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Lessons for Patient Education Around Long-Acting Injectable PrEP: Findings from a Mixed-Method Study of Phase II Trial Participants

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Abstract

This study aimed to identify patients' physical and psychosocial experiences of an investigational long-acting injectable PrEP product to aid in the development of patient and provider education materials. Twenty-eight participants of a Phase 2 safety, tolerability, and acceptability study of long-acting integrase inhibitor cabotegravir (CAB-LA) were interviewed on their physical and psychosocial experiences of the injections. Five themes emerged through a framework analysis on

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Compliance with Ethical Standards

Conflicts of interest Kathrine Meyers has received grant support from GlaxoSmithKline. Kristina Rodriguez declares that she has no conflict of interest. Atrina Brill declares that she has no conflict of interest. Yumeng Wu declares that she has no conflict of interest. Melissa La Mar declares that she has no conflict of interest. Debora Dunbar has received salary support from GlaxoSmithKline. Beryl Koblin received a research grant from GlaxoSmithKline for the ECLAIR study. David Margolis is a fulltime employee and shareholder of ViiV Healthcare, who sponsored the ECLAIR Study. Magdalena Sobieszczyk received a research grant to the institution from GlaxoSmithKline for the ECLAIR study. Hong Van Tieu received a research grant from GlaxoSmithKline for the ECLAIR study and has received a research grant from Merck. Ian Frank has received research grants from ViiV/GlaxoSmithKline and is a member of an advisory board for Gilead Sciences. Martin Markowitz receives grant support from Gilead Sciences, GlaxoSmithKline, ViiV and Merck Laboratories, is a paid consultant to Merck and ViiV and receives honoraria for speaking from Gilead Sciences. Sarit Golub received free study drug from Gilead Sciences for a PrEP demonstration project (R01AA02267).

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent It was obtained from all individual participants included in the study.

these interview transcripts: (1) injection-related pain is highly variable across individuals; (2) pain is more impactful after the injections than during; (3) patient anxiety is critical, but does not determine the experience of injections and decreases over time; (4) intimacy and awkwardness of gluteal injections impacts patients' experiences; (5) patient education and care strategies can mitigate the above factors. These findings can inform further sociobehavioral research within Phase 3 efficacy trials of CAB-LA, as well as patient education and provider guidance for future injectable PrEP products.

Keywords

PrEP; Long-acting injectable; HIV; MSM; Patient education; Providers

Introduction

Clinical trials and demonstration projects have shown that tenofovir-based oral pre-exposure prophylaxis (PrEP) is extremely effective in reducing the risk of HIV infection among patients who adhere to daily dosing [1–4] or at least four pills a week [5, 6]. With the exception of three documented cases to date [7–9], all individuals who have seroconverted with HIV infection while on PrEP have been found to have suboptimal adherence, either by self-report or by drug levels in plasma [1, 5]. As PrEP use expands beyond early adopters and patterns of real world use of PrEP are better characterized, adherence to daily oral pills and persistence to PrEP over time are likely to be key challenges to population-level prevention effectiveness of daily oral PrEP.

Long-acting injectable PrEP has been posited as an alternative formulation with potential for improved prevention-effective adherence [10], especially among individuals for whom adherence to a daily oral regimen is challenging. Cabotegravir, an integrase inhibitor that can be administered through intramuscular injection, is one such product currently under clinical investigation for PrEP indication. Several papers have documented acceptability of a hypothetical long-acting injectable PrEP product; study results vary, with some studies demonstrating high acceptability and preference for an injectable product [11–14] and others reporting lower acceptability and preference rankings [14, 15]. This variation suggests that individuals' personal preferences and priorities will impact acceptability of different PrEP modalities. As has been shown in the contraceptive field, the ability to choose among multiple methods is associated with increased population coverage [16, 17] as women find a method that matches their preferences and priorities.

