Best Papers in Infectious Diseases 2022: Infezione da HIV

Daniele Tomasoni

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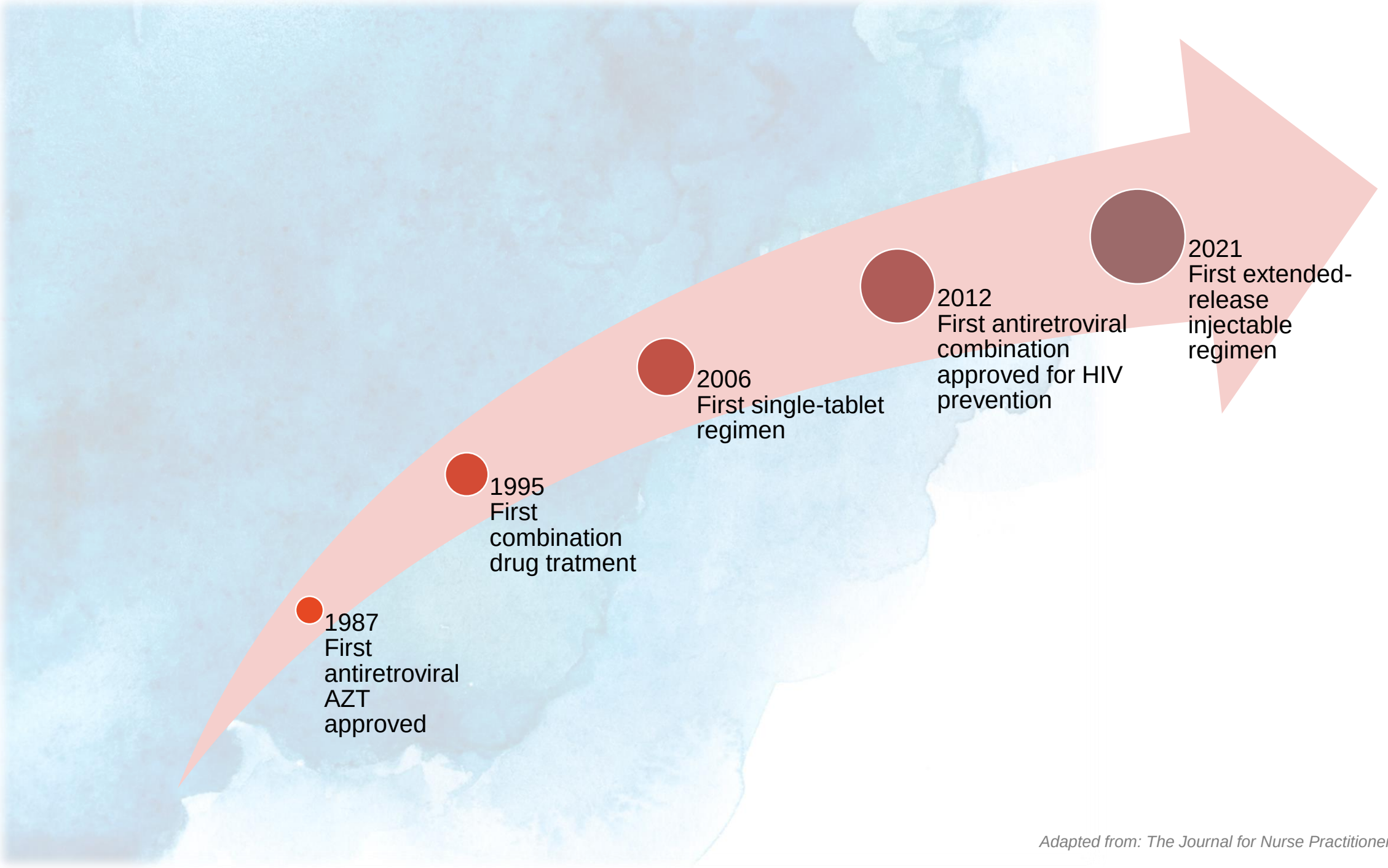
Università degli Studi di Milano – Polo San Paolo



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Drug Given Every Two Months Rather Than Daily Pill is Important Tool in Effort to End the HIV Epidemic
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For Immediate Release: December 20, 2021
Today, the U.S. Food and Drug Administration approved Apretude (cabotegravir extended-release injectable suspension) for use in at-risk adults and adolescents weighing at least 35 kilograms (77 pounds) for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV. Apretude is given first as two initiation injections administered one month apart, and then every two months thereafter. Patients can either start their treatment with Apretude or take oral cabotegravir (Vocabria) for four weeks to assess how well they tolerate the drug.
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Clinical Infectious Diseases

MAJOR ARTICLE

First Demonstration Project of Long-Acting Injectable Antiretroviral Therapy for Persons With and Without Detectable Human Immunodeficiency Virus (HIV) Viremia in an Urban HIV Clinic

Katerina A. Christopoulos,[1] Janet Grochowski,[1] Francis Mayorga-Munoz,[1] Matthew D. Hickey,[1] Elizabeth Imbert,[1] John D. Szumowski,[1] Samantha Dilworth,[2] Jon Oskarsson,[1] Mary Shiels,[1] Diane Havlir,[1] and Monica Gandhi[1]

[1]Division of HIV, ID, and Global Medicine, University of California–San Francisco, San Francisco, California, USA; and [2]Division of Prevention Science, University of California–San Francisco, San Francisco, California, USA

Background. Long-acting injectable antiretroviral therapy (LAI-ART) is approved for treatment-naive or experienced people living with human immunodeficiency virus (HIV; PLWH) based on trials that only included participants with viral suppression. We performed the first LAI-ART demonstration project to include PLWH unable to achieve or maintain viral suppression due to challenges adhering to oral ART.

Methods. Ward 86 is a large HIV clinic in San Francisco that serves publicly insured and underinsured patients. We started patients on LAI-ART via a structured process of provider referral, multidisciplinary review (MD, RN, pharmacist), and monitoring for on-time injections. Inclusion criteria were willingness to receive monthly injections and a reliable contact method.

Results. Between June 2021 and April 2022, 51 patients initiated LAI-ART, with 39 receiving at least 2 follow-up injections by database closure (median age, 46 years; 90% cisgender men, 61% non-White, 41% marginally housed, 54% currently using stimulants). Of 24 patients who initiated injections with viral suppression (median CD4 cell count, 706 cells/mm^3), 100% (95% confidence interval [CI], 86%–100%) maintained viral suppression. Of 15 patients who initiated injections with detectable viremia (median CD4 cell count, 99 cells/mm^3; mean $\log_{10}$ viral load, 4.67; standard deviation, 1.16), 12 (80%; 95% CI, 55%–93%) achieved viral suppression, and the other 3 had a 2-log viral load decline by a median of 22 days.

Conclusions. This small demonstration project of LAI-ART in a diverse group of patients with high levels of substance use and marginal housing demonstrated promising early treatment outcomes, including in those with detectable viremia due to adherence challenges. More data on LAI-ART in hard-to-reach populations are needed.

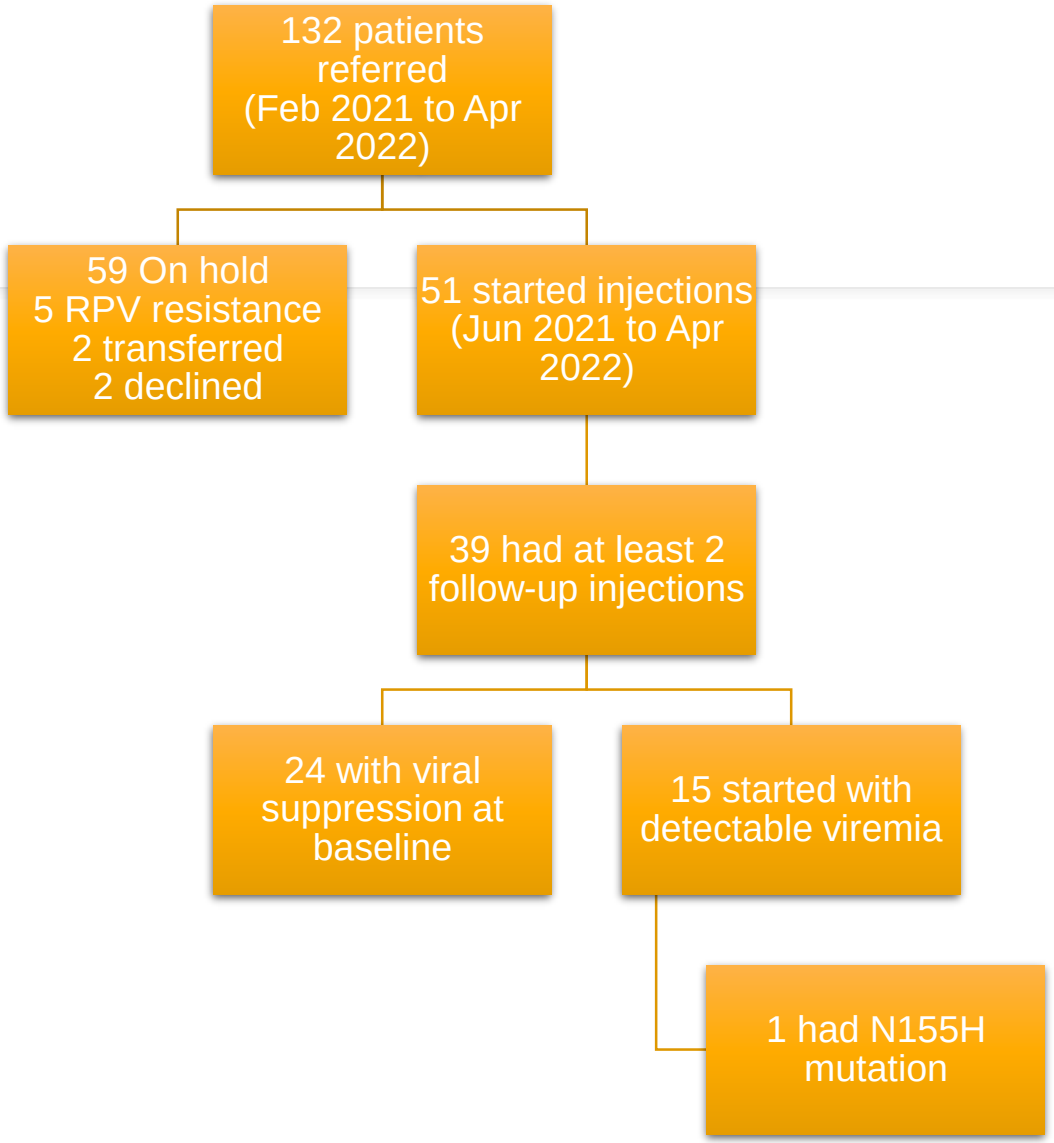
Keywords. HIV/AIDS; long-acting antiretroviral therapy; injectable cabotegravir and rilpivirine; viral suppression; engagement in care.

Long-Acting Injectable Antiretroviral Therapy for People who won’t take oral ART?

- Ward 86 is a «safety net» HIV clinic in San Francisco. It serves >2400 PLWH with government or municipal insurance. **Approximately 10% of patients have chronic viremia.**
- In 2019, the clinic developed a multidisciplinary drop-in primary care model called **POP-UP** to better meet the needs of chronically unsuppressed patients with marginal housing, who struggle to adhere in traditional HIV care.
- They developed a program to support patients and providers to **initiate CAB/RPV-LA** and promote patients’ adherence to injections.

Methods

- **Observational study**
- **Inclusion criteria**: PLWH with or without viral suppression, willing to receive CAB/RPV-LA every 4-week and providing a reliable form of communication (phone, text, family, friend).
- Patients with **≤1 INSTI mutation** were allowed in the program
- **Exclusion criteria**: RPV-associated resistance mutation
- **Objective**: viral suppression outcomes, stratified by viral suppression status at the time of CAB/RPV-LA initiation



Results

- Study population: **39 patients**,
- Median age **46 years** (IQR 39-55); 3 cisgender women and 1 transgender woman
- 61% non-white ethnicity
- 41% **unstable housing or homelessness**
- 54% reported current stimulants use (**cocaine, methamphetamines**)
- Two patients **received injections in community locations** (a harm reduction mobile van and a community clinic) in collaboration with street-based nursing services.

- All patients who initiated CAB/RPV-LA with viral suppression (median CD4 cell count, 706 cells/mm3) **manteined viral suppression** after starting injections.
- Of 15 patients who started with detectable viremia (median CD4 cell count 99 cells/mm3; mean log10 viral load 4.67, SD 1.16), **12 (80%) achieved and mantained viral suppression**, including the patient with baseline N155H mutation.
- The 3 patients who did not achieve viral suppression had a **2-log decline of viral load** by a median of 22 days.

