Review of clinical experiences: Long Acting

- Lorenzo Albertini
- ASST Santi Paolo e Carlo
- UOC Malattie Infettive
- Università degli Studi di Milano

Introduzione e obiettivi

La terapia antiretrovirale long-acting, ovvero la somministrazione intramuscolare di cabotegravir e rilpivirina, rappresenta una svolta nel trattamento dell'infezione da HIV-1, offrendo un'alternativa altamente efficace e ben tollerata alla somministrazione orale giornaliera nei pazienti virologicamente soppressi.

Vantaggi principali[1]:

- Elevata efficacia virologica comparabile alla terapia orale standard
- Miglioramento dell'aderenza terapeutica e della qualità di vita
- Riduzione dello stigma e del burden psicologico associato alla terapia quotidiana
- Regime ben tollerato, con profilo di sicurezza favorevole

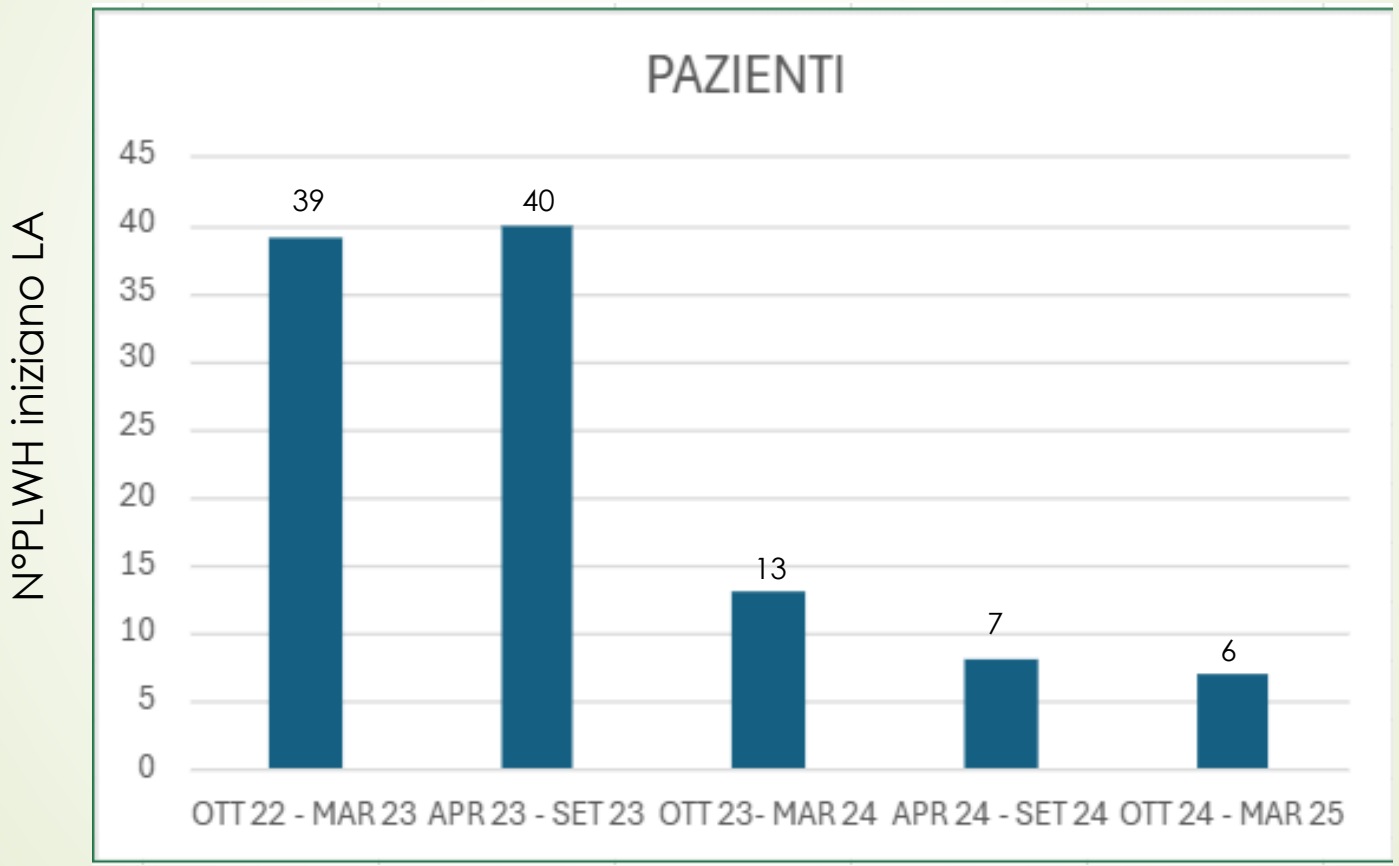
Obiettivo: caratterizzazione della coorte long-acting (profilo viro-immunologico e metabolico; stigma percepito; tollerabilità e motivi di sospensione) c/o la UO Malattie Infettive, ASST Santi Paolo e Carlo, Università degli Studi di Milano

1 Switch to long-acting cabotegravir and rilpivirine in virologically suppressed adults with HIV in Africa (CARES): week 48 results from a randomised, multicentre, open-label, non-inferiority trial; *C. Kityo et al;* Lancet Oct 2024

Materiali e Metodi

- Arruolamento di PLWH afferenti alla Clinica di Malattie Infettive, ASST Santi Paolo Carlo, Università degli Studi di Milano che hanno intrapreso LAI dall'ottobre 2022 al marzo 2025
- Database dedicato (Redcap) con estrazione dei seguenti dati:
  - Caratteristiche demografiche, comorbidità, pregresse cART
  - Parametri viroimmunologici e metabolici durante le iniezioni dei primi 12 mesi di LAI
  - PROs e questionari su tollerabilità e stigma dei primi 12 mesi di LAI

PLWH che hanno iniziato la terapia LA presso la Clinica di Malattie Infettive, ASST Santi Paolo e Carlo, Università degli Studi di Milano



Caratteristiche della popolazione in studio

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%)
cART at switch - TAF/FTC/BIC - ABC/3TC/DTG - TAF/FTC/DRV/c - TAF/FTC/RPV - RPV/DTG - 3TC/DTG - other	 18 (16%) 4 (4%) 3 (3%) 22 (21%) 27 (25%) 27 (25%) 6 (6%)
HIV subtype - B - B/F - F - CRF02-AG - CRF01	 52 (80%) 3 (5%) 6 (9%) 2 (4%) 1 (2%)

Efficacia virologica- 1

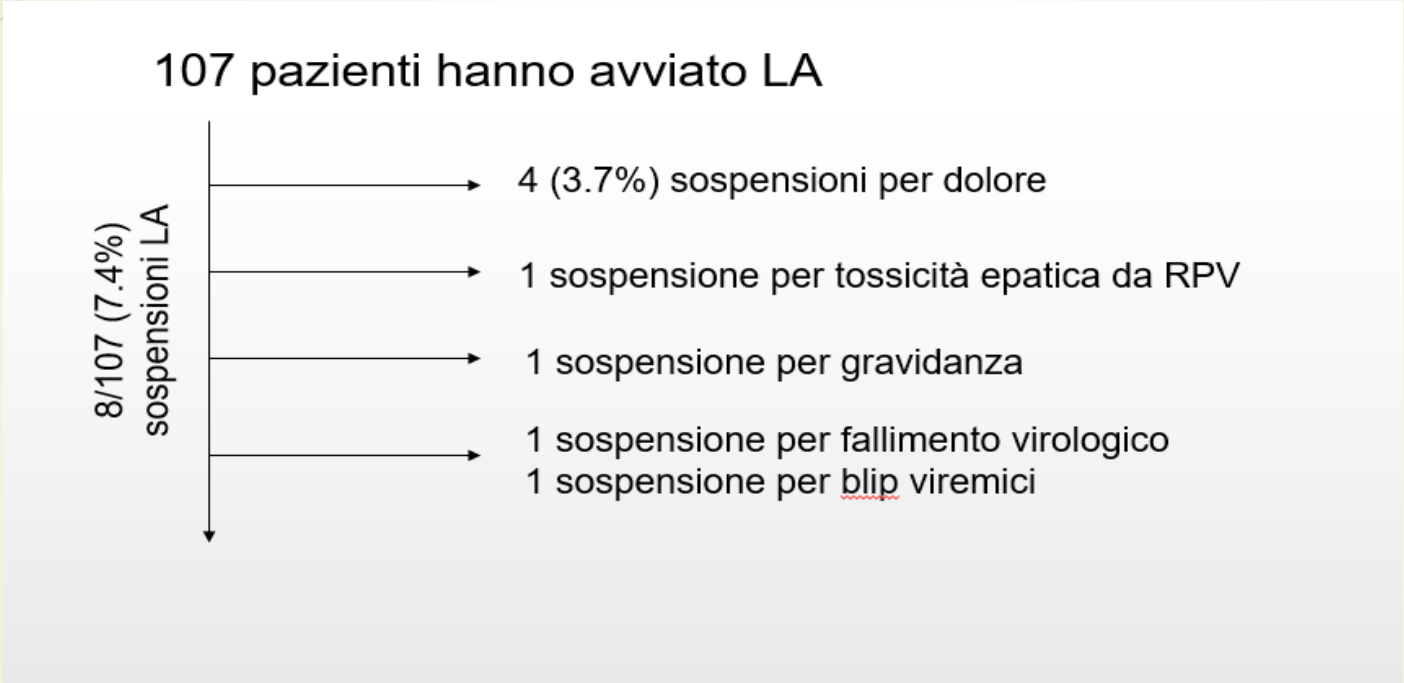
- 17/107 (14%) BLIP virologici non confermati >50 e <400cp/mL
- 1/107 (0.9%) Viremia >50 e <400cp/mL confermata
  (HIV-RNA: 55 cp/mL → 69cp/mL → NR)
- 1/107 (0.9%) Viremia >400cp/mL non confermata
- 1/107 (0.9%) Viremia >400 confermata
  (HIV-RNA: 438cp/mL → 1100cp/mL)

Efficacia virologica- 2

- 2 interruzioni per motivi virologici:
  - 1 interruzione per blip (3 blip: 56cp/mL → 21cp/mL → 27cp/mL in 4 mesi)
  - 1 fallimento virologico (HIV-RNA: 438cp/mL → 1100cp/mL)

    Test di Resistenza al fallimento: Nessuna mutazione su RT e PR
    INSTI non amplificabile

Sospensioni LA



99 pazienti attualmente in LA

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ABSTRACT BOOK

Virology and pharmacology

P 217 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). 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.

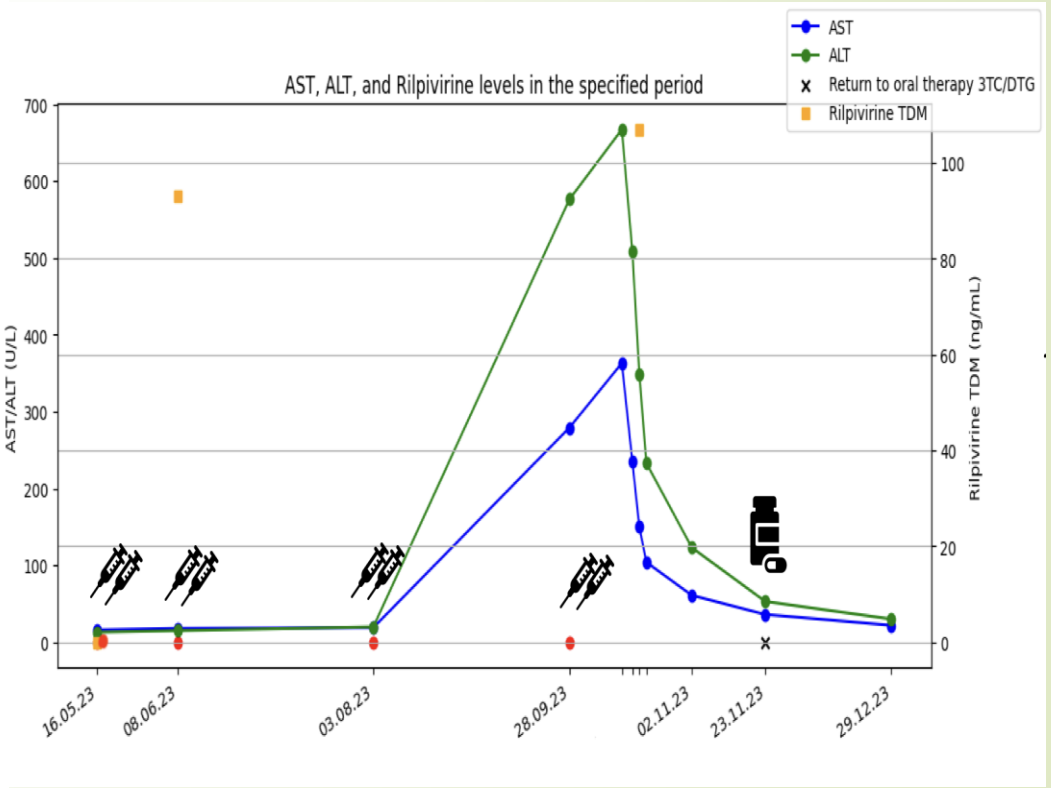
Case Presentation: We describe a 68-year-old man diagnosed with HIV since 2015, with a nadir CD4 count of 122 cells/mm³ and peak HIV-RNA of 302174 cp/mL (CDC stage A3). Virologically suppressed for years, he had been on combination ART since diagnosis with 3TC/DTG since 2019.

