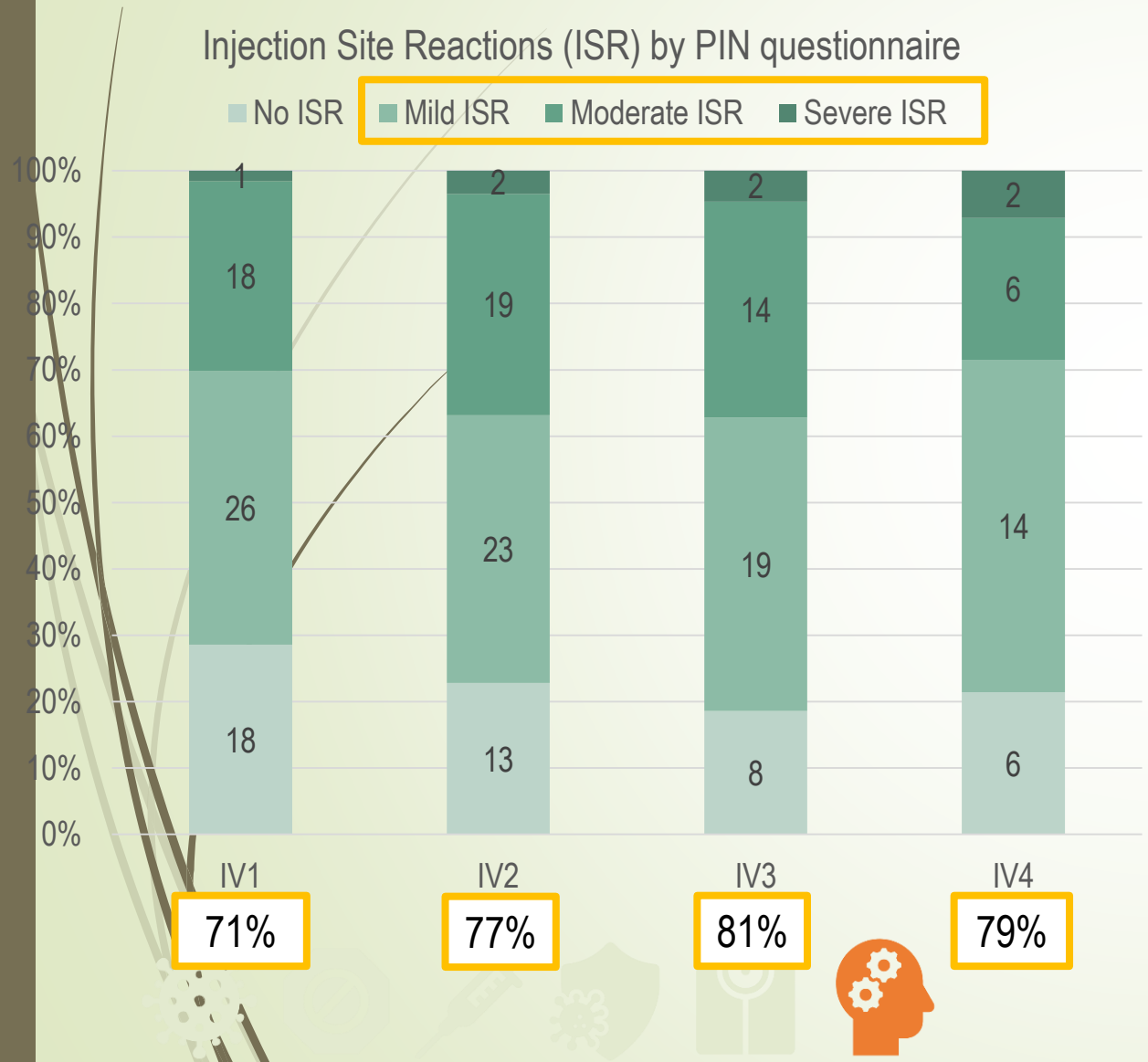
Quanto fastidio Le ha dato l'indurimento (la presenza di un bozzo) al sito di iniezione?

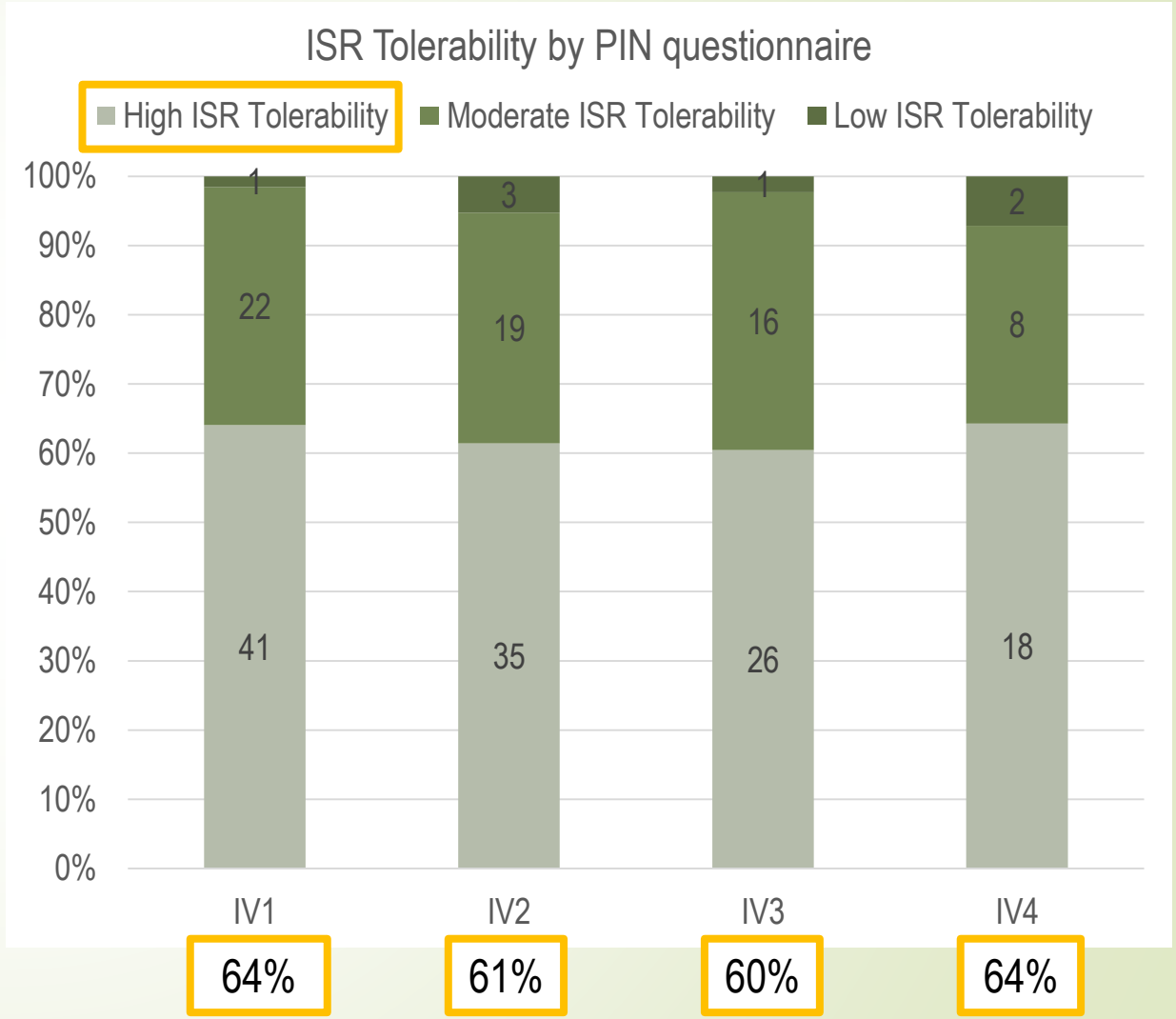
Per niente	Poco	Abbastanza	Molto	Moltissimo
O	O	O	O	O

Quanto fastidio Le hanno dato i lividi presenti al sito di iniezione?

Per niente	Poco	Abbastanza	Molto	Moltissimo
O	O	O	O	O

PROs


Injection Site Reactions (ISR) by PIN questionnaire
No ISR
Mild ISR
Moderate ISR
Severe ISR
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1
18
26
18
2
19
23
13
2
14
19
8
2
6
14
6
IV1
IV2
IV3
IV4
71%
77%
81%
79%


ISR Tolerability by PIN questionnaire
High ISR Tolerability
Moderate ISR Tolerability
Low ISR Tolerability
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1
22
41
3
19
35
1
16
26
2
8
18
IV1
IV2
IV3
IV4
64%
61%
60%
64%

HIV DRUG THERAPY GLASGOW 2024

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T-cell homeostasis parameters following switch to injectable cabotegravir plus rilpivirine in virally suppressed people living with HIV (PLWH)

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Regione Lombardia
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T-CELL HOMEOSTASIS

- Serrano-Villar et al *(PLoS Pathog, 2014)*: association between low CD4/CD8 ratio and increased morbidity and mortality with a significant shift of CD8 homeostasis towards terminally differentiated cells as well as higher cell activation and senescence
- Martinez-Sanz et al *(EBioMedicine, 2023)*: low CD4/CD8 ratio (<0.3) or a high total CD8+ cell count (>1500 cell/microL) after two years of cART are associated with a greater risk of serious non-AIDS events
- Ron et al *(Front. Immunol, 2024)*: increased mortality risk in individuals with CD4/CD8 ratio lower than 0.5 and a trend towards a negative outcome with a total CD8+ count above 1138 cell/microL
- Hunt et al *(J Infect Dis, 2004)*: activated CD8+ cells correlate inversely with CD4+ recovery
- Marchetti et al *(AIDS, 2006)*: higher values of activated CD8/CD38 in INRs compared to immunological responders

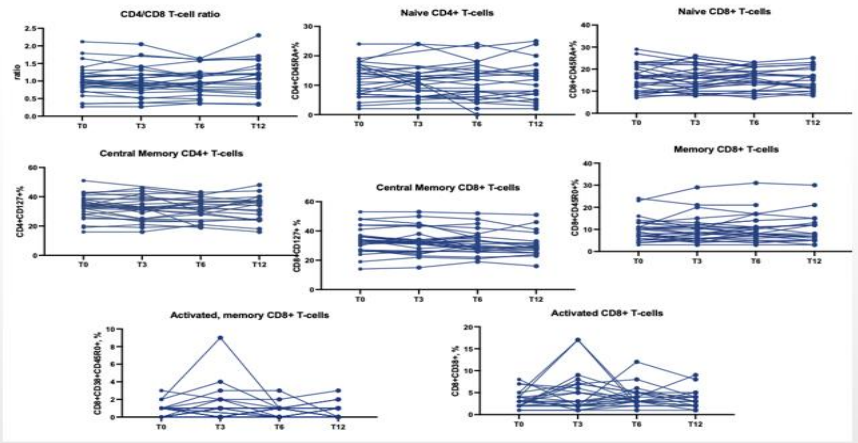
CAB/RPV

- Clinical efficacy of injectable CAB plus RPV reported in several clinical trials (ATLAS, FLAIR, ATLAS-2M, LATTE, SOLAR)
- Preliminary reports of efficacy also with archived mutations (CARES)
- Potential option in patients with adherence issues and detectable viremia (IAS-USA update 2024)
- Lower genetic barrier compared to other oral 2-DR

Few data regarding T-cell homeostasis

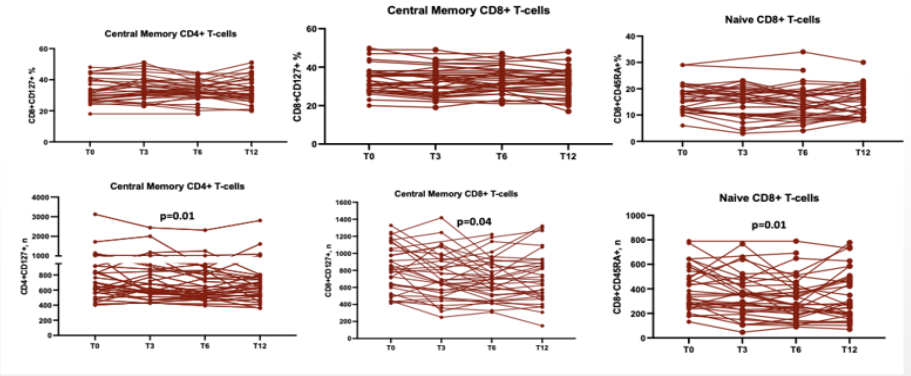
- Muccini et al. *(AIDS, 2024)*: significant increase in CD4/CD8 ratio reported (overall 0.08 per year, p<0.0001) after switch to LAI CAB/RPV from all previous regimens except for DTG/RPV
  - 0.08 per year from BIC/TAF/FTC, p=0.001
  - 0.09 per year from DTG/3TC, p=0.001
  - 0.06 per year from DTG/RPV, p=0.15

T-cell homeostasis from 3-DR



No major changes in T-cell homeostasis switching from 3-DR to CAB/RPV

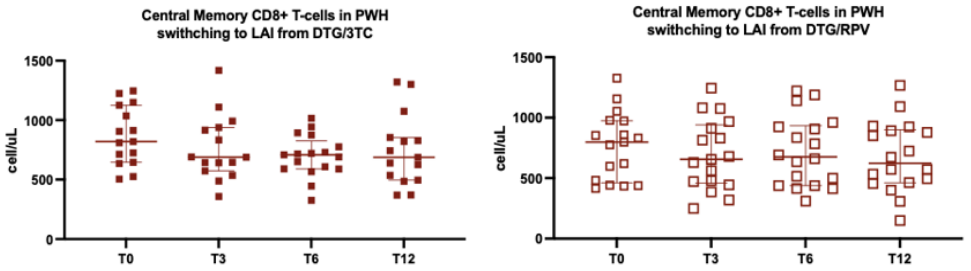
T-cell homeostasis from 2-DR



Decline in absolute:

- CD4+/CD127+ (T0: 703/uL, IQR [567-966]; T12: 647/uL, IQR [524-786], p=0.01)
- CD8+/CD127+ (T0: 819/uL, IQR [609-1045]; T12: 673/uL, IQR [490-885], p=0.004)
- CD8+/CD45RA+ (T0: 354/uL, IQR [267-562]; T12: 281/uL, IQR [188-486], p=0.01)

CM T-cells from DTG/3TC and DTG/RPV



Only subjects switching from DTG/3TC showed a tendency to a significant decrease in CD8+ central memory cells (T0: 819/uL, IQR [645-1125]; T12: 687/uL, IQR [496-854], p=0.05)
No differences in individuals switching from DTG/RPV

- No major impact were observed in T-cell homeostasis after switching from oral cART to injectable CAB/RPV
- Central memory CD4+ and CD8+ and naive CD8+ show a decreasing trend in PLWH switching from 2-DR but further investigation are needed to study the mechanisms and to confirm the finding

Grazie a: G.C.Marchetti, C.Tincati,L, Gazzola,L. Rezzonico, D.Tommasoni, L.Albertini, E.Ferrante