Conclusions

- Preliminary short-term effectiveness of 4-week CAB/RPV-LA in patients with and without viral suppression in urban clinic with **high levels of marginal housing and stimulant use**.
- Consistent with clinical trial populations, those who initiated injections with viral suppression **mantained suppression**.
- Those who began injection with detectable viremia **successfully achieved viral suppression or had a 2-log decrease in viral load** within 1 month from first injection,

Limitations:

- Outside of FDA/EMA indications
- Small number of patients
- Relatively short follow-up (<1 year)
- No information about drop-out
- How many will develop two-class drug resistance (INSTI+NNRTI)?

Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial

Sinead Delany-Moretlwe, James P Hughes, Peter Bock, Samuel Gurrion Ouma, Portia Hunidzarira, Dishiki Kalonji, Noel Kayange, Joseph Makhema, Patricia Mandima, Carrie Mathew, Elizabeth Spooner, Juliet Mpendo, Pamela Mukwekwerere, Nyaradzo Mgodi, Patricia Nahirya Ntege, Gonasagrie Nair, Clemensia Nakabiito, Harriet Nuwagaba-Biribonwoha, Ravindre Panchia, Nishanta Singh, Bekezela Siziba, Jennifer Farrior, Scott Rose, Peter L Anderson, Susan H Eshleman, Mark A Marzinke, Craig W Hendrix, Stephanie Beigel-Orme, Sybil Hosek, Elizabeth Tolley, Nirupama Sista, Adeola Adeyeye, James F Rooney, Alex Rinehart, William R Spreen, Kimberly Smith, Brett Hanscom, Myron S Cohen, Mina C Hosseinipour, on behalf of the HPTN 084 study group

Summary

Background Oral pre-exposure prophylaxis has been introduced in more than 70 countries, including many in sub-Saharan Africa, but women experience considerable barriers to daily pill-taking, such as stigma, judgement, and the fear of violence. Safe and effective long-acting agents for HIV prevention are needed for women. We aimed to evaluate the safety and efficacy of injectable cabotegravir compared with daily oral tenofovir diphosphate plus emtricitabine (TDF-FTC) for HIV prevention in HIV-uninfected women.

Methods HPTN 084 was a phase 3, randomised, double-blind, double-dummy, active-controlled, superiority trial in 20 clinical research sites in seven countries in sub-Saharan Africa. Participants were eligible for enrolment if they were assigned female sex at birth, were aged 18–45 years, reported at least two episodes of vaginal intercourse in the previous 30 days, were at risk of HIV infection based on an HIV risk score, and agreed to use a long-acting reversible contraceptive method. Participants were randomly assigned (1:1) to either active cabotegravir with TDF-FTC placebo (cabotegravir group) or active TDF-FTC with cabotegravir placebo (TDF-FTC group). Study staff and participants were masked to study group allocation, with the exception of the site pharmacist who was responsible for study product preparation. Participants were prescribed 5 weeks of daily oral product followed by intramuscular injections every 8 weeks after an initial 4-week interval load, alongside daily oral pills. Participants who discontinued injections were offered open-label daily TDF-FTC for 48 weeks. The primary endpoints of the study were incident HIV infection in the intention-to-treat population, and clinical and laboratory events that were grade 2 or higher in all women who had received at least one dose of study product. This study is registered with ClinicalTrials.gov, NCT03164564.

Findings From Nov 27, 2017, to Nov 4, 2020, we enrolled 3224 participants (1614 in the cabotegravir group and 1610 in the TDF-FTC group). Median age was 25 years (IQR 22–30); 1755 (54·7%) of 3209 had two or more partners in the preceding month. 40 incident infections were observed over 3898 person-years (HIV incidence 1·0% [95% CI 0·73–1·40]); four in the cabotegravir group (HIV incidence 0·2 cases per 100 person-years [0·06–0·52]) and 36 in the TDF-FTC group (1·85 cases per 100 person-years [1·3–2·57]; hazard ratio 0·12 [0·05–0·31]; p<0·0001; risk difference –1·6% [–1·0% to –2·3%]. In a random subset of 405 TDF-FTC participants, 812 (42·1%) of 1929 plasma samples had tenofovir concentrations consistent with daily use. Injection coverage was 93% of the total number of person-years. Adverse event rates were similar across both groups, apart from injection site reactions, which were more frequent in the cabotegravir group than in the TDF-FTC group (577 [38·0%] of 1519 *vs* 162 [10·7%] of 1516]) but did not result in injection discontinuation. Confirmed pregnancy incidence was 1·3 per 100 person-years (0·9–1·7); no congenital birth anomalies were reported.

