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Preference for Sayana® Press versus intramuscular Depo-Provera among HIV-positive women in Rakai, Uganda: a randomized crossover trial☆,☆☆,★

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Abstract

Introduction: Sayana Press (SP), a subcutaneous formulation of depot medroxyprogesterone acetate (DMPA) prefilled in a Uniject injection system, could potentially improve and expand contraceptive injection services, but acceptability of SP is unknown. HIV-positive women need contraception to avoid unintended pregnancy and risk of vertical HIV transmission. We assessed acceptability of SP versus intramuscular DMPA (DMPA-IM) among HIV-positive women and their care providers in Rakai, Uganda.
Methods: Women were randomized to DMPA-IM or SP at baseline, received the alternate product at 3 months, and chose their preferred method at 6 months. We determined preferences among new and experienced contraceptive injectable users who had tried both types of injection during the trial, and from providers before and after providing both types of injectables to clients.
Results: Among 357 women randomized, 314 were followed up at 6 months (88%). Although SP caused more skin irritation than DMPA-IM (3.8% vs. 0% at 6 months, p=.03), it was associated with marginally fewer side effects (30.4% vs. 40.4% at 6 months, p=.06). Participants reported high levels of willingness to recommend the DMPA contraception to a friend and satisfaction with the injection received, and these did not differ by injection type. Sixty-four percent of women and 73% of providers preferred SP to DMPA-IM at 6 months; women's preferences did not differ by previous experience with injectable contraception.
Conclusions: SP is acceptable to HIV-positive women and health care providers in this rural Ugandan population.
Implications: SP appears to be acceptable to HIV-positive women and their care providers in Rakai, Uganda, and strategies for appropriate rollout of this innovative technology should be explored.
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Keywords: Injectable; Contraception; Subcutaneous; Intramuscular; Acceptability

☆ Disclaimer: The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the United States Agency for International Development.

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★ The trial was registered on Clinicaltrials.gov under the Johns Hopkins Bloomberg School of Public Health Protocol Record 00003213.

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1. Introduction

Expanding access to effective contraceptive methods is critical to reducing unmet need for contraception; preventing unintended pregnancy; reducing maternal and infant morbidity; and, for women living with HIV, reducing vertical HIV transmission. Hormonal contraceptive methods are among the most effective methods available. Injectable contraceptives are the most widely used hormonal contraceptive method in sub-Saharan Africa [1]. Still, 25% of married reproductive-aged women in sub-Saharan Africa (and 34% in Uganda) are considered to have an unmet need for contraception [1,2]. Innovations to simplify contraceptive provision could improve access, which is particularly important for rural and underserved populations.

One such innovation is Sayana® Press (SP), which contains 104 mg of depot medroxyprogesterone acetate (DMPA) (Depo-SubQ Provera 104) intended for subcutaneous administration using a prefilled, sterile, single-dose, nonreusable subcutaneous injection system (3/8", 23-gauge needle) called Uniject. Intramuscular Depo-Provera (DMPA-IM) is packaged in a glass vial with a separate syringe (1", 21–23-gauge needle) and at a dose of 150 mg. Both products are delivered every 3 months and have equivalent contraceptive efficacy [3–5]. One study found more skin reactions among women receiving subcutaneous versus intramuscular injections (8% vs. 0.4%) [4].

SP could improve contraceptive injection services by ensuring correct dosing, minimizing wastage, simplifying procurement and logistics, and avoiding transmission of blood-borne pathogens. Also, it could potentially be administered by lower-echelon health workers to facilitate task-shifting to address shortages of medical personnel in rural Africa. Acceptability studies assessing delivery of other drugs in Uniject suggest that most clients and providers prefer Uniject to intramuscular injections [6–8].

Use of progestin-only injectable contraception does not appear to accelerate HIV disease progression in women living with HIV [9], and in a study in Rakai, Uganda, hormonal contraceptive use was associated with a reduced hazard of progression to AIDS or death [10]. Some studies suggest that progestin-only injectable contraceptives may increase the risk of HIV transmission from an HIV-positive woman not on antiretroviral therapy (ART) to her male sexual partner, but evidence is limited and inconsistent, and additional data are needed [11]. The World Health Organization notes that women living with HIV can use hormonal methods without restriction and that consistent and correct use of condoms is critical to prevent sexual HIV transmission [12]. HIV-positive women need contraception to avoid unintended pregnancy and the risk of vertical HIV transmission. Contraceptive methods may be experienced differently by HIV-positive women as compared with uninfected women [13]. HIV-positive women, including those on ART, may have different concerns and preferences regarding injectable contraception. We conducted a randomized crossover study to assess acceptability of SP versus DMPA-IM among HIV-positive women requesting injectable contraception in Rakai, Uganda.

2. Methods

We enrolled HIV-positive women aged 18–45 interested in using injectable contraception at one of 13 Rakai Health Sciences Program community-based HIV care clinics. In these clinics, HIV-positive individuals are provided with cotrimoxazole prophylaxis, bed nets for malaria prevention, water sterilization, and access to ART and prevention of vertical transmission in accordance with Ugandan Ministry of Health guidelines. Safe sex counseling and a range of free contraceptive options are provided, including condoms, oral contraceptive pills and injectables, or referrals for implants, intrauterine devices (IUDs) or voluntary sterilization. A recent study indicated that injectable contraceptive use comprises approximately 77% of all hormonal contraceptive use among HIV concordant and serodiscordant couples in Rakai [14].

After a general health education session, women received information about the range of contraceptive options available and were informed about the study. In a one-on-one family planning (FP) counseling session, clients requesting injectables were invited to learn more about the study.

Study eligibility criteria included the following: age 18–45, wanting to receive injectable contraception, not desiring pregnancy within the next 9 months, intention to use injectable contraception and live in the area for 9 months, capable of providing informed consent, agreement to participate in trial, and no social or medical condition that could make study participation unsafe. Medical eligibility criteria included no current pregnancy as assessed by urine human chorionic gonadotropin (hCG) testing, no medical contraindication to using injectable contraception and being either ART naïve or on a first-line (as defined by Ugandan guidelines) regimen [15–19]. The written informed consent explained study procedures, risks and benefits, and strongly encouraged condom use to prevent HIV transmission to male partners. Consent forms were translated into Luganda, back translated into English and certified by the Makerere University Institute of Languages. Clients were assured that although SP was not available outside of the study, they would receive any other desired contraceptive method and HIV care regardless of study participation. We based power calculations on choice of receiving DMPA-IM or SP at the 6-month visit. We estimated that, assuming an alpha of 0.05 and a power of 80%, if 480 women completed the study, we would be able to detect a significant difference in acceptability between injectable methods if 56.4% or more participants chose to receive one product over the other.

Consented, enrolled participants completed a preinjection baseline questionnaire, were randomized to either SP or

DMPA-IM, and then completed a postinjection baseline questionnaire. At the 3-month visit, they crossed over to the alternate type of injection and completed a postinjection questionnaire. At 6 months, they chose which injection type they preferred to receive and completed a postinjection questionnaire (Fig. 1) [20]. Randomization was computer generated by a study statistician using a block size of four. Sequentially numbered, opaque, sealed envelopes contained treatment allocations. Neither participants nor providers were blinded, given obvious differences in study products. Questionnaires (available upon request) were adapted from those originally developed by FHI 360. Twenty-two providers were trained to administer SP using training materials developed by PATH and FHI 360. They practiced at least two injections on a nonhuman model and were observed during training to ensure proper technique.

Participants choose the site of administration (for DMPA-IM: upper arm, hip or buttock; for SP: abdomen, upper thigh or upper arm). Women newly beginning contraceptive injectables who were not within 7 days of their last menstrual period were encouraged to use condoms for the next 7 days. Urine hCG testing was performed at all visits, including prior to the first study injection. We performed intensive follow-up to encourage women to return within 12–13 weeks after their previous injection. For participants who failed to return for scheduled visits, we attempted to contact women up to three times by telephone within 1 week of a missed appointment. If we did not make contact, we visited women at home (with permission) to administer the injection and questionnaire. Women were considered lost to follow-up after three failed contact attempts. Women lost to follow-up who later returned could continue to receive injections as part of clinical care but were censored from analysis. Participants were provided with 5000 Ugandan shillings (approximately US$2) at each visit to compensate them for time and travel costs.

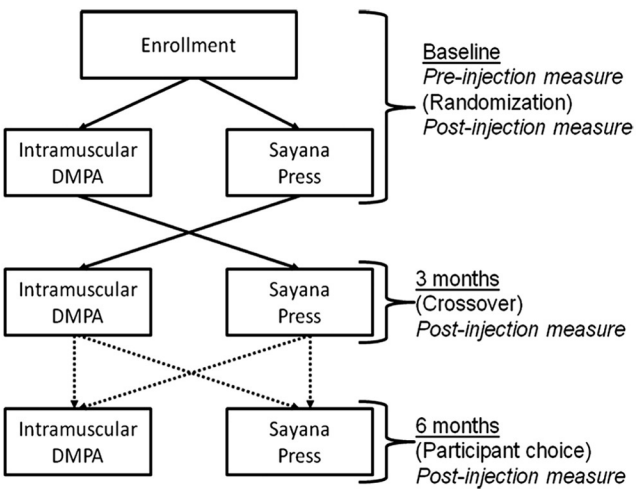

Fig. 1. Study design.

The study received ethical approval from the Johns Hopkins Bloomberg School of Public Health (JHSPH) Institutional Review Board, the Ugandan National Council on Science and Technology, and the Science and Ethics Committee of the Uganda Virus Research Institute. We obtained approval from the Ugandan National Drug Authority to import SP, which was donated by Pfizer; Pfizer also reviewed the study protocol. The trial was registered on Clinicaltrials.gov under the JHSPH Protocol Record 00003213.

2.1. Statistical analysis

We compared sociodemographic characteristics and injection experiences at baseline by randomization group using χ^2 tests, *t* tests and Fisher's Exact Tests. Our primary aim was to assess preference for SP versus DMPA-IM at 6 months at which time all study participants had experienced both types of injectables. We hypothesized that if no difference in preference existed between the two methods, 50% would choose SP and 50% would choose DMPA-IM. We assessed choice between the two injection methods at the 6-month visit using a test for the difference in proportions, compared against an expected proportion of 50% and adjusted for clustering by clinic. We also assessed pain/irritation at the injection site, side effects including menstrual disturbances and other indicators related to acceptability. To examine which baseline factors predicted choice of SP at 6 months, we selected all baseline factors associated in univariate analysis at $p<.10$, removed collinear variables and performed Wald tests to select independently associated variables in a modified multivariate Poisson regression model with robust variance [21], stratified by never versus ever use of injectables as reported at baseline.

3. Results

Recruitment began in April 2012 and ended in August 2012; follow-up continued through March 2013. Fig. 2 describes participant flow. Of 357 women enrolled, 314 (88%) received an injection at 6 months. The number of women who received an injection at home did not differ by randomization group at 3 months (16% of injections at home) or 6 months (12% of injections at home).

3.1. Baseline characteristics

Baseline characteristics were balanced between randomization groups (Table 1). Over half of women (52%) were aged 25–34, with 11% aged 18–24 and 37% aged 35–45. Most women had some schooling (88%) and were currently (57%) or previously (37%) married. Nearly half of women (49%) reported work for pay. The sample was predominantly Catholic (64%), with 22% Protestant, 8% Muslim and 7% Saved/Pentecostal. All but one woman had previously been pregnant, and 14% had 1–2 previous pregnancies, 50% had 3–5, and 36% had 6 or more. Among recent pregnancies,

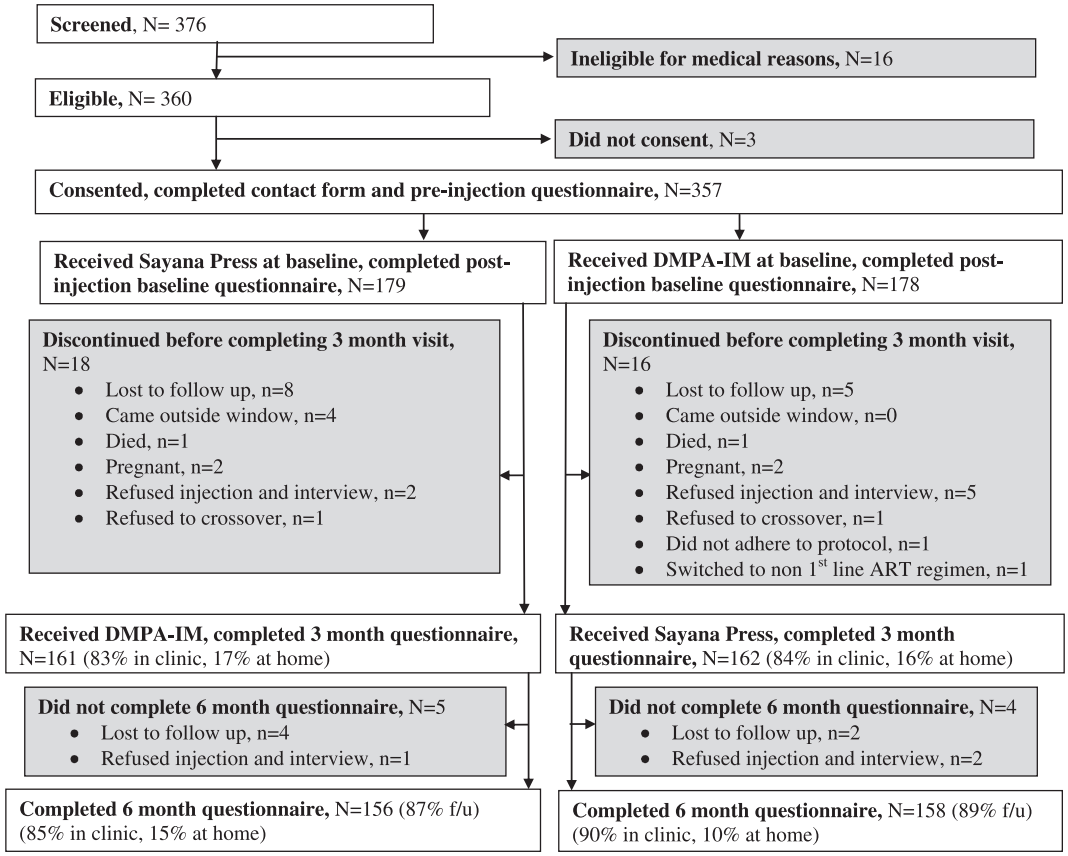

Fig. 2. Study flowchart.

half were intended, while 18% were mistimed and 31% were unwanted. Almost half of women had regular menstruation (46%), but 35% were irregular and 19% had amenorrhea (half of women with amenorrhea were currently using DMPA). The majority of clients were willing to use an FP method that causes irregular menstruation (98%) or amenorrhea (92%), largely due to the strong desire to prevent pregnancy and to the knowledge that menstrual disturbances with injectable use are not harmful to health. Most women (72%) said they did not desire another pregnancy. On average, it took participants 96 min to reach the clinic. Over half (56%) were receiving ART. Seventeen percent reported having an HIV-negative partner, 45% reported having an HIV-positive partner, 27% did not know their partner's status, and 11% had no regular ongoing partner.

Half of the women (52%) had previously used injectables, 19% were currently using injectables at enrollment, and 29% had never used them before. The major perceived benefit of injectables was effectiveness, cited by 98%. Although 91% of women had no concerns about using SP, only 68% had no concerns about using DMPA-IM ($p \leq .01$); this difference was largely due to concerns about side effects with DMPA-IM. At baseline, most women (94%) felt very relaxed about the upcoming injection.

Prior to receiving any injection, but after receiving education about the study product, 57% predicted they would ultimately prefer SP, 41% predicted that they would prefer DMPA-IM, and 2% were unsure. This differed by previous contraceptive injectable experience; 60% of "never" or "previous" DMPA-IM users believed they would prefer SP at 6 months ($p=.05$ and $p<.01$ for differing significantly from 50%, respectively), while only 51% of "current" DMPA-IM users did ($p=.90$). Most women predicting a preference for SP noted they were curious to try the new injectable (50%), or believed it would be less painful (38%) or cause fewer side effects (7%). Among women predicting a preference for DMPA-IM, 57% were comfortable using DMPA-IM, