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SOMMINISTRAZIONE A LENTO RILASCIO DELLA TERAPIA ANTI-HIV: QUALI SARANNO LE SFIDE, LE OPPORTUNITÀ E LE CRITICITÀ?

Venerdì, 16 settembre 2016

Le formulazioni a lento rilascio: una nuova gestione del paziente?

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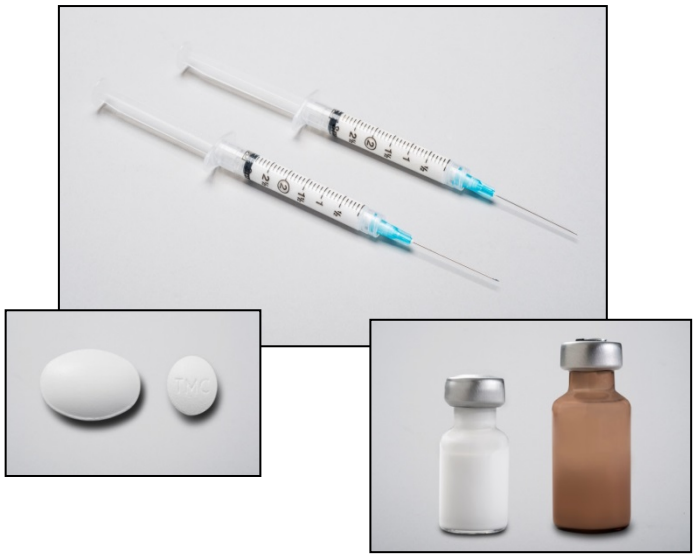
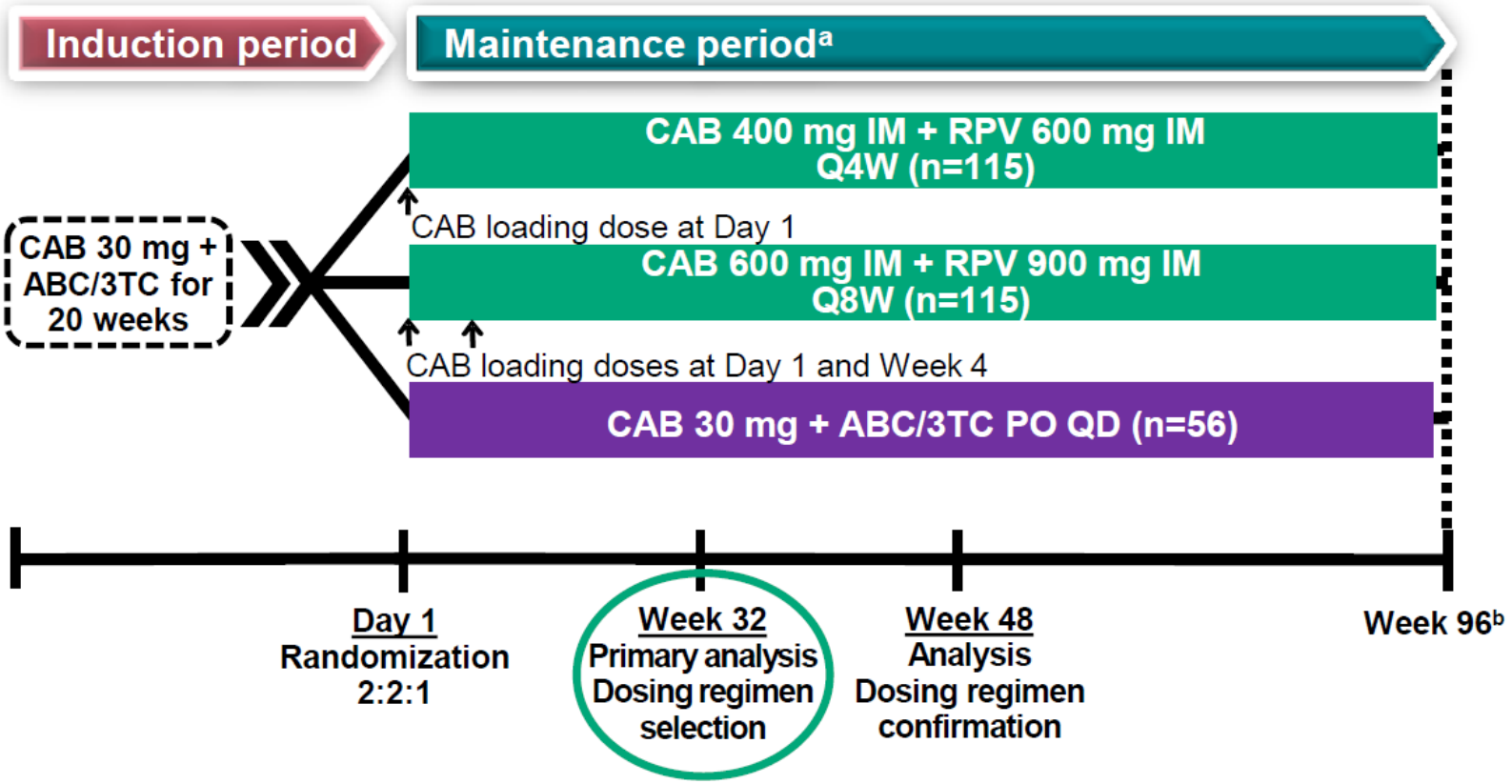
Background

- CAB is an HIV-1 integrase inhibitor
  - Oral 30 mg tablet ($t_{1/2}$, ~40 hours)
  - LA nanosuspension 200 mg/mL ($t_{1/2}$, ~20-40 days)
- RPV is an HIV-1 NNRTI
  - Oral 25 mg tablet ($t_{1/2}$, ~50 hours)
  - LA nanosuspension 300 mg/mL ($t_{1/2}$, ~30-90 days)
- Oral 2-drug CAB + RPV proof of efficacy through Week 96 in LATTE-1



LATTE-2 Study Design



ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; ULN, upper limit of normal. [a]Subjects can elect to enter LA extension phase beyond week 96.