Interpretation Although both products for HIV prevention were generally safe, well tolerated, and effective,

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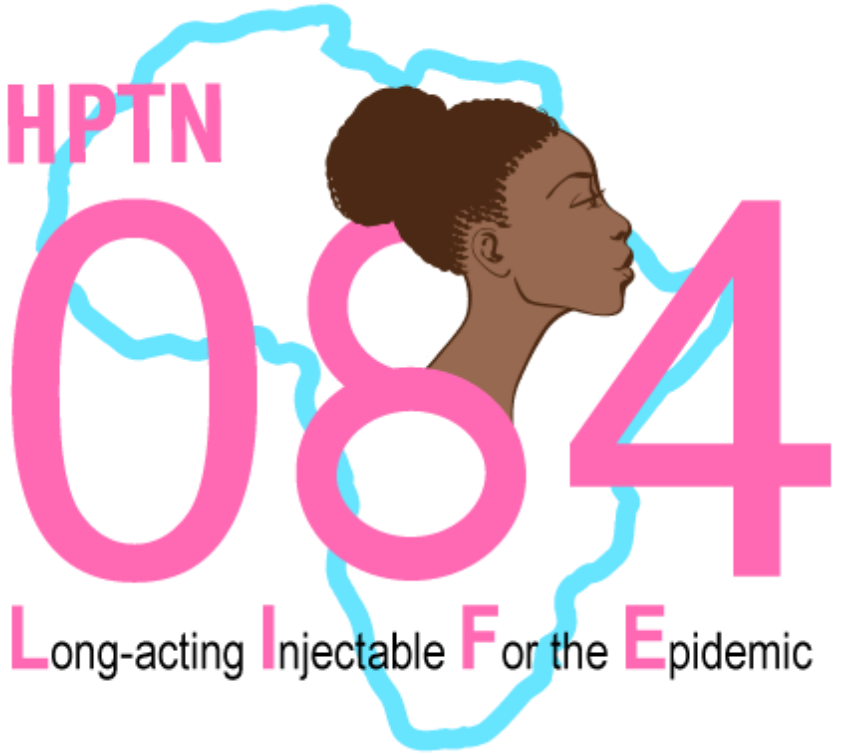
This online publication has been corrected. The corrected version first appeared at thelancet.com on May 5, 2022

See **Comment** page 1754

Wits Reproductive Health and HIV Institute (Prof S Delany-Moretlwe PhD, C Mathew MBBCh) **and Perinatal HIV Research Unit** (R Panchia MBBCh), **University of the Witwatersrand, Johannesburg, South Africa; Statistical Center for HIV/AIDS Research and Prevention, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA** (Prof J P Hughes PhD, S Beigel-Orme BA, B Hanscom PhD); **Desmond Tutu TB Centre, University of Stellenbosch, Stellenbosch, South Africa** (Prof P Bock PhD); **Kisumu Clinical Research Site, Centre for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya** (S Gurrion Ouma MD); **Clinical Trials Research Centre, University of Zimbabwe, Harare, Zimbabwe** (P Hunidzarira MBChB,