Real world implementation of oral PrEP has taught us that it takes time for new biomedical interventions to be adopted by providers and at risk populations [18]. New interventions are commonly resisted, as has been seen with related products such as the HPV vaccine [19] or HIV post-exposure prophylaxis [20]. By the time an injectable PrEP product is available commercially, some barriers to PrEP may have been overcome; however, we anticipate an injectable formulation will raise distinct implementation issues for both patients and providers. In order to move beyond the hypothetical acceptability literature described above toward data that can guide the development of patient education and engagement materials,

it is important to collect data from real users of injectable PrEP agents. The purpose of this study was to collect data on physical and psychosocial experiences of the PrEP injections among participants in a study evaluating the safety, tolerability, and pharmacokinetics of injectable long-acting cabotegravir (CAB-LA). These data are intended to guide the development of patient and provider education materials for long-acting injectable PrEP formulations.

Methods

Procedures and Participants

We interviewed a subset of participants in the ECLAIR study, a double-blind, randomized, multi-center Phase 2 safety and acceptability trial of CAB-LA. In ECLAIR, healthy, at risk volunteers took a 4-week oral lead-into safeguard against adverse reactions and were then administered CAB-LA as two injections in the buttocks at three, 12-week intervals [21]. The ECLAIR study randomized participants 5:1 active versus placebo. The final sample receiving injections was 115, including 94 participants in the active arm and 21 in the placebo arm [21].

Between December 2014 and February 2015, eligible ECLAIR participants at four sites (Columbia University, New York Blood Center, Aaron Diamond AIDS Research Center/Rockefeller University, and University of Pennsylvania) were informed of this substudy through the site study coordinator and/or a recruitment post-card. Eligible participants ($n = 47$) were men or transgender women who reported sex with men. Interested participants called the research team directly to schedule an interview or, in the case of University of Philadelphia, scheduled an interview slot through the University of Pennsylvania study coordinator. This mixed-methods sub-study consisted of a onetime in-person structured interview of participants. Participants provided written informed consent, including granting permission for audio-recording of the interview and for sites to inform the research team whether the participant was randomized to the active or placebo arm upon unblinding of the study. Study visits consisted of a 60-min, semi-structured interview including questions about: (a) overall ECLAIR trial experience; (b) experience with injections and the injection site; (c) factors motivating persistence and return for study visits; (d) HIV-related risk perception and (e) demographics and risk behaviors. The study was approved by The Rockefeller University Hospital, and received approval or waiver from the review boards at the remaining participating sites.

Out of 47 eligible participants across the four sites, 30 individuals were interviewed, at which point the research team felt that qualitative data saturation had been achieved. Unblinding revealed 28 participants had received active injection (92%) consistent with the active and placebo proportions in the larger ECLAIR trial (83% active injection, 95% CI for difference in proportions -0.03 to 0.26). Analyses below are restricted to those receiving active injection because of concerns that the experiences of injections would differ for placebo participants, yielding a final analytic sample of 28 individuals.

Measures and Analyses

Participants were asked to respond to three scale-based questions that are included in the current analysis. Satisfaction with the ECLAIR study was assessed on a five-point Likert-type scale from (1 = very dissatisfied to 5 = very satisfied). Participants were asked to rate their pain both *during* the first injection and *after* the first injection on a six-point scale ranging from zero (no pain) to six (intense pain). Participants who reported post-injection pain were also asked the duration of this pain in days.

Interviews were digitally recorded and answers to open-ended questions were transcribed verbatim and entered into the qualitative analysis software DeDoose [22]. We chose framework analysis [23, 24] as our analytic approach due to the specificity of the questions we were asking: patient experience with the injections. The analysis proceeded along five steps outlined in framework analysis, beginning with (a) *familiarization*: three members of the research team familiarized themselves with the content by listening to the interviews and reading transcripts, noting themes and emerging issues. Based on these themes and emerging issues, we developed a (b) *thematic framework* by which to code the excerpts. Two interviews were (c) *indexed* independently by two researchers and the thematic framework was refined further. All transcripts were subsequently indexed and (d) *charted* with a specific focus on the experience of injections at physical and psychosocial level. A subset of five transcripts were double coded; reliability across two coders was assessed across 81 excerpts (Cohen's kappa = 0.9). Differences in coding were resolved through discussion with the research team and coders then returned to revise indexing of the remaining transcripts. In the final stage the research team (e) *mapped* the range and nature of the injection experience and interpreted the themes that emerged with the specific goal of generating recommendations for the development of patient education materials that were true to the attitudes, values, and beliefs of the participants [24].

Results

The 28 participants ranged in age from 21 to 55 ($M = 31.21$; $SD = 9.48$) years, with almost two-thirds of the sample in their twenties ($n = 18$). Over 60% of the sample were MSM of color, including 32% ($n = 9$) who identified as Black and 14% ($n = 4$) who identified as Latino. The sample was relatively diverse in regards to socioeconomic status, with 39% ($n = 11$) reporting less than a college education and 60% ($n = 17$) reporting an annual income of less than \$30,000 per year. The majority of participants were recruited at the University of Pennsylvania site ($n = 12$, 43%) and the Aaron Diamond AIDS Research Center/Rockefeller University site ($n = 10$, 36%). An additional four participants came from Columbia (14%) and two (7%) from the New York Blood Center. Median time since last injection was 29 days post-injection (range same day to 92 days post-injection).

Overall, participants reported very favorable attitudes toward both the ECLAIR study and the PrEP injections. Participants' mean satisfaction toward the ECLAIR study was 4.7 out of 5 ($SD = 0.45$, range 4–5). When a subset of the 28 participants ($n = 16$) was asked about future CAB-LA use, 88% ($n = 14$) reported they would definitely or very likely use CAB-LA, and 63% ($n = 10$) reported that they would prefer to use CAB-LA every twelve weeks to daily oral PrEP. Five key themes emerged from mixed-methods analyses of participants'

experiences with injections. Below, we describe each theme in terms of its implications for patient care and present both qualitative and quantitative supporting data.

Theme 1: Patients Vary in Their Experience of Injection Pain

On pain scales presented to participants, 34% of injections were rated as zero (or “no pain”), 38% were rated as 1 (“mild”), 16% were rated as 2 (“minor”), and 12% were rated as 3 (“moderate”). Interestingly, both participants who reported no pain and participants who reported mild or moderate pain said that the experience felt “like a shot”. For example: “Just a shot, it went in and out” (34 year old Pacific Islander, pain scale = 0), and “Big needle going in my butt, it’s gonna hurt. Nothing surprising there” (28 year old Latino, pain scale = 3). Of the ten participants who reported having previously received a flu shot, five (50%) said the CAB-LA injection was more painful than a flu shot, two (20%) responded that the flu shot was more painful, and three (30%) reported that the pain was about the same. Participants compared CAB-LA shots to a range of other injection experiences, from tetanus shots to the hepatitis B vaccine to HIV tests, blood draws, and growth hormones. Participants described other sensations they experienced during the injection, including “sting” or “pierce” (n = 5), “sensation of liquid dispersing”, (n = 4) “warm” (n = 2), and “tingling” (n = 2).

Theme 2: Pain is More Impactful for Patients in the Period After (Rather than During) Their Injections

Participants reported pain following almost 75% of injections, with 36% resulting in mild to minor pain, 22% resulting in moderate pain, and 16% resulting in severe or intense pain. For those who reported pain after the injection, all but one reported that the pain began the day after the injection, with mean duration of 4.3 days after first injection, 3.7 days after second injection and 3.9 days after third injection (range for all three injections, 0.5–9 days). Almost 50% (n = 13) reported that pain lasted for more than 3 days. Eleven (39%) noted that they took over-the-counter medication to manage the pain.

Many participants described the sensation following injection as “soreness” or “bruising”. One 37-year-old White participant described it: “Like an ache, like I got punched in my muscle...it’s not like a throbbing pain, it’s just there.” Another respondent explained: “It was almost distantly numb pain, it was almost like I had bumped myself the day before and it was like a very tiny bruise was forming in the recesses of my buttocks” (age: 28; multiracial).

Participants noted the impact of this pain on every-day motions like tying shoes, putting on pants, and walking up stairs. Participants also spoke of the impact on their jobs. A restaurant manager, on his feet for more 9 hours a day, stated: “I’d be fine standing, but if I were sitting down for like more than an hour and a half, I would start walking like an old man” (age: 34; Pacific Islander).