In May '23, he switched to LAI with intramuscular cabotegravir 600 mg/3mL and rilpivirine 900mg/3mL and received no 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.



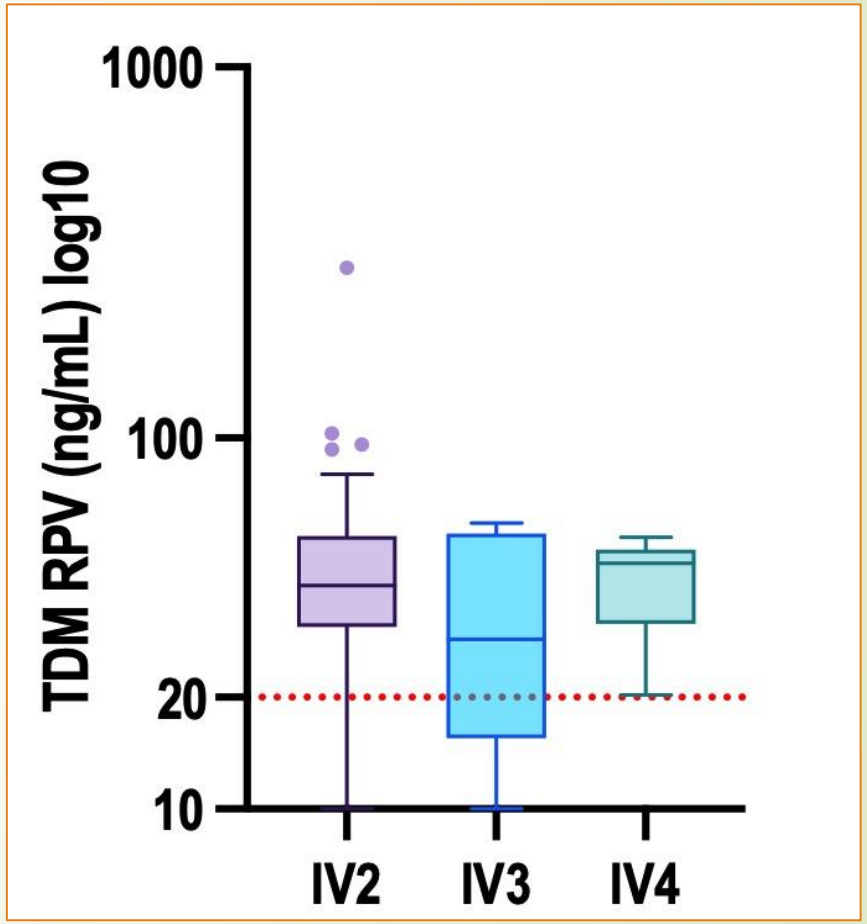
TDM RPV

TDM RPV assessed in 65 PLWH

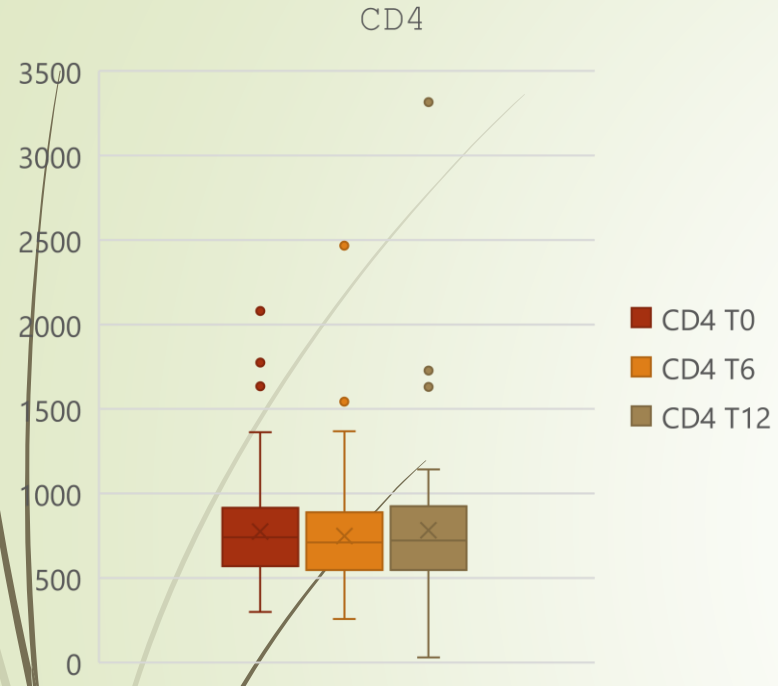
Prevalence of TDM RPV <20ng/mL at IV2: **11** (**16.9%**)

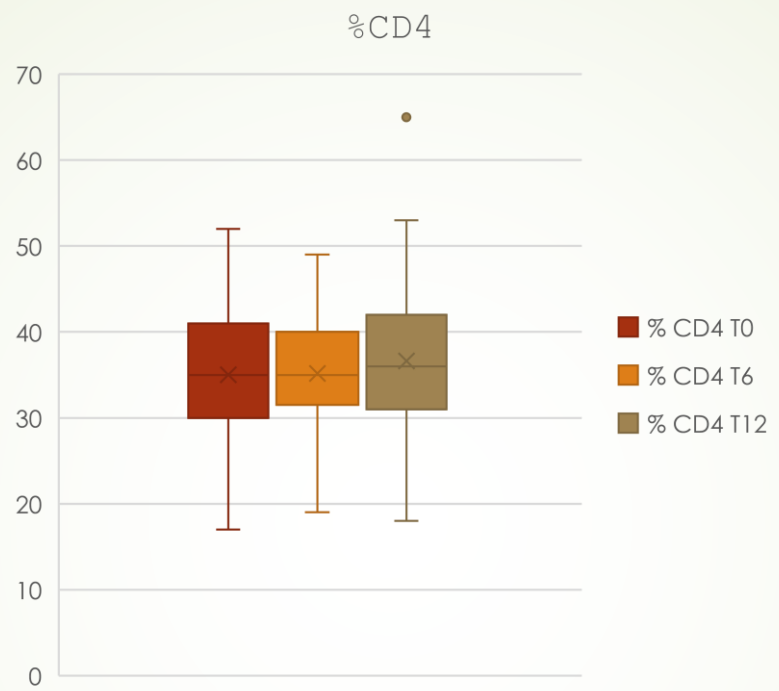
- 5/11 (45.5%) reached the target at IV3
- 2/11 (18.2%) at IV4
- 4/11 (36.4%) did not further assess TDM RPV

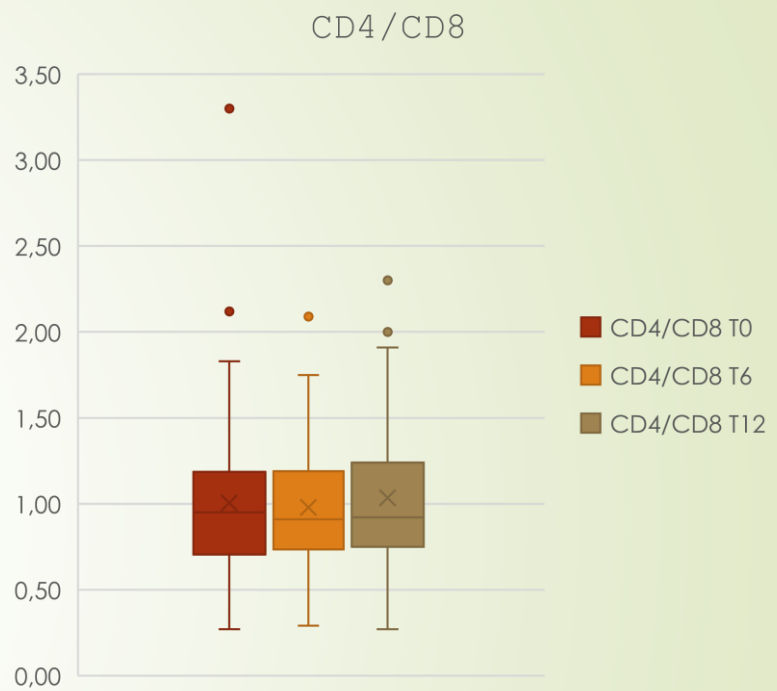
	Unadjusted OR TDM RPV <20 ng/mL	P
OLI, no	**8.23 (1.62-42.34)**	**0.011**
BMI, >30Kg/m2	2.18 (0.36-13.01)	0.393
Hip circumference, >100cm	3.07 (0.72-12.98)	0.127



Parametri immunologici

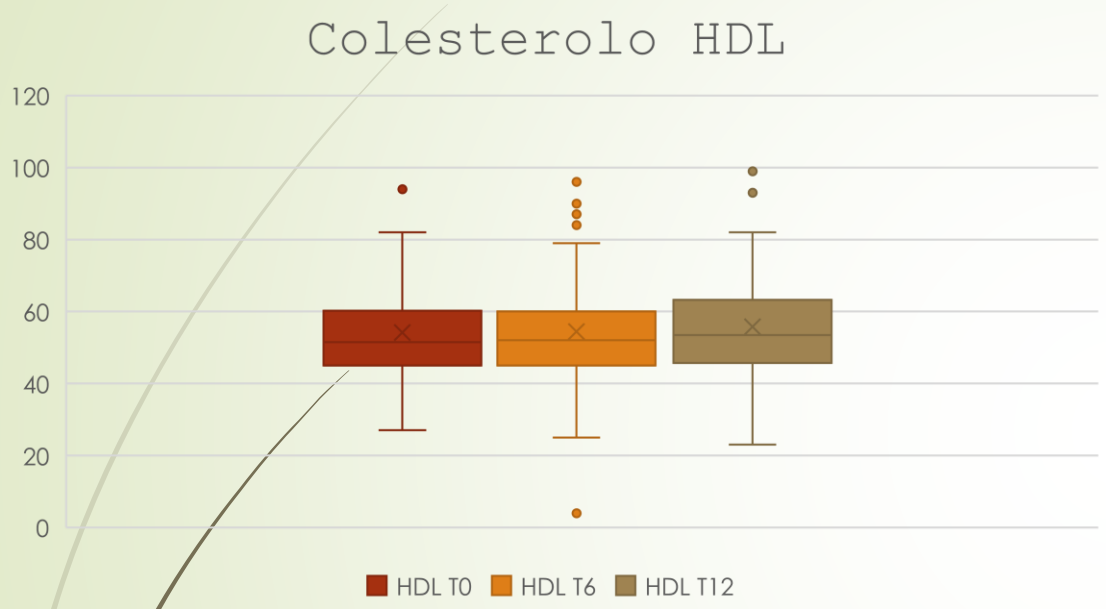


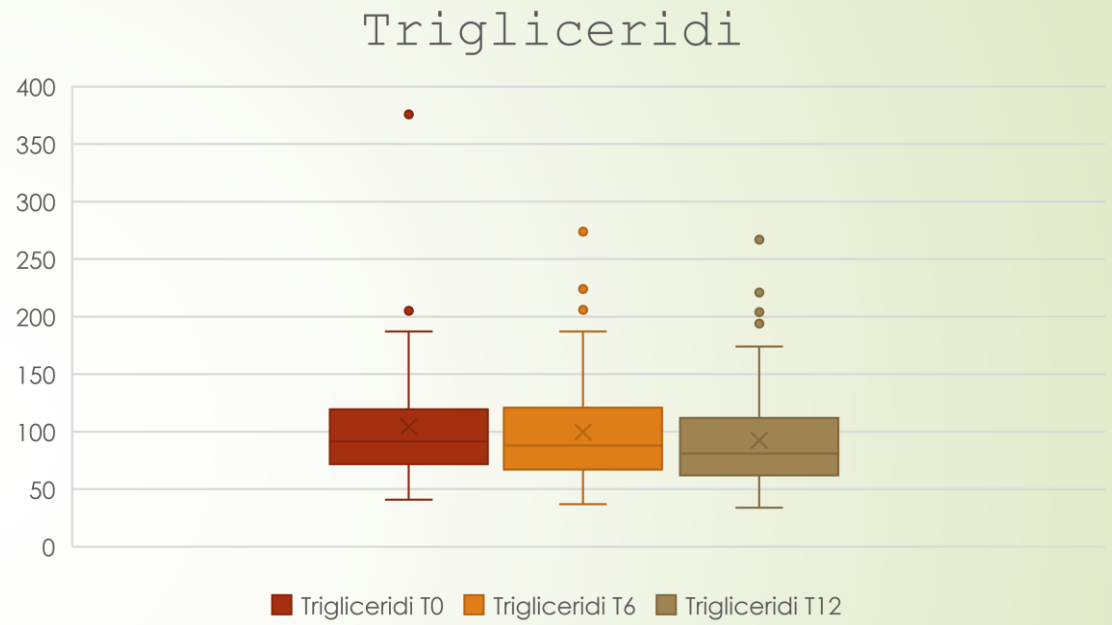




Mediana (IQR)	T0	T6	T12	p
CD4	741 (581-901)	710 (559-881)	721 (548-925)	**0,04**
% CD4	35 (30-41)	35 (32-40)	36 (31-42)	0,16
CD4/CD8	0,95 (0,72-1,16)	0,91 (0,74-1,19)	0,92 (0,75-1,24)	0,36

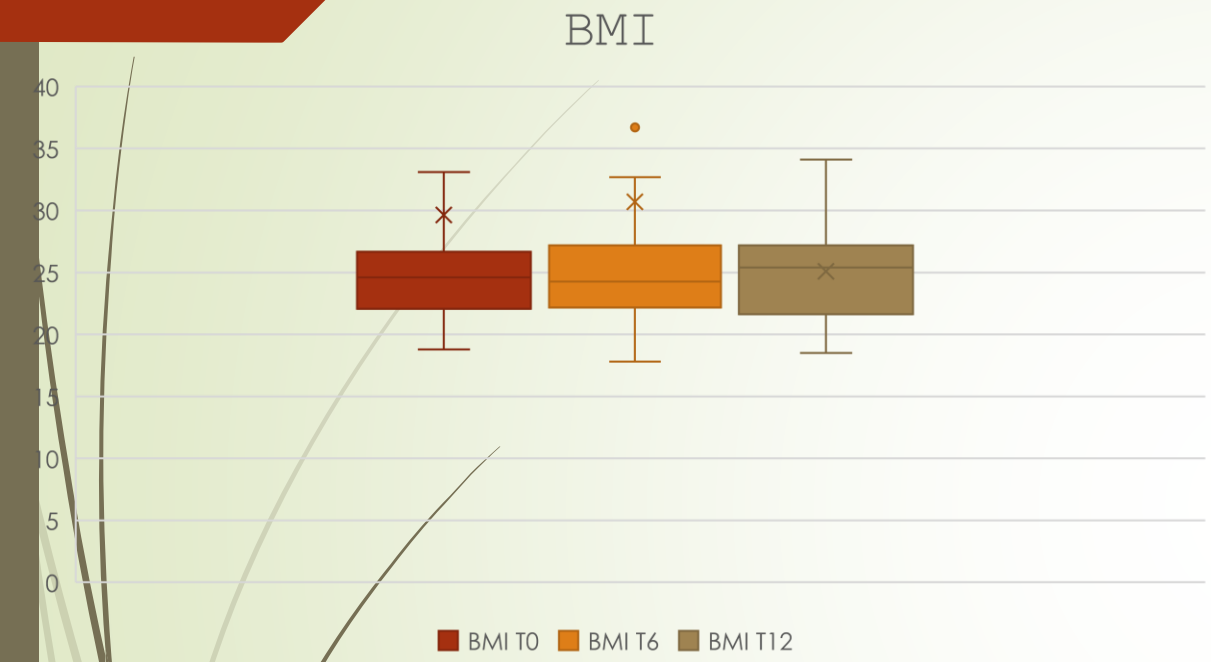
Parametri metabolici

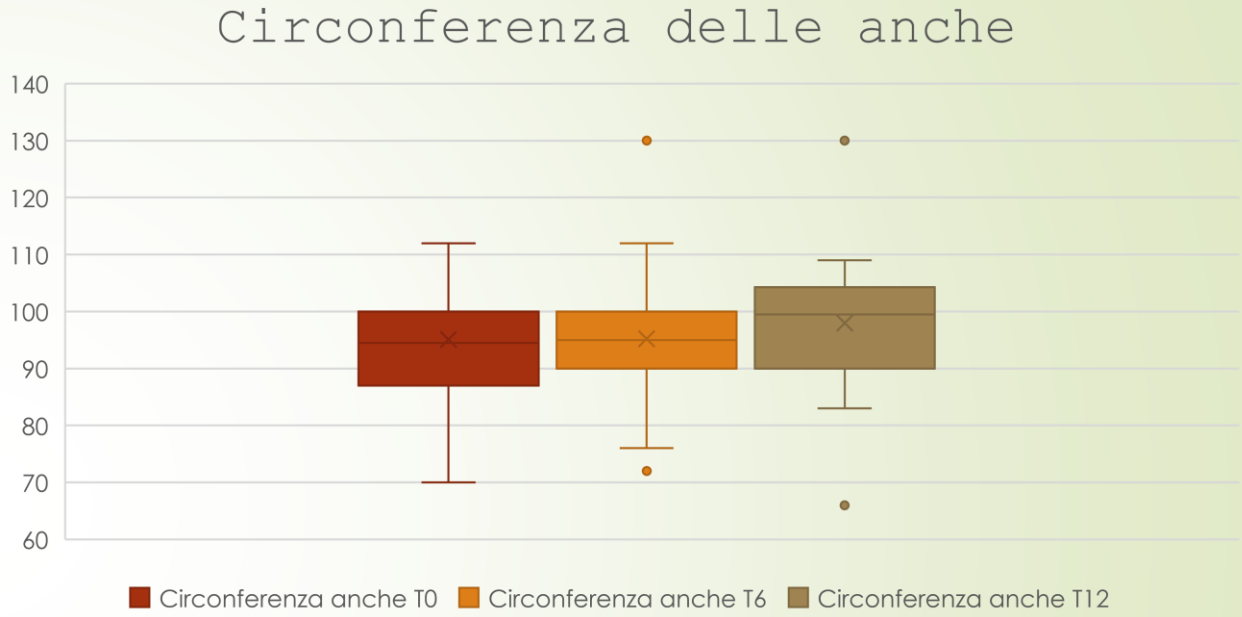




Mediana (IQR)	T0	T6	T12	p
Colesterolo totale	182 (167-204)	183 (161-205)	183 (157-210)	0,29
HDL	52 (45-60)	52 (45-60)	54 (47-63)	**<0,01**
LDL	114 (96-135)	109 (94-129)	111 (88-138)	0,62
Trigliceridi	92 (73-117)	88 (67-119)	81 (63-110)	**0,02**