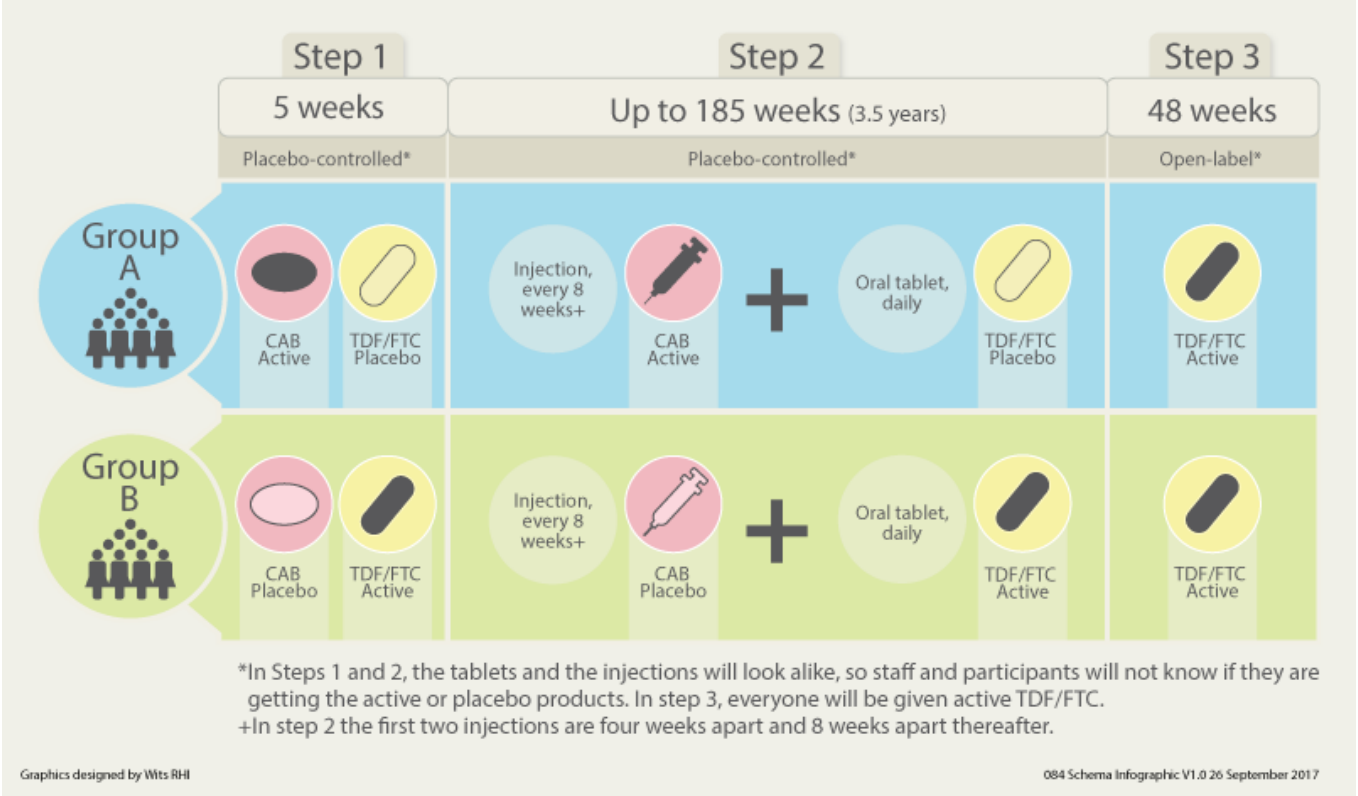
CAB-LA is superior to TDF/FTC in preventing HIV infection in HIV-negative women

- Only **daily dosing** is recommended in women to achieve optimal benefits for HIV prevention.
- **Women experience considerable barriers to daily pill-taking**, including stigma, judgement and fear of violence; long-acting cabotegravir might overcome many of these challenges.
- The **HPTN-083** study showed that cabotegravir was safe and effective in preventing HIV in **cisgender men and transgender women** who have sex with men.
- The **HPTN-084** trial was designed concurrently to evaluate safety and efficacy of injectable cabotegravir compared with daily oral TDF-FTC for HIV prevention in HIV-uninfected **women**.



Methods

- **Phase III, randomized, multicenter, double-blind** trial in sub-Saharian Africa
- **Inclusion criteria**: female sex at birth, aged 18-45 years, at risk of HIV infection.
- **Exclusion criteria**: pregnant or breastfeeding; renal, hepatic or cardiovascular disease; history of seizures, coagulopathy, or allergy; previous enrolment in HIV vaccine or mAb.
- Required non-reactive test results at site-visit, at least one HIV rapid antibody test, a laboratory-based antigen-antibody test and undetectable HIV-RNA up to 14 days before enrolment.
- **Primary outcomes**: incident HIV infection in step 1 + step 2; grade 2 or higher clinical or laboratory adverse event.



Results

- **3224 women** (median age, 25) randomized, 1614 to CAB and 1610 to TDF/FTC. **3178 included in ITT analysis**.
- **40 incident infections** met primary endpoint and were included in analysis: **4 with CAB** (0.20 per 100 person-years, 95%CI 0.06-0.52) and **36 with TDF/FTC** (1.85 per 100 person-years, 95%CI 1.3-2.7).
- One infection in CAB group was **re-classified as baseline infection.**
- Compared with TDF/FTC, **CAB reduced risk for HIV infection by 91%** (HR 0.09 95%CI 0.04-0.27, p<0.0001).
- No significant difference in grade 2 or higher adverse events, except from **injection-site reactions**, more common in CAB group (38.0% vs 10.8%).
- Participants in both group experienced **weight gain** (2.4Kg with CAB and 2.1Kg with TDF/FTC; P=0.041)

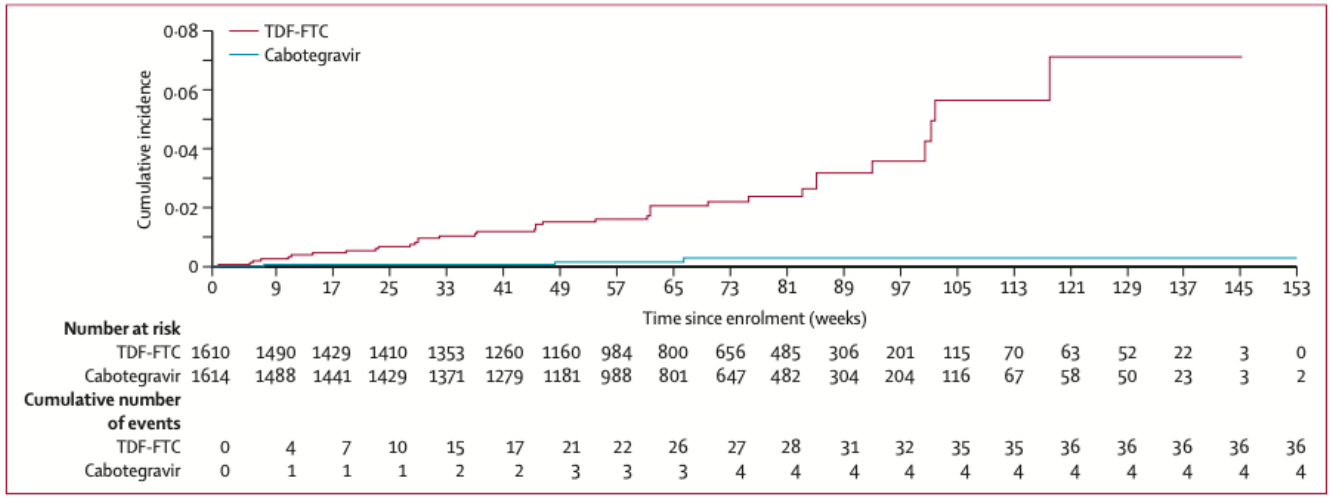


***Figure 3*: Cumulative HIV incidence by study group**
Kaplan-Meier estimates of HIV infection are shown. Four HIV infections were observed in the cabotegravir group (HIV incidence 0·20 per 100 person-years [95% CI 0·06–0·52]) and 36 in the TDF-FTC group (1·85 per 100 person-years [1·3–2·57]). Participants in the cabotegravir group had an 88% lower risk of HIV infection than those in the TDF-FTC group (hazard ratio 0·12 [0·05–0·31]; p<0·0001). TDF-FTC=tenofovir disoproxil fumarate plus emtricitabine.

Conclusions

- Cabotegravir administered intramuscularly every 8 weeks was **effective in preventing HIV infection in women** at risk for acquiring HIV in sub-Saharian Africa.
- HIV infection was about **90% lower** in the CAB group, showing **superiority** of cabotegravir over TDF/FTC in preventing HIV in this population.

Take home messages

- Options for people who won’t take oral ART have been highly limited.
- CAB/RPV-LA might provide an effective option to reduce ART discontinuation, AIDS-related complications and HIV-related deaths.
- A multidisciplinary approach and community-based intervention are needed to fully implement CAB/RPV-LA in this population.

- Cabotegravir provided an adherence advantage over daily oral pill-taking for PrEP.
- Long-acting CAB is approved by FDA and recommended by CDC for PrEP in men, cis- and transgender women at risk for acquiring HIV through sex.
- Next challenge: making the drug more available, implementing CAB in preventive interventions.