Almost 40% (n = 11) reported that the injections impacted their recreational physical activity, i.e. going to the gym, playing tennis, or running. Activities that involved impact on the buttocks (such as rowing, stationary bike, crunches) or targeted the buttocks directly (such as lunges) were particularly uncomfortable and in the words of several respondents,

“aggravated” the pain. However, several participants (n = 4) who reported regularly running long distances or playing tennis tournaments noted that while the injections made their bodies feel sore, it was no different from regular “soreness” and did not negatively impact their exercise. Several respondents (n = 3) even noted that the “soreness felt good.”

When asked about the impact of the injection on their sex and social life, only two out of 17 noted a negative impact, reporting that the pain diminished their interest in sex: “In the week of pain, I was like, I’m not going to lift up my legs in the air or doing crazy shit. Yeah, totally wasn’t interested” (age: 34; Pacific Islander). A third responded that he decided to stay in on a Friday night rather than go out dancing due to the general discomfort, which he noted was unusual.

Participants shared that they learned from the experience of the first shot and changed their exercise patterns as a result for subsequent injection visits. A 23-year old Black respondent related: “The third shot was the least amount of side effects, because by then I knew exactly what to do and how I should change my activities during that week to fit in with the shot and not over work my body too much.”

Theme 3: Anxiety Is a Critical Factor for Patients, But it Does Not Determine their Experience of the Injections and it Decreases Over Time

A large proportion of participants, 64% (n = 20) felt anxiety before the first injection; however, this decreased to 29% (n = 8) by the second and third injections. Importantly, there was no correlation between anxiety and injection or post-injection pain. Three-quarters (n = 21) stated that the first injection hurt less than expected.

Participants reported two distinct but related sources of anxiety: anxiety related to needles themselves (32%, n = 9) and anxiety around expectation of pain from the injections (54%, n = 15). A 55-year old White participant shared: “You see the needle and you’re like holy crap! It was a nice size. So I have all these visions like this is going to hurt like hell, and really it was nothing.” Another respondent elaborated:

“First shot I was very apprehensive and nervous because of the possible side effects and the soreness, and I bruise very easily and I had some misgivings about walking around with these big bruises from the injection site. It was all for nothing. I worked myself up into a frenzy for nothing” (age: 50; multiracial).

Many of the individuals who expressed anxiety at the first injection noted that this decreased after the first experience: “After the first one, I knew what to expect and was accustomed and used to it” (age: 24, White). The following excerpt touches on each of these themes (needle size, expectation of pain, decrease in anxiety):

“Have you seen the needle? I don’t know why it’s so long but I guess because a butt is a butt, it’s a muscle, so she’s like grabbing my butt cheek...I could feel the fluid entering... It wasn’t like “I never want to do this again,” it was just like...the first time, I wasn’t ready. I wasn’t prepared for that big of a needle. But then by the second time I was like, ‘well I’ve done this before” (age: 24, Black).

A few participants expressed their initial fear that the needle could get lodged inside the body if they made a wrong motion during the injection:

“Because I’m used to arm injections so this injection felt more like something could go terribly wrong because it seemed a bit deeper. So it felt like if I twitched, that thing’s going to get lodged in me. But I’ve had a bunch of injections in my arm that I’m very used to” (age: 37, White).

Theme 4: The Intimacy and Awkwardness of Gluteal Injections is a Key Component of Patients’ Experiences

Although many participants noted that the injection itself was very tolerable and felt like “nothing,” a subset of participants expressed feelings of awkwardness and vulnerability associated with receiving injections in the buttocks (12/28, 43%). Several noted that the process itself was awkward:

“That was a little awkward the first time because I had no idea what was happening. [The nurse] was just like ‘okay, so I need you to pull your pants down and then lay on your side and then bend your knee and arch your back’ and I felt like I was bottoming” (age: 24; Black).

“[Receiving the injection was] uncomfortable. You have to put yourself in like the fetal position and bend over and take off your pants” (age: 27; Multiracial).