Parametri metabolici

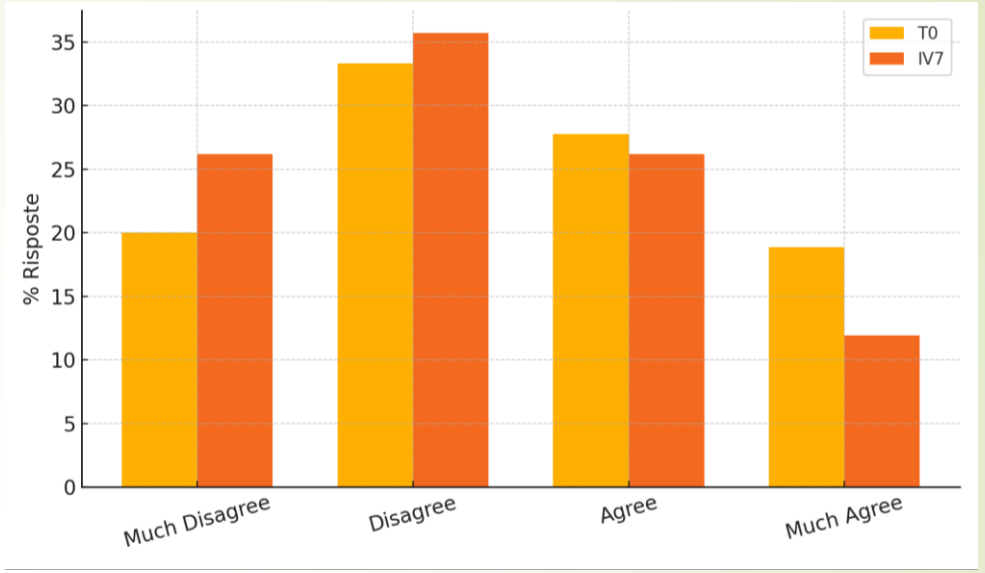




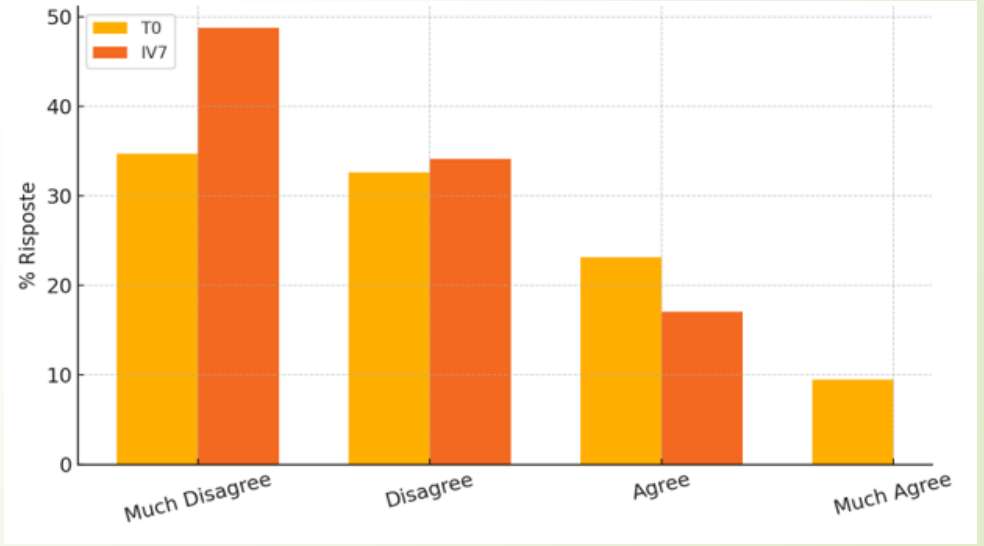
Mediana (IQR)	T0	T6	T12	p
BMI	24,6 (22,1-26,7)	24,3 (22,1-27,2)	25,2 (21,6-27,2)	0,36
Circonferenza vita	88 (83-96)	89 (84-97)	90 (83-99)	0,52
Circonferenza anche	94,5 (87-100)	95 (90-100)	99,5 (90-104)	**<0,01**

Questionari: Stigma

- Mi sento in colpa perché ho l'HIV

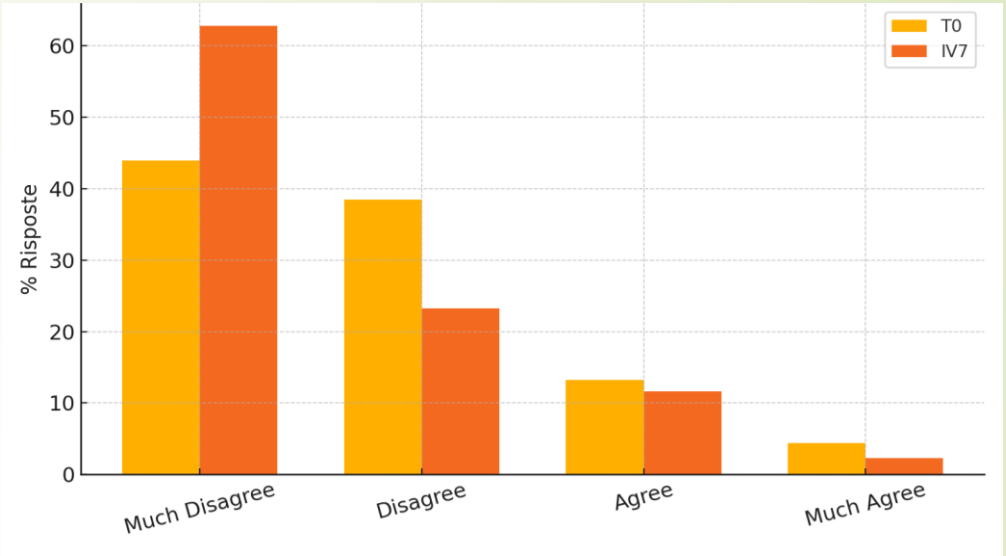


- Faccio molti sforzi per nascondere che ho l'HIV

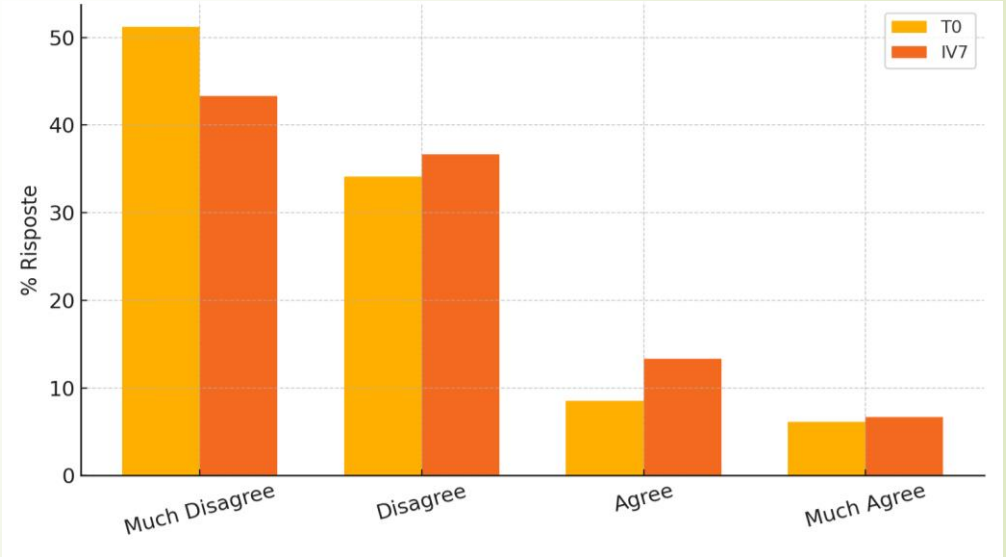


Questionari: Stigma

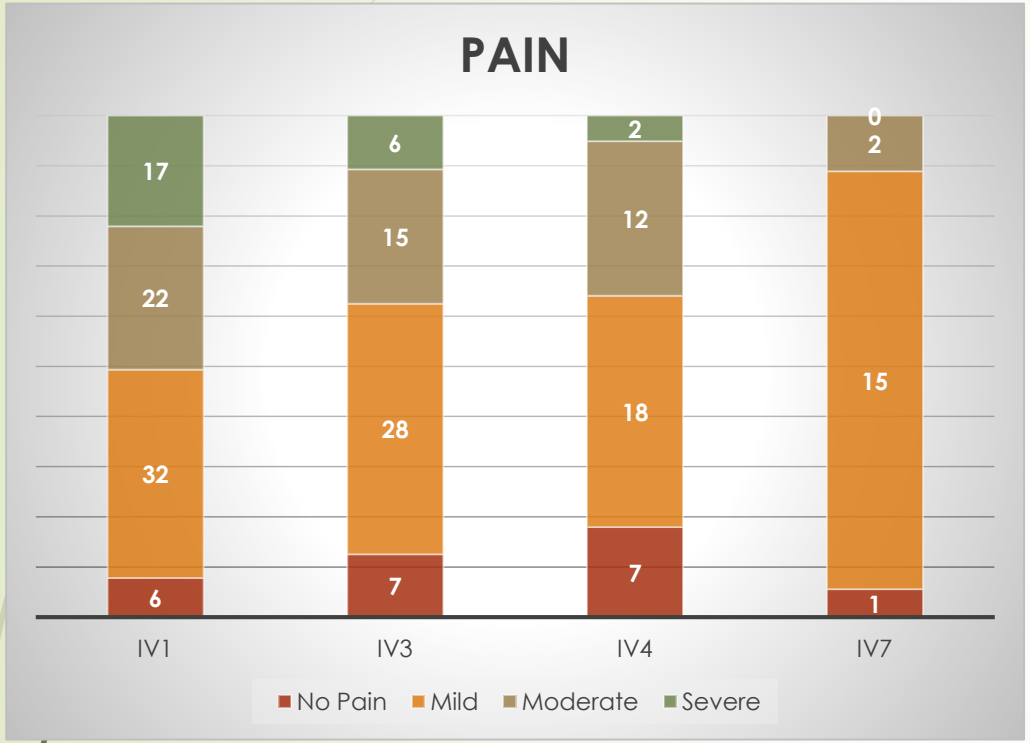
- Mi sento una persona peggiore rispetto agli altri perché ho l'HIV

