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Single-Dose Ceftriaxone Versus Benzathine Penicillin G in Early Syphilis: a Pilot Randomized Trial

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BACKGROUND

- Single-dose benzathine penicillin G (BPG) is the preferred therapy for early syphilis. However, BPG is ineffective against other coexisting bacterial sexually transmitted infections (STIs).
- BPG shortages prompt an urgent need to identify alternative treatments for early syphilis.
- Ceftriaxone (CRO) and doxycycline both demonstrate activity against syphilis and bacterial STIs. However, the efficacy of their combination for early syphilis remains unclear.

METHODS

- **Design:** Pilot randomized controlled, open-label, non-inferiority study, March 2023 to September 2024
- **Study site:** National Taiwan University Hospital
- **Inclusion criteria:** Adult people with HIV (PWH) with early syphilis
- **Exclusion criteria:** Rapid plasma reagin (RPR) titers <4; exposure to antibiotics with activity against *Treponema pallidum* within the preceding 4 weeks; a known or suspected infection other than syphilis requiring additional antibiotics that are active against *T. pallidum*; a history of intolerance to penicillin, ceftriaxone, or doxycycline; or pregnancy
- **Procedures:**
  - 1-g single-dose CRO IM plus doxycycline 100 mg BID for 7 days (CRO/Doxy)
  - 2.4-MU single-dose BPG IM plus doxycycline 100 mg BID for 7 days (BPG/Doxy)
- **Primary outcome:** Serologic response of syphilis at week 24, defined as a 4-fold or greater decline of RPR titer compared to baseline, or seroreversion to a nonreactive result
- **Secondary outcomes:** Microbiologic response of syphilis (PCR Ct value >38) at week 4; microbiologic response of bacterial STIs (negative PCR) at week 4; serologic responses at weeks 12 and 48; adverse events

A single-dose ceftriaxone in combination with a 7-day course of doxycycline was not non-inferior to benzathine penicillin G plus doxycycline for treatment of early syphilis among PWH with early syphilis.

Figure 1. Study flow

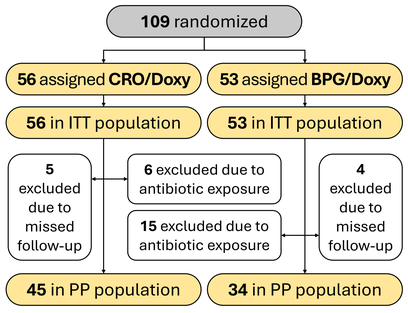


Table 1. Baseline characteristics of the participants

	CRO/Doxy	BPG/Doxy
Age, median (IQR), years	38 (33-46)	40 (35-46)
CD4 count, median (IQR), cells/mm^3	556 (477-794)	565 (446-733)
History of syphilis, n (%)	49 (87.5)	44 (83.0)
Primary syphilis, n (%)	3 (5.4)	4 (7.5)
Secondary syphilis, n (%)	22 (39.3)	16 (30.2)
Early latent syphilis, n (%)	31 (55.4)	33 (62.3)
RPR titer, median (IQR)	128 (64-256)	128 (64-256)
Detection of *Chlamydia trachomatis*, n (%)	19 (33.9)	15 (28.3)
Detection of *Neisseria gonorrheae*, n (%)	5 (8.9)	10 (18.9)

Figure 2. Serologic Responses at Weeks 12, 24, 36 and 48 in ITT analysis

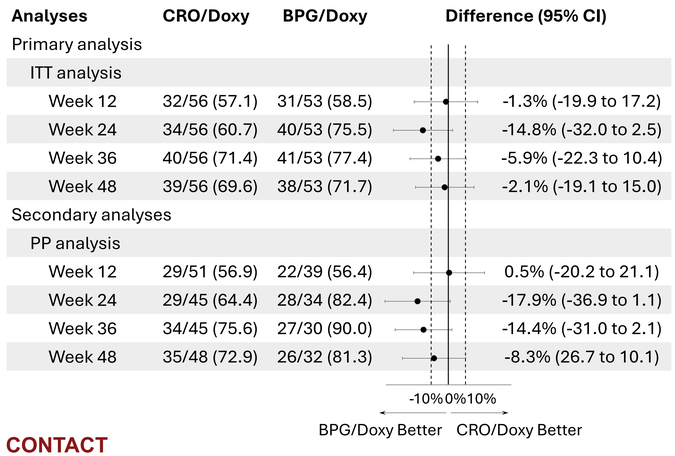
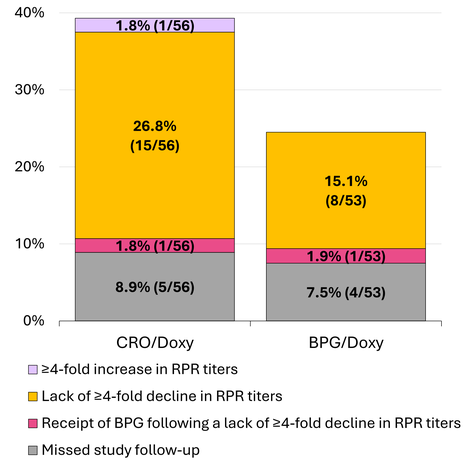


Figure 3. Reasons for Failure at Week 24



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RESULTS

- 56 and 53 PWH (100% men, median CD4 count 558 cells/mm^3) with early syphilis were randomized to receive CRO/Doxy and BPG/Doxy, respectively (Figure 1).
- The baseline rates of co-infection with chlamydia and gonorrhea were 31.2% (n=34) and 13.8% (n=15), respectively (Table 1).
- In the intention-to-treat (ITT) analysis, compared to PWH receiving BPG/Doxy, those receiving CRO/Doxy showed lower serologic response rate at 24 weeks (60.7% vs 75.5%; difference, -14.8 percentage points; 95% CI, −32.0 to 2.5) (Figure 2).
- The microbiologic response rates of syphilis, chlamydia and *M. genitalium* infection at week 4 were comparable between the two groups (Table 2).
- Compared to PWH receiving BPG/Doxy, those receiving CRO/Doxy demonstrated more local reaction (42.9% vs. 20.8%) and Jarisch-Herxheimer reaction (17.9% vs. 3.8%) (Table 2).

Table 2. Secondary outcomes of ITT analysis

	CRO/Doxy	BPG/Doxy	*P*
Microbiologic response at week 4 (%)			
T. pallidum	94.4 (17/18)	95.2 (20/21)	>0.999
C. trachomatis	84.2 (16/19)	86.7 (13/15)	>0.999
M. genitalium	0.0 (0/3)	50.0 (2/4)	0.429
Adverse drug events (%)			
Injection site pain or local swelling	24 (42.9)	11 (20.8)	0.014
Jarisch-Herxheimer reaction	10 (17.9)	2 (3.8)	0.029

CONCLUSIONS

- In the ITT analysis, CRO/Doxy was not noninferior to BPG/Doxy for early syphilis treatment in PWH at 24 weeks.

PLAIN LANGUAGE SUMMARY

After 24 weeks, PWH who had early syphilis and received one injection of ceftriaxone plus one week of doxycycline did not show a serologic response as fast as those who received the standard benzathine penicillin G injection plus doxycycline.