Participants noted vulnerability in terms of the positioning and requirement for the removal of clothing, which some felt was akin to a sexual act. Additionally, some noted this vulnerability itself was related to sensations in the injection area distinct from injection-related pain.

“I was a little apprehensive because I was getting my first injection and I am extremely ticklish, so especially in the position in which they give me the shot is probably my most vulnerable position in the world” (age: 28; Multiracial).

Theme 5: Each of the Above Factors can be Better Managed with Specific Patient Education and Care Strategies

A large number of participants commented specifically about the ways in which ECLAIR study staff impacted their experience of CAB-LA, with three subthemes emerging. First, many participants (46%, $n = 13$) spoke specifically about the importance of nurses and staff being caring, friendly, and warm, and treating them like human beings rather than just study subjects. One participant noted this was particularly important for him given the intimacy of the injections: “This is a little intimate, what we’re doing, so you need to have someone who is understanding and caring and nice...It’s very very very important” (age: 24; Black). “I like that the staff is caring. I think sometimes in these type of studies ... people become a little complacent or jaded and maybe even cynical. But these folks here they are aces all the way through; really humanistic approach, it wasn’t at all clinical” (age: 50; Multiracial). Several noted that the caring attitudes of the staff impacted retention to study visits: “The staff was so nice, it made me want to come back” (age: 24; Black). They also appreciated the calm and reassuring manner of the nurses who administered the injections, as evidenced by these comments: “[The nurse] had a great demeanor; she was very relaxing and reassuring

and calm and before I knew it, it was all over” (age: 23; Black). “When I first got there I was calm, like, because my doctor. X, she’s amazing, she keeps me calm” (age: 26; Black).

Second, a large proportion of participants (43%, $n = 12$) discussed the importance of providers managing patients’ expectations and providing information about the process. Participants expressed appreciation for clear communication: “The nurse really did explain what to expect and while she was administering the shot, she was telling me ‘okay, you’re going to feel a little pressure, you’re going to feel this.’ So she was really talking to me along the way which made it really helpful” (age 23; Black). In contrast, participants expressed exasperation when they felt this type of communication was lacking: “I always feel like people are so crap at telling you stuff at hospitals. Yeah, when she was like, ‘you may experience some discomfort’... no, you need to tell people that it’s going to hurt. Always err on the side of telling people it’s gonna hurt. And probably you will be sore. And not the chance you are not going to be” (age 28; White).

Third, a number of participants (4/28, 14%) mentioned the importance of the skill-level of study nurses in terms of drawing blood and giving injections and the fact that they liked having the same person each time. “I don’t mind shots. I don’t mind the bloodwork. The nurses that did it, they’re really good” (age: 27; White). “It was usually all the same people. It was the same woman that gave me the first injection... that gave me the second and third. It’s usually the same person drawing our blood, taking my vitals...it’s always the consistency of having the provider there as well” (age: 29; Multiracial).

Discussion

The ECLAIR study reported high acceptability of CAB-LA injections, with 79% of subjects reporting willingness to continue the CAB-LA injections after their third and final injection [21]. Our finding of 88% reporting willingness to definitely or probably use CAB-LA themselves in the future is somewhat higher, but within a similar range. Most participants (82%) included in this relatively small sample of ECLAIR participants experienced pain associated with CAB-LA injections, findings that are in line with results from the total sample in the ECLAIR study in which 82% of participants in the CAB arm experienced injection-site pain [21]. Demographically, the subsample had a similar age distribution, but higher non-White representation in the sample compared to the overall study population (~44% in the overall study population vs. 60% in substudy). Overall, these data suggest that our subsample is broadly similar to the ECLAIR population from which it was sampled, and the 94 ECLAIR participants who received active CAB-LA injections specifically.

This mixed-methods analysis offers five lessons for the development of patient education materials and suggests additional avenues of inquiry in future long-acting injectable PrEP trials. The current and planned Phase 3 efficacy studies of CAB-LA, which will enroll many thousands of men [25] and women [26], offers an opportunity to build on this formative research and expand upon these findings. This may be particularly important as the pharmacokinetic analysis in the ECLAIR study showed blood plasma concentrations that were too low to be considered protective from HIV acquisition at the end of the 12-week dosing interval [23]. Consequently, Phase 3 studies of CAB-LA will administer injections

every eight weeks in one 3ML injection instead of two 2ML injections [25]. This change in dosing interval and administration may alter aspects of the injection experience and acceptability.