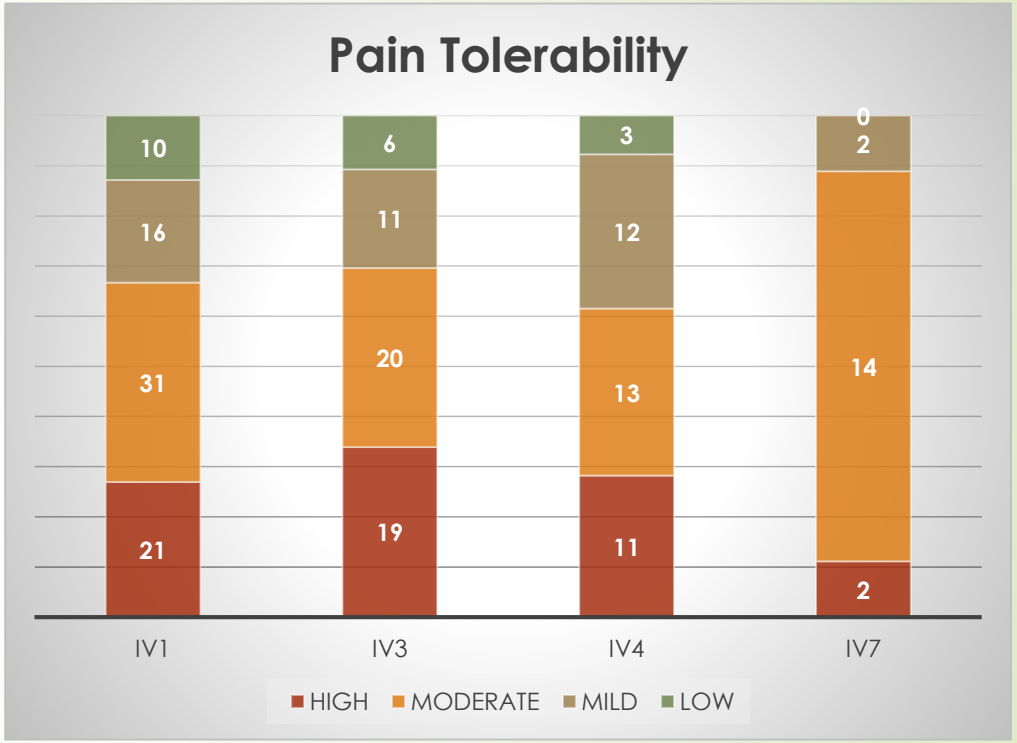


- Ho perso delle amicizie dopo aver detto che ho l'HIV

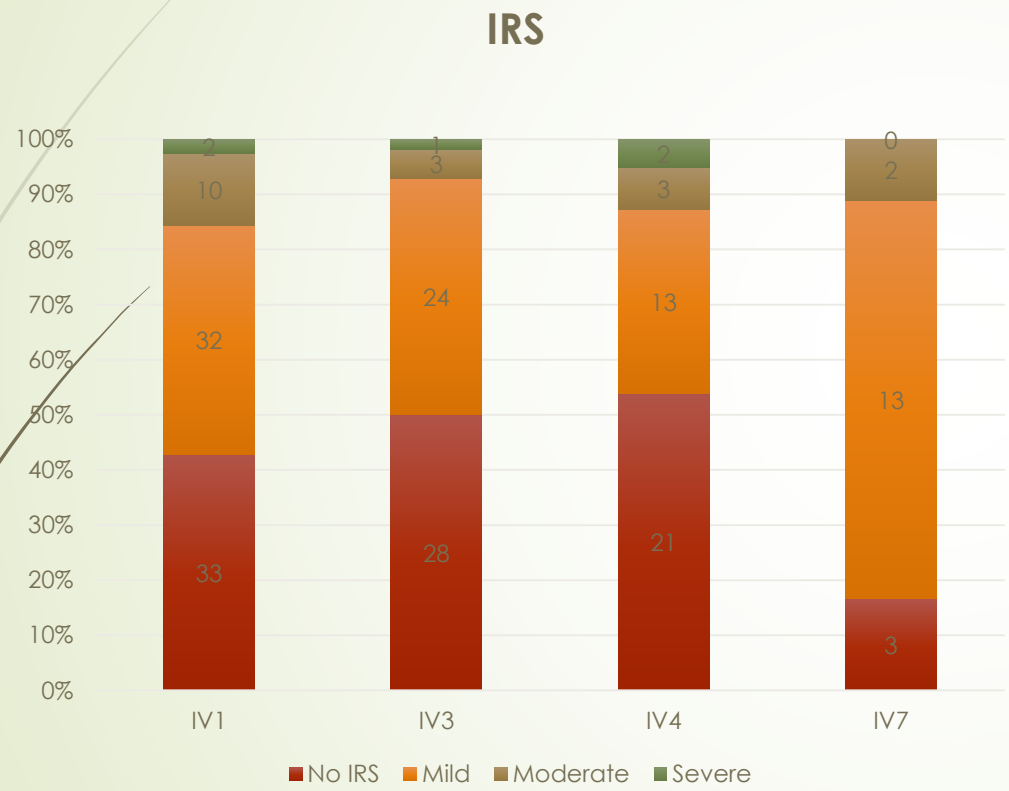


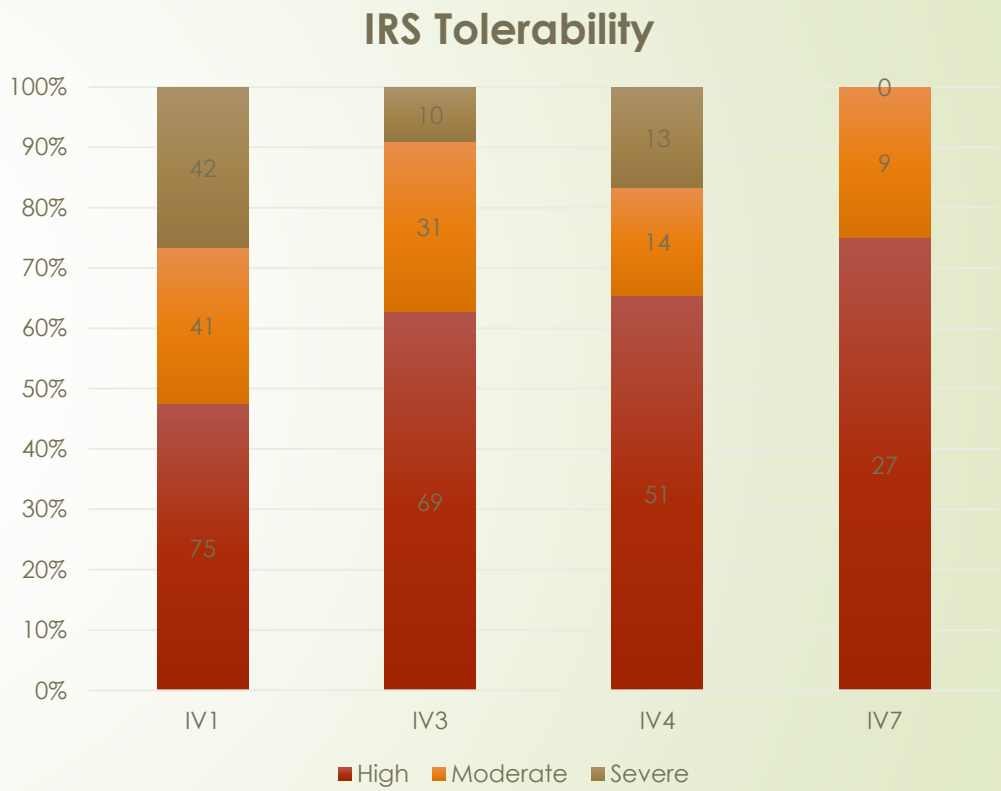
Questionari: Dolore





Questionari: Reazioni avverse





Conclusioni

- Nei primi 12 mesi dalla introduzione, la terapia LAI ha mostrato:
  - buona efficacia viro-immunologica
  - miglioramento del profilo metabolico e dello stigma percepito
  - miglioramento delle reazioni avverse locali e del dolore nel tempo

- La maggior parte delle sospensioni non è dovuta a motivi virologici
  - la TDM della rilpivirina potrebbe essere un tool utile per il monitoraggio della tossicità del farmaco, ma sono necessari ulteriori studi per identificare i range terapeutici

- Il numero di switch a LAI si è progressivamente ridotto dall'introduzione della terapia. Le motivazioni potrebbero essere:
  - Timore per IRS e dolore
  - Aumento del numero di accessi annuali in ospedale
  - Poca flessibilità del calendario di iniezioni correlato ad impegni personali

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