Murray et al. AIDS 2016; Durban, South Africa. Poster THPEB052.

Study Periods

- **Part 1:** *Screening period*: 28 days
- **Part 2:** *Induction period*: Eligible subjects were enrolled into the study and began a 20-week induction period of an oral regimen of CAB 30 mg plus ABC/3TC 600/300 mg once daily
- **Part 3:** *Maintenance period*: Subjects with undetectable HIV-1 RNA (<50 c/mL) at Week -4 were randomly assigned on a 2:2:1 basis to an IM regimen of CAB LA 400 mg + RPV LA 600 mg every 4 weeks (Q4W) for 96 weeks
  - IM regimen of CAB LA 600 mg + RPV LA 900 mg every 8 weeks (Q8W) for 96 weeks
  - Continue oral CAB 30 mg plus ABC/3TC for 96 weeks

Murray et al. AIDS 2016; Durban, South Africa. Poster THPEB052.

Baseline Characteristics: ITT-ME Population

	Q8W IM (n=115)	Q4W IM (n=115)	Oral CAB (n=56)	Total (N=286)
Median age, years	35.0	36.0	35.0	35.0
Female, n (%)	8 (7)	6 (5)	10 (18)	24 (8)
African American/African heritage, n (%)	17 (15)	12 (10)	15 (27)	44 (15)
CDC class C, n (%)	1 (<1)	2 (2)	0	3 (1)
Median HIV-1 RNA, $\log_{10}$ c/mL	4.4	4.5	4.3	4.4
≥100,000, n (%)	16 (14)	28 (24)	7 (12)	51 (18)
Median CD4+, cells/mm^3	449.0	499.0	517.5	489.0

CDC, Centers for Disease Control and Prevention; ITT-ME, intent-to-treat maintenance exposed.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

Phase III CAB/RPV LAI in Pts with HIV-RNA < 50 copies/ml

- Initial or second antiretroviral regimen
- <50 copies since 12 months

- Esclusion
- DTG/ABC/3TC
- HbsAg+
- Need of HCV therapy
- Risk of suicide
- Risk of seizure

ATLAS e FLAIR

Procedure	Screening Visit[a]	Maintenance Phase											Extension Phase								Withdrawal	Follow-up Phase
		Baseline, Day 1	Week 4A	Week 4B[b]	Week 5[b]	Week 8, 12,16,20	Week 24	Week 28, 32, 36,40	Week 41[b]	Week 44	Week 48	Week 52	Week 56A	Week 56B[b]	Week 60	Week 64, 72, ,80, 88	Week 68, 76, 84, 92	Week 96	Every 4 Weeks After Week 96	Every 12 Weeks After Week 96		
Clinical and Other Assessments																						
Written informed consent	X																					
Eligibility Verification (Inclusion/Exclusion Criteria)	X	X[c]									X[c]											
Randomization		X																				
Demography	X																					
Medical History[d]	X																					
Medication History/ Prior ART history	X																					
Symptom Directed Physical Exam and Medical Assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Protocol-Defined Virologic Failure (PDVF): Genotype

Maintenance period[a]	Q8W IM (n=115)	Q4W IM (n=115)	Oral CAB (n=56)
Subjects with PDVF	2 (1%)[b]	0	1 (2%)
INI-r mutations	1[c]	0	0
NRTI-r mutations	0	0	0
NNRTI-r mutations	1[c]	0	0

- NNRTI—**K103N, E138G, and K238T** (FC RPV=3.3; Etravirine=1.9); INI—**Q148R** (FC CAB=5.1; Dolutegravir=1.38)[c]
- No additional PDVFs beyond W48 on any arm (all subjects through W72)[d]

PDVF: <1.0 $\log_{10}$ c/mL decrease in plasma HIV-1 RNA by Week 4, OR confirmed HIV-1 RNA ≥200 c/mL after prior suppression to <200 c/mL, OR >0.5 $\log_{10}$ c/mL increase from nadir HIV-1 RNA value ≥200 c/mL. [a]One additional PDVF without treatment-emergent resistance occurred during oral Induction Period due to oral medication non-adherence. [b]One PDVF at Week 4: no detectable RPV at Week 4 and Week 8, suggesting maladministration. [c]One PDVF at Week 48 at HIV-1 RNA 463 c/mL (confirmed at 205 c/mL). [d]Contains data beyond W48.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

Clinical Infectious Diseases

MAJOR ARTICLE

HIV/AIDS

Transmitted HIV Drug Resistance Is High and Longstanding in Metropolitan Washington, DC

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Background. Washington, DC, has 2.5% human immunodeficiency virus (HIV) prevalence, 3.9% among African Americans. Antiretrovirals (ARTs) are the cornerstone for treatment and prevention. Monitoring changes in transmitted drug resistance (TDR) is critical for effective HIV care.

Methods. HIV genotype data for individuals enrolled in research studies in metropolitan Washington, D.C., were used to identify TDR using the World Health Organization mutation list [Bennett DE, Camacho RJ, Otelea D, et al. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. PloS One 2009; 4:e4724]. HIV phylogenies were reconstructed using maximum likelihood and Bayesian methods. HIV transmission clusters were supported by 1000 bootstrap values >0.70 and posterior probability >0.95 of having a common ancestor.

