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Concomitant administration of long acting cabotegravir/rilpivirine and intramuscular antibiotics for the treatment of sexually transmitted infections: no evidence of pharmacodynamic interference.

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Introduction

- People living with HIV (PLWH) receiving cabotegravir/rilpivirine long acting (CARLA) treatment are often also at high risk of sexually transmitted infections (STIs) acquisition requiring intramuscular antibiotic injections.
- Both CARLA's drugs relies on depots based on polymeric nanosuspension technology. Magnetic resonance imaging of depot location demonstrated high deposition variability between participants.
- Muscular blood flow could impact the release of the drug from the depot and contribute to pharmacokinetic variations. High physical activity with injection of anabolic steroids have showed to be responsible of virologic failure. The same effect might be expected after the intramuscular injection of other drugs that could alter muscle blood flow through local inflammatory response. Benzathine benzylpenicillin, that forms a depot in the site of injection, it is dissolved and slowly hydrolysed to penicillin G over a time span longer than 10 days, might cause an even stronger interference.
- Although no pharmacokinetics interactions are expected, concurrent intramuscular administrations might result in perturbations in drug dissolution and absorption from the depots of both CARLA and benzathine penicillin.
- Aim of this study is to assess whether concomitant intramuscular CARLA and antibiotic injections might lead to inadequate antimicrobial response.

Study Design & Methods

- A double comparative, retrospective, monocentric analysis was designed. Study included all eligible individuals since CARLA availability in Italy (September 2022 onwards).
- Study population was represented by PLWH receiving CARLA and benzathine penicillin, ceftriaxone or gentamycin to treat an STI.
  - To assess antiretroviral efficacy, study population was compared to 2 to 4 PLWH who received CARLA the same day but were not exposed to antibiotics. HIV RNA values before and after injections were collected. Proportions of undetectable viral load before and after injections was compared.
  - To assess antibacterial efficacy, study population was compared to individuals who received benzathine penicillin but were not exposed to CARLA; RPR titres were collected. Time to 4-fold decrease in RPR was evaluated.
- Descriptive statistics, nonparametric tests and standard survival analyses (Kaplan-Meier estimation curves and adjusted Cox regression analysis) were used.

Results (1)

- The study enrolled 421 individuals: 34 (8.1%) received CARLA and antibiotics (benzathine penicillin, ceftriaxone or gentamycin) to treat syphilis (18, 52.9%), gonorrhoea (7, 20.6%) or as management following partner notification (9, 26.5%); 132 (31.3%) received only CARLA representing the control for HIV RNA; 255 (60.6%) received only benzathine penicillin representing the control for RPR titre decay.
- PLWH included in the syphilis control group were 51 (20.0%).

Results (2)

- Enrolled subjects were mainly males (401, 95.3%), born in Italy (328, 77.9%), and with a median age of 40 (IQR 33-50) years; 217 (51.5%) were living with HIV.
- Immunologic and virologic parameters were excellent, but PLWH belonging to syphilis control group were frequently treatment naïve thus HIV RNA was more commonly detectable.
- Median RPR titre was 16 (IQR 8-64) in study population and 14 (IQR 4-32) in syphilis control group (p=0.170).

Table 1. Demographic and clinical features of enrolled individuals.

		PLWH receiving LA and antibiotics (N=34)	Controls for HIVRNA (N=132)	Controls for Syphilis (N=255)	p
Age, years, median (IQR)		43 (36-49)	49 (40-56)	36 (30-45)	0.069
Born in Italy, n (%)		28 (82.4)	111 (84.1)	189 (74.1)	0.066
Gender, n (%)	Males	34 (100)	120 (90.9)	247 (96.8)	0.008
	Females	--	12 (9.1)	5 (2.0)	
	TGW	--	--	3 (1.2)	
CD4 cell count, cell/mmc, median (IQR)		838 (600-933)	824 (647-1,041)	716* (531-908)	0.223
HIV RNA class, n (%)	TND	24 (70.6)	99 (75.0)	31 (63.3) *	0.002
	BLQ	5 (14.7)	23 (17.4)	7 (14.3) *	
	20-200 cp/mL	5 (14.7)	10 (7.6)	4 (8.1) *	
	>1,000 cp/mL	--	--	7 (14.3) *	
HIV RNA, log_{10} cp/mL, median (IQR)		1.55 (1.51-1.69)	1.64 (1.41-1.88)	4.33 (1.98-5.13)	<0.001

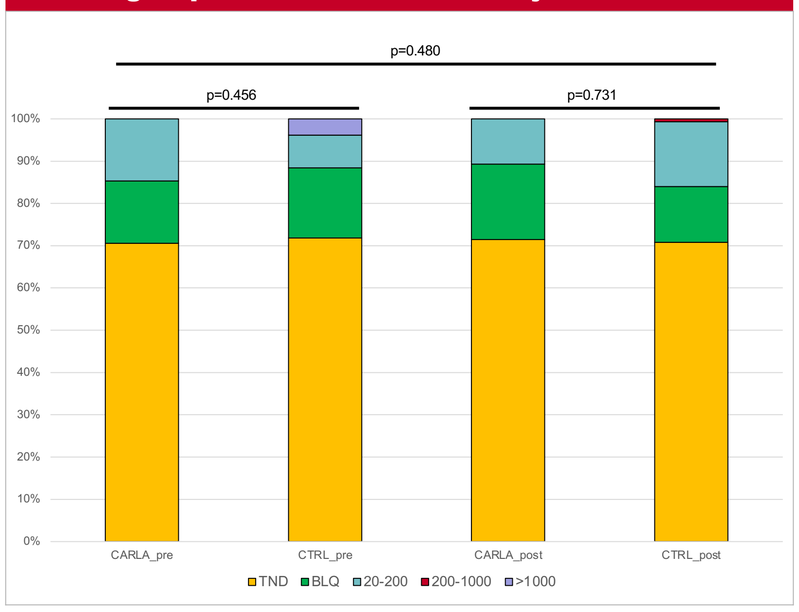
TGW: transgender women; TND: target not detected; BLQ: below the limit of quantification.
* Data available for 49 individuals.

- The median interval between CARLA and antibiotic injections was 8 (IQR 6-24) days. Since most of STI cases were asymptomatic and were detected with routine tests performed the day of injection, CARLA was generally administered before antibiotics. Longer time intervals were due to symptomatic STIs that required an injection the day of presentation at the Clinic.

Results (3)

- There were no differences in HIV RNA classes between groups before (p=0.456) and after (p=0.731) the injections nor within the same group before and after the administration (p=0.480).
- Similarly, there were no differences in median HIV RNA values between study population and control group before (p=1.000) and after (p= 1.000) the injections nor within the same group before and after LA and antibiotic administration (p=0.889).

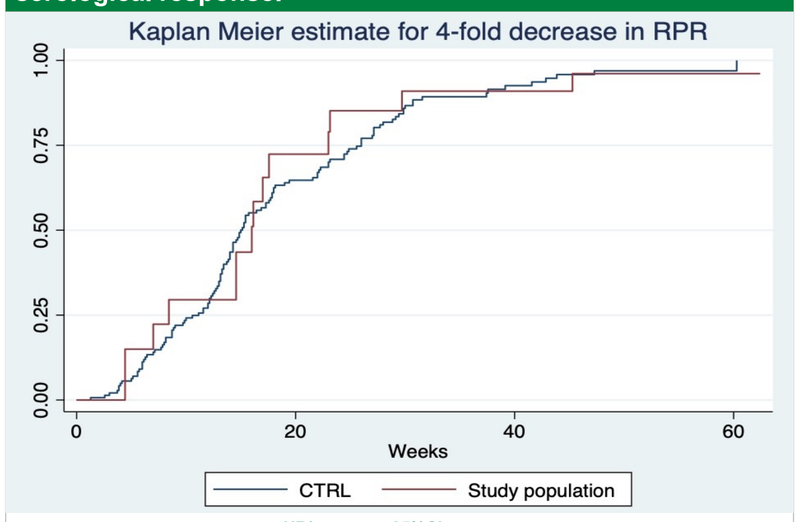
Figure 1. HIV RNA classes in study population and control group before and after the injections.



Results (4)

- Time to RPR 4-fold decrease was comparable between study population and the syphilis control group (log rank test 0.31, p=0.576).
- Cox regression analysis adjusted for presence of HIV infection and baseline RPR titre did not find an effect of CARLA administration on serological response in terms of 4-fold RPR decrease (aHR 1.01, 95%CI 0.52-1.95, p=0.980).

Figure 2. Kaplan Meier estimates for RPR 4-fold decrease and adjusted Cox regression analysis for factors associated to serological response.



	aHR*	95%CI	p
CARLA (yes vs no)	1.01	0.52-1.95	0.980
HIV infection	0.78	0.50-1.21	0.259
Baseline RPR titre	1.00	0.99-1.01	0.224

* Adjusted for all the variables listed.

Conclusion

- Since CARLA is the first complete long-acting regimen so far available, several information of management in everyday clinical practice are still missing. The potential impact of a concomitant intramuscular injection is one of the new issues that clinicians need to face in this new era.
- Although the sample size of our study population was small, these data suggest that concomitant intramuscular CARLA and antibiotic injections 8 days apart did not lead to inadequate antiretroviral and antibacterial responses.
- Long-acting injectable cabotegravir was recently approved also as pre-exposure prophylaxis (PrEP) in individuals at major risk of HIV exposure. These subjects are also disproportionally affected by bacterial STIs frequently requiring treatments with benzathine penicillin, ceftriaxone or gentamycin injections. Our results might reassure clinicians who need to treat concomitant STIs in individuals receiving cabotegravir as PrEP.
- These observations might be useful also for the management of other drugs that are frequently used in clinical practice and that are administered into the gluteal muscles (i.e., steroids, non-steroidal anti-inflammatory drugs, and so on).
- Further studies — potentially including pharmacokinetic assessment — are needed to provide details on the interactions and clinical relevance of concomitant intramuscular injections.

Reference

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