1. **Variability of pain** Patient education materials should highlight the variability of pain experienced by study participants, but also note that participants generally experienced the shot as “just another shot” rather than something altogether different. Patients should be told of the potential range of pain from the prick of a blood draw to the intensity of a tetanus shot. Systematically collecting data from Phase 3 participants around their experiences with other relevant injections—particularly intramuscular injections administered in the buttocks such as long-acting benzathine penicillin G for treatment of syphilis—would be useful to inform patient education materials and to give providers information with which to give concrete descriptions to help manage patient anxiety before injections. Additional research among Phase 3 participants would be useful to build on the findings generated in this study to develop accurate descriptions of the experience of the injections, especially in women, and to validate these findings on a broader scale. In addition, CAB-LA trials could explore whether any aspect of the administration of the injection impacts pain. For example, as introduced above, while the injections in ECLAIR were administered as two 2ML injections [21], ongoing and future CAB-LA efficacy studies will dose one 3ML injection [25, 26]. It would be important to capture whether a larger volume in a single injection is associated with differing pain profile and will affect acceptability of the injection.
2. **Pain in the post-injection period** Patients should be told to expect pain during the post-injection period which may have an impact on activities of daily living. Materials could specify that the intensity of the pain may range from slight discomfort in routine motions like crossing of legs, walking stairs, or sitting down to more significant impacts like changing exercise routines or decreasing interest in social activities and sex. The CAB-LA trials could usefully collect data on whether more or less activity after the injection impacts duration of pain and identify whether there are other strategies for minimizing pain after injections.
3. **Anxiety** Patients should be told that anxiety around injections is expected and that it is common for anxiety to decrease with subsequent injections. Patients could also be reassured that the gauge and length of needle used for the administration of the CAB-LA injections is in line with those used in the delivery of regular medical care.
4. **Intimacy** Providers should recognize the intimacy of the injection administration and take extra care to promote privacy and comfort during the injection process. The CAB-LA efficacy trials could consider data collection on patient experiences of the administration of the injections, eliciting descriptions of the number of health care workers involved in the injections, the degree of privacy afforded for

the injections, and potential strategies for altering injection practices to assuage concerns around intimacy and awkwardness of the injections.

5. **Providers as critical component of experience of the injections** Providers should recognize the extent to which their own behavior comprises part of the experience of the injections. Caring, attentive study staff who communicate what to expect before and during administration of the injection can mitigate the anxiety some patients may feel about the injections. Their kindness and engagement with participants is likely to impact retention to study visits in the context of clinical trials. It is important to consider how the types of interaction with study staff that participants extolled may be recreated in “real-world” busy healthcare clinics.

This study is subject to several limitations. It was conducted in healthy MSM who were assessed to be at low risk for HIV at the time of ECLAIR enrollment which may limit the generalizability of the findings. A second limitation is the long interval between the last injection and the conduct of the interview. This may have led to recall bias among participants, particularly around pain and impact of the injection on daily life. However, when we compared pain scores for participants interviewed close to their last injection and those with a longer interval, we found no difference in mean pain scores.

Conclusion

This formative and behavioral research study is the first to report on the physical and psychosocial experience of MSM receiving HIV prevention injections. The research, conducted in parallel with clinical development, generated experiential data to inform the development of education materials for future CAB-LA trial participants and future real-world users (should CAB-LA obtain regulatory approval), in order to reduce the time gap between proving efficacy in clinical trials and making injectable PrEP available widely and equitably. The high acceptability of the injections, despite the frequent experience of pain, suggests that for some people CAB-LA injections would be a welcomed addition to the biomedical HIV prevention toolkit. Additional research among Phase 3 study participants would allow us to further elucidate the physical sensations of injections and the impact of provider-interactions on the psychosocial experience.

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