Results. Among 710 individuals enrolled in 1994–2013, the median age was 38.6 years, 46.2% were female, and 53.3% were African-American. TDR was 22.5% among 566 treatment-naive individuals; 15.8% had nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) resistance, 9.8% had nonnucleoside reverse-transcriptase inhibitor (NNRTI) resistance, and 4.2% had protease inhibitor (PI) resistance. Single class TDR was 10.0%, 5.1%, and 1.6% to NRTIs, NNRTIs, and PIs. Dual TDR to PI and NRTI was seen in 1.6%, NRTI and NNRTI in 3.4%, and triple class TDR in 0.9%. TDR frequency decreased from 1994–2006 (27.1%) to 2007–2013 (19.4%; $P = .02$). Only 6/79 (7.6%) individuals within transmission clusters had evidence of TDR.

Discussions. We identified high prevalence of TDR among HIV-infected individuals in metropolitan Washington, DC, regardless of gender. Active surveillance for TDR is needed to guide ART usage and analyses of risk group contributions to HIV transmission and resistance.

Keywords. HIV; transmitted drug resistance; transmission dynamics; HIV clusters; women.

Selection of Rilpivirine-Resistant HIV-1 in a Seroconverter From the SSAT 040 Trial Who Received the 300-mg Dose of Long-Acting Rilpivirine (TMC278LA)

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Abstract

The injectable long-acting formulation of rilpivirine (TMC278LA) is a promising preexposure prophylaxis (PrEP) candidate for prevention of human immunodeficiency virus type 1 (HIV-1) infection. We evaluated HIV-1 in plasma obtained from an unexpected seroconverter in the 300-mg arm of the SSAT040 TMC278LA pharmacokinetic study for rilpivirine (RPV) resistance. Infection with wild-type HIV-1 was confirmed on day 84 after TMC278LA injection, and the K101E mutation was detected on day 115. Plasma-derived HIV-1 clones containing K101E had 4-fold increased resistance to RPV and 4–8-fold increased cross-resistance to etravirine, nevirapine, and efavirenz compared with wild type HIV-1 plasma-derived clones from the same individual. This case is a unique instance of infection with wild-type HIV-1 and subsequent selection of resistant virus by persistent exposure to long-acting PrEP.

Adverse Events During Maintenance Period

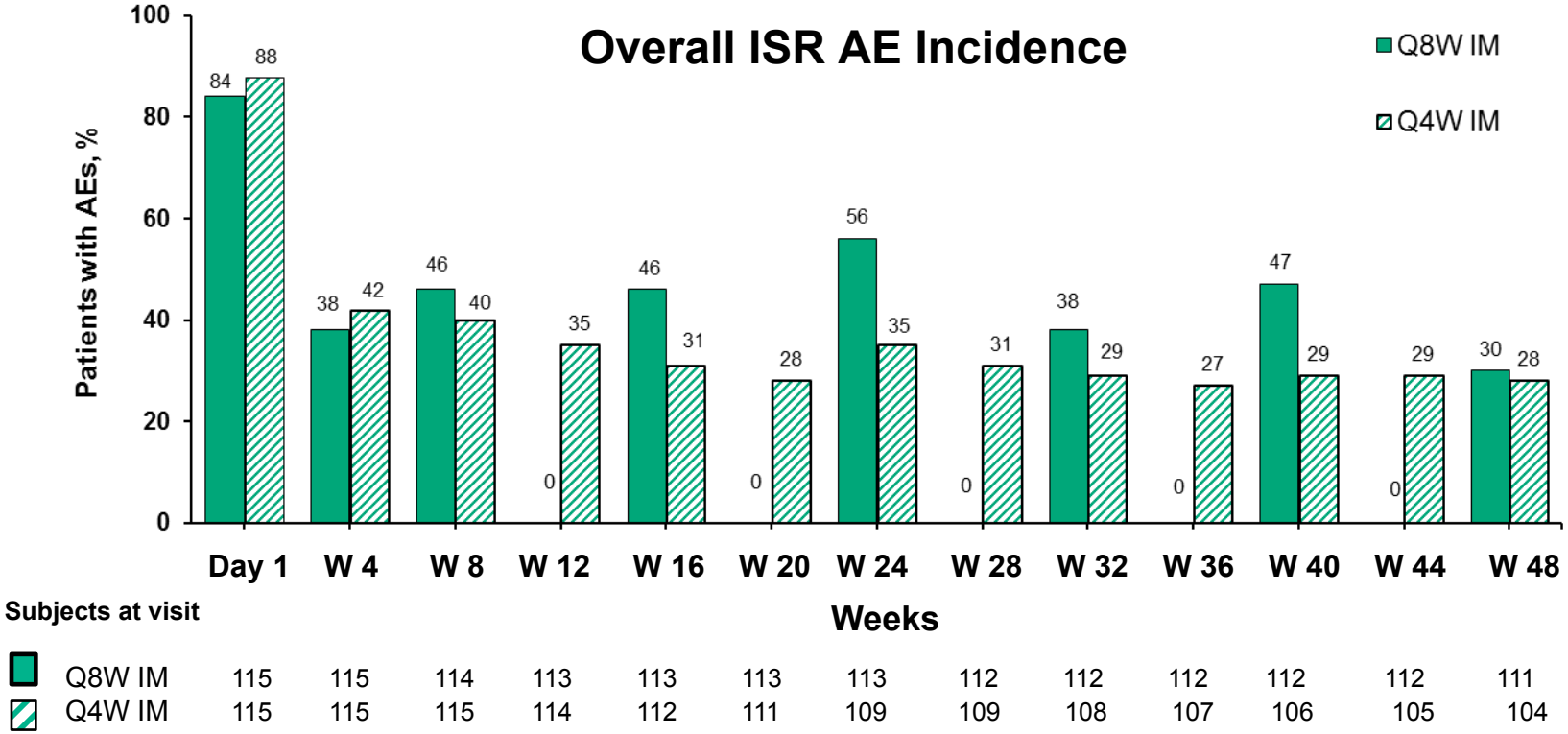
	Q8W IM (n=115)	Q4W IM (n=115)	IM subtotal (N=230)
Number of injections	1623	2663	4286
Number of ISRs (events/injection)	1054 (0.65)	1228 (0.46)	2282 (0.53)
Grades			
Grade 1	839 (80%)	1021 (83%)	1860 (82%)
Grade 2	202 (19%)	197 (16%)	399 (17%)
Grade 3	12 (1%)	10 (<1%)	22 (<1%)
Grade 4	0	0	0
Duration, days			
≤7	943 (89%)	1121 (91%)	2064 (90%)
Median	3.0	3.0	3.0

- Number of subjects reporting ISRs decreased over time, from 86% (Day 1) to 33% (Week 32)[a,b]

[a]Represents percent of participants with a Week 32 visit (n=220). [b]Data through data cutoff for the Week 32 primary analysis.

Murray et al. AIDS 2016; Durban, South Africa. Poster THPEB052.

ISRs for CAB LA or RPV LA Over Time



Subjects at visit

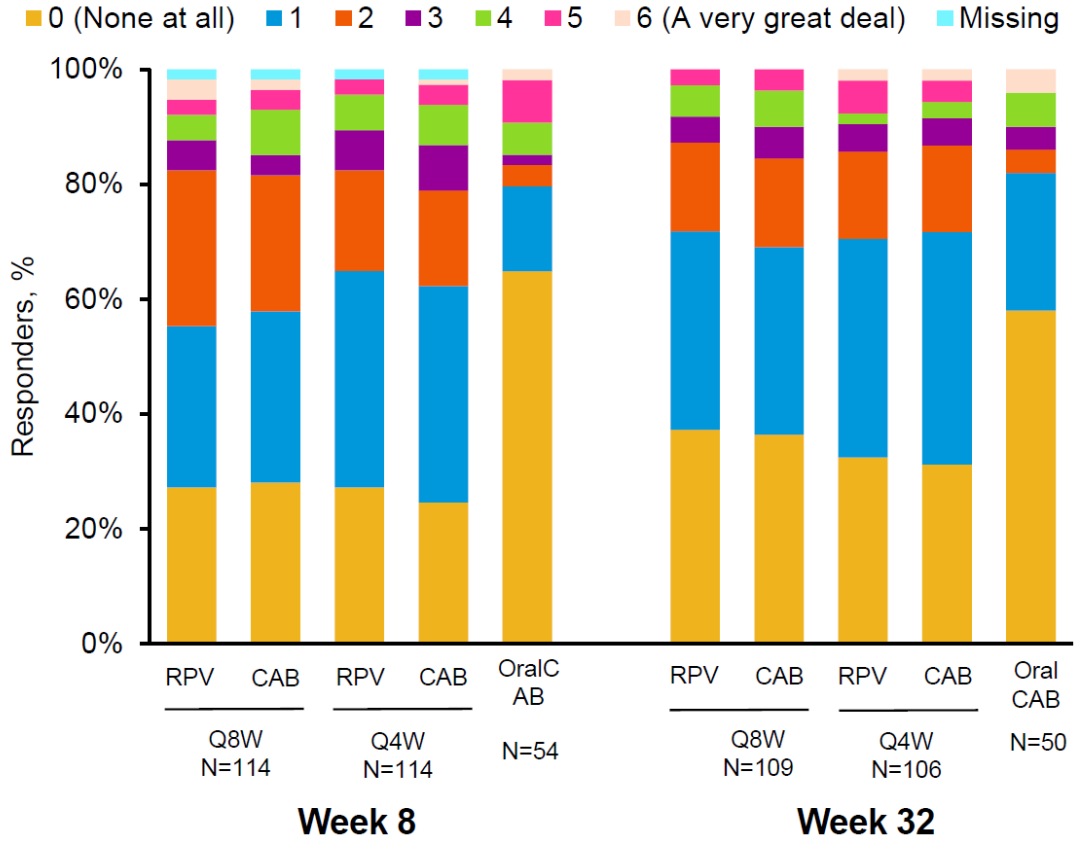
	Day 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48
Q8W IM	115	115	114	113	113	113	113	112	112	112	112	112	111
Q4W IM	115	115	115	114	112	111	109	109	108	107	106	105	104

- **99% of ISRs were mild (82%) or moderate (17%), and 90% resolved within 7 days**
- **Most common ISR events overall were pain (67%), nodules (7%), and swelling (6%)**
- **2/230 subjects (<1%) withdrew as a result of injection reactions (Q8W)**

Bars represent incidence of onset ISR events relative to the most recent IM injection visit.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

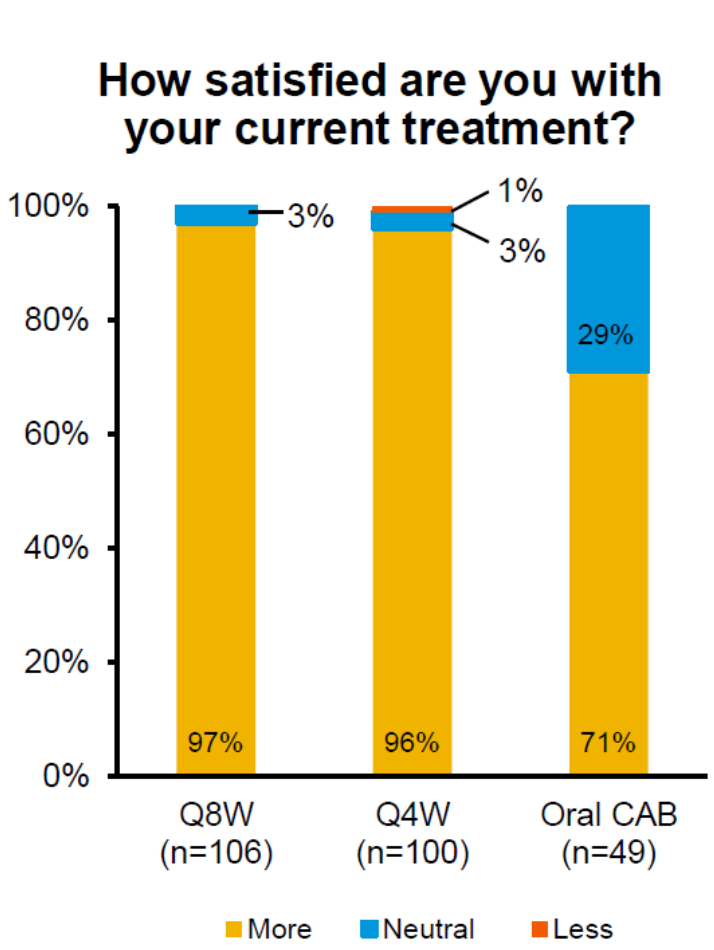
Amount of Pain and Discomfort With CAB LA + RPV LA and Oral CAB at Week 8 and Week 32 (HIV-MQ)

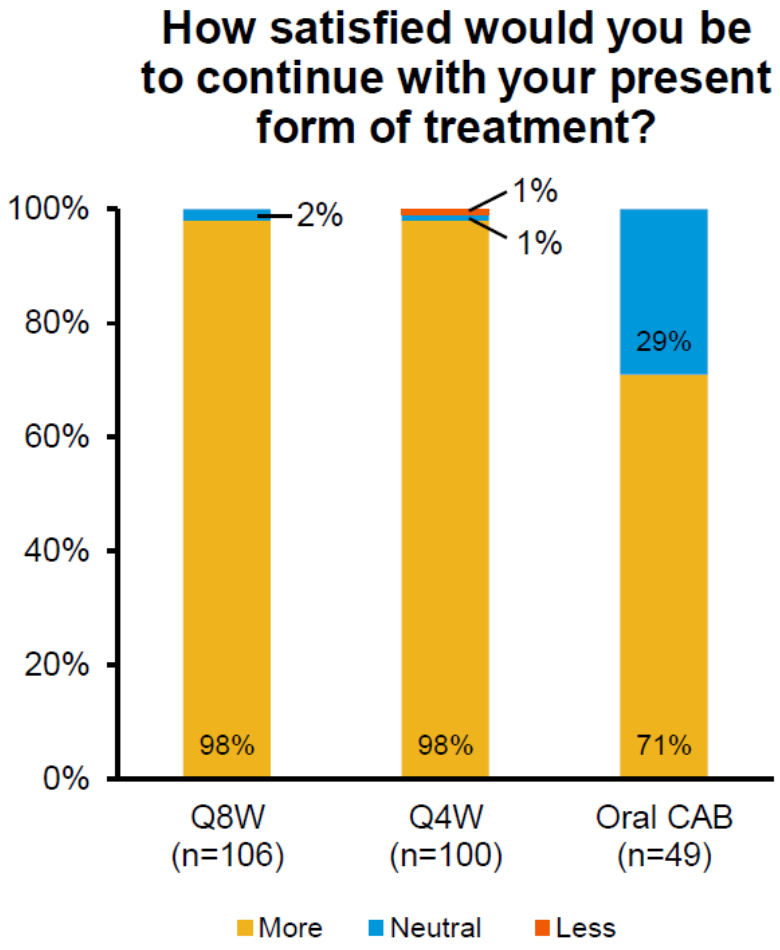


- The percentage of subjects rating their pain/discomfort as 0 (“none at all”) was similar for CAB LA + RPV LA with both the Q8W and Q4W arms, with decreasing pain/discomfort over time; Week 8: Q8W (CAB LA=28%; RPV LA=27%), Q4W (CAB LA=25%; RPV LA=27%); Week 32: Q8W (CAB LA=37%; RPV LA=38%), Q4W (CAB LA=31%; RPV LA=32%)

Murray et al. AIDS 2016; Durban, South Africa. Poster THPEB052.

Satisfaction With Treatment at Week 32 and Comparing LA With Oral Induction Phase (HIV-TSQ [c])





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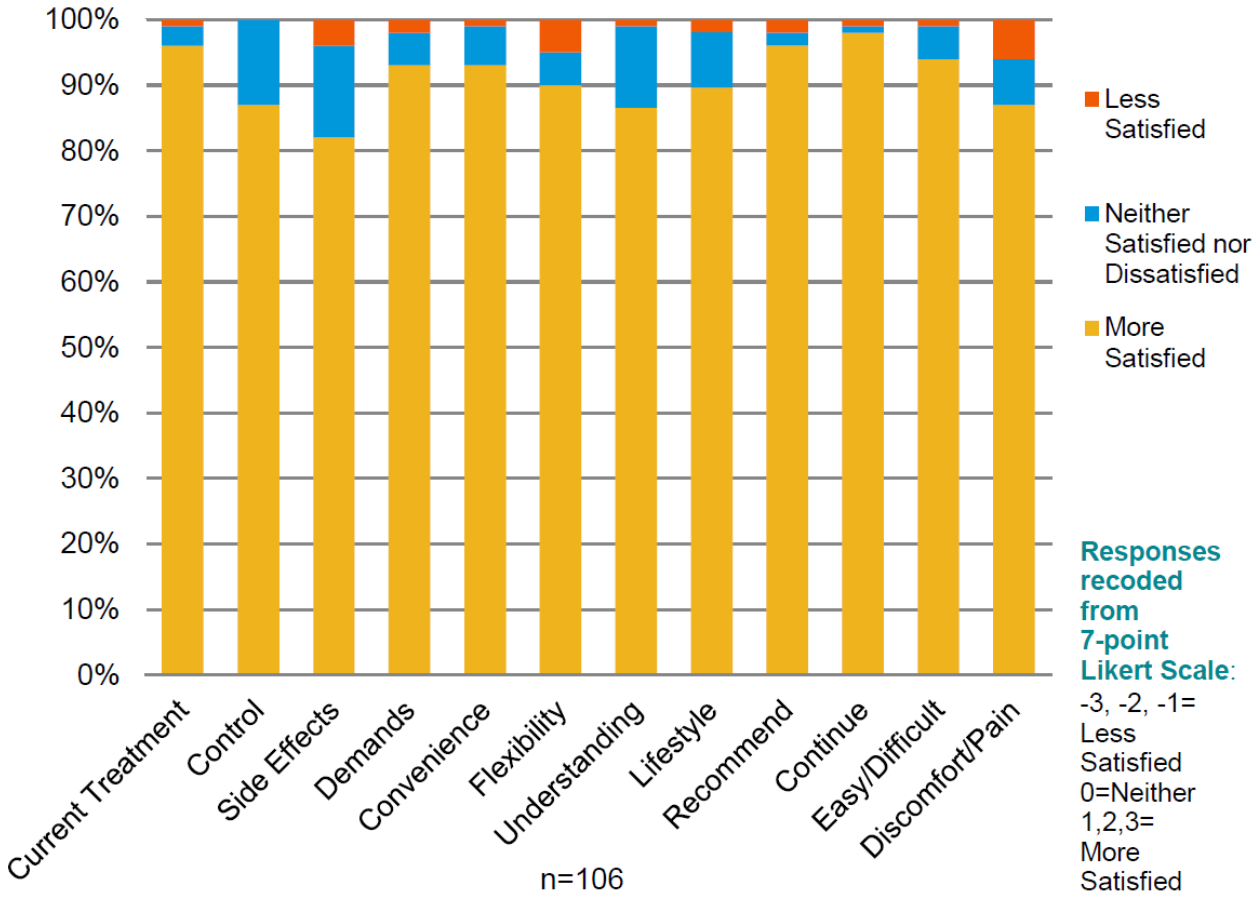
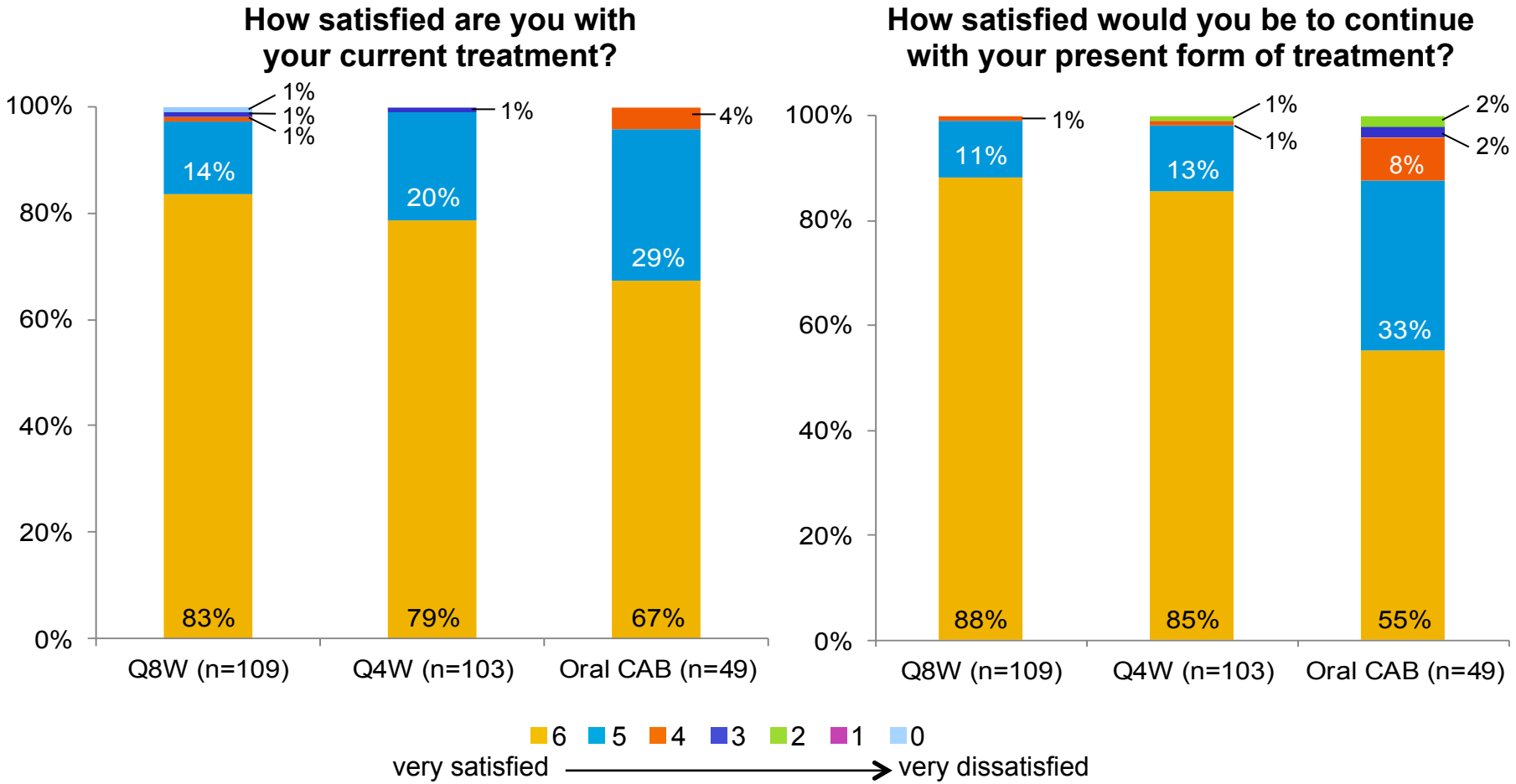
Individual Item Scores for Patients on LA Therapy, Q4W, Week 32 Compared With the Induction Phase (HIV-TSQ [c])



Murray et al. AIDS 2016; Durban, South Africa. Poster THPEB052.

Patient-Reported Outcomes at Week 48: Maintenance Treatment[a]



Note: based on observed case data set of subjects who completed Week 48 questionnaires.

[a]HIV Treatment Satisfaction Questionnaire status version (HIVTSQs).

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

Experiences With Long Acting Injectable ART: A Qualitative Study Among PLHIV Participating in a Phase II Study of Cabotegravir + Rilpivirine (LATTE-2) in the United States and Spain

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Specific Aims

- Qualitatively explore perspectives and experiences with LAI ART among LATTE-2 trial participants and clinical care providers
  - How do patients experience the injections?
  - How do patients experience coming to clinic?
  - How does LAI ART compare to daily oral?
  - Who are the “right” patients for LAI ART?
  - How and where to best deliver LAI ART?

All trial interview participants had completed at least 32 weeks of LAI ART following 20 weeks of oral ART

Kerrigan et al. AIDS 2016; Durban, South Africa. Slides THAB0204.

Demographics

Trial Participants	United States (n=11)	Spain (n=16)
Gender	10/11 Male 1/11 Female	15/16 Male 1/16 Female
Sexual orientation	9/11 MSM 1/11 Heterosexual male 1/11 Heterosexual female	14/16 MSM (1 bisexual) 1/16 Heterosexual male 1/16 Heterosexual female
Race/ethnicity	6/11 Caucasian 2/11 African American 2/11 Asian 1/11 Haitian	13/16 Caucasian/Spanish 3/16 Latino/South America
Age (mean, range)	38 (24-59)	37 (25-51)

- Providers included physician investigators, nurses and study coordinators (n=12)

Kerrigan et al. AIDS 2016; Durban, South Africa. Slides THAB0204.

Injection Experiences

- **Majority of participants reported some level of side effects**
  - Mostly soreness and minor bruising at site for 1-2 days
    - Some managed these effects with Ibuprofen/Acetaminophen
  - Minority of participants reported more intense reactions
    - Hardness at injection site, fever, impaired mobility issues
- **Broad agreement that side effects were "worth it"**
  - *"One day is nothing…it's as if you have a day with a headache. You take Ibuprofen and that's it. You put up with it. It's temporary"*. –Spain, Male trial participant
  - *"It might be painful, but it's better than pills"*. –US, Male trial participant

Kerrigan et al. AIDS 2016; Durban, South Africa. Slides THAB0204.

Injection Experiences (cont)

- **Convenience**
  - Perceived as simple and easy to integrate into one's daily life
- **Greater confidentiality, privacy**
  - Seen as more "discrete", with less opportunity for discrimination
- **Psycho-social, emotional benefits**
  - For some, LAI ART provided relief from the unwanted daily reminder of HIV associated with pills

*"It seems to me that it's much better because you simply **don't have to worry about anything**. If you go on a trip, you don't have to bring your pills or take anything at all along. You follow your '**normal life**'. You come once a month. You get the shot and it's over. You don't have to be thinking everyday …oh I forgot to take the pill. Or …when did I take it last... You just don't worry about anything. In reality, **taking the pill everyday keeps it present [HIV]**…and the shot is just once a month…you remember it when you come in and the rest of the time you **can basically forget it**."* -Spain, Male trial participant.

Kerrigan et al. AIDS 2016; Durban, South Africa. Slides THAB0204.

Clinic Experiences

- Participants felt very comfortable coming to the clinics; they expressed feeling well-treated, respected and supported
- A few participants expressed concern around the number of clinic visits involved and potential disclosure dynamics

"I was a little nervous about seeing the doctor so often*. Even my carpool buddy asked a couple of times, 'Wow. You go to the doctor a lot. They draw a lot of blood.' Then, I started saying, 'Well, I just have an appointment for my roofer, and my plumber is going to be coming in a second.' I stopped saying I was going to the doctor so much"*. –US, Male trial participant.

Kerrigan et al. AIDS 2016; Durban, South Africa. Slides THAB0204.

Comparison: LAI vs. Oral ART

- In addition to being more convenient, participants reported feeling:
  - **Less Stigma:**
    - *"It's less and less stigmatized with the injection, because I don't feel like I'm reminding myself of [HIV]…with the injection you go through days and weeks…two months not having to worry about that, so it's less stigmatized"*.–US, Male trial participant
  - **Less Pressure:**
    - *"I love it because I don't have to take a daily medication, so that's just one less thing on my plate that I have to worry about… I definitely feel there's less pressure. I like the injection because it's not a daily, in my face, I have to do this"*.– US, Female trial participant

Kerrigan et al. AIDS 2016; Durban, South Africa. Slides THAB0204.

“Right” Patients

- **Many participants felt LAI ART could be appropriate for:**
  - “Everyone” living with HIV
  - Tolerant of needles
  - Younger people or those who don’t take other medications
  - “Unstable” populations

“If you don't know where you're going every night, [it’s hard to] to make sure that you take your medication*. If you can know that once a month or every other month you take an injection, that's one less worry.”* -US, Female trial participant.

Kerrigan et al. AIDS 2016; Durban, South Africa. Slides THAB0204.

Provider Views

- **Supportive but not as definitive as patients**
  - Need to consider on case by case basis
  - Many patients can take pills just fine
  - Still need to be able to come to clinic as scheduled
  - Concerns about resistance, clinical management

"The fear is that the patient does not reappear*…[and] after the injection, if there is an allergy or intolerance,* ***the medication cannot be removed****…it may be many months without really knowing its secondary effects."* –Spain, Provider.

Kerrigan et al. AIDS 2016; Durban, South Africa. Slides THAB0204.

Delivery: Who, Where, How

- Who: Agreement on the need “skilled” or “trained” professional to administer injections such as doctor or nurse
- Where: In context of ongoing clinical care (HIV or primary care); some participants mentioned community centers
- How/how often: ***“Less is better”***; many participants relayed the hope for quarterly or less frequent injection schedules

Kerrigan et al. AIDS 2016; Durban, South Africa. Slides THAB0204.

Safety and acceptability of Iniectable Cabotegravir Compared to daily oral TDF/FTC for Preexposure Prophilaxis in HIV –Uninfected cisgender men and transgender women who have sex with men (NCT02720094)

NIAID

Phase IIB/III double blind

Estimated enrollment 4500

Estimated completion date 2020

Experiences With Long Acting Injectable (LAI) Cabotegravir (CAB) as PrEP: a Qualitative Study Among Men Participating in a Phase II Study (ECLAIR) in New York and San Francisco

Deanna Kerrigan,[1] Andrea Mantsios,[1] Robert Grant,[2] Martin Markowitz,[3] Patricia Defechereux,[2] Melissa La Mar,[3] David Margolis,[4] Miranda Murray[4]

[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [2]Gladstone Institutes, University of California, San Francisco, CA, USA; [3]Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY, USA; [4]ViiV Healthcare, London, UK and Research Triangle Park, NC, USA

Sample Characteristics

Participant Characteristics

Variables	New York (N=15)	San Francisco (N=11)
Age	32 (22-58)	39.5 (25-59)
Sexual Orientation	8/15 MSM 7/15 non-MSM	10/11 MSM 1/11 non-MSM
Race/Ethnicity	4/15 Caucasian 5/15 African American 3/15 Hispanic 3/15 Asian	7/11 Caucasian 2/11 Asian 1/11 Hispanic 1/11 Native Hawaiian
Prior PrEP use	0/15	3/11
Post trial PrEP plans	2/15	4/11

- Four clinical care providers (2 per site) were also interviewed including study investigators, nurses and coordinators

Kerrigan et al. AIDS 2016; Durban, South Africa. Poster WEPED393.

Results

- Almost all participants described some adverse effects associated with receiving LAI CAB, mostly minor injection site soreness
  - However, all reported being satisfied with and interested in continuing LAI CAB as PrEP if it became available post-study completion
- Participants described the convenience of LAI CAB and perceived advantage of not having to worry about adhering to a daily oral
  - They described the peace of mind associated with LAI CAB given the possibility for missed oral doses among themselves or their partners

Kerrigan et al. AIDS 2016; Durban, South Africa. Poster WEPED393.

Results (cont)

- Due to both convenience and adherence challenges with oral PrEP, LAI CAB was seen by many participants as an important additional option, that may be appealing to many, but not all
- MSM participants, particularly in San Francisco, described a prevailing culture whereby MSM were now expected to be on PrEP to be seen as safe sex partners
  - LAI CAB was seen as conducive to the realities of participants' lives and risk dynamics

Kerrigan et al. AIDS 2016; Durban, South Africa. Poster WEPED393.

Results (cont)

"Oh totally, especially if they're already on PrEP, on Truvada, I would definitely recommend this as an alternative. And the fact that they don't have to remember to take it every day, I think would make a big difference and people probably don't need to be convinced very hard, or very much, to make the switch". - MSM, SF

Kerrigan et al. AIDS 2016; Durban, South Africa. Poster WEPED393.

Results (cont)

- Providers expressed the need for guidelines to assist patients in choosing when to start, stop and/or transition between oral PrEP and LAI CAB
- They also emphasized the idea that potential candidates need information and a menu of options, not judgment, reflecting on prior judgmental attitudes in the media and broader community towards oral PrEP use

> *"We should celebrate people who act to protect themselves."*
> -Provider, San Francisco

Kerrigan et al. AIDS 2016; Durban, South Africa. Poster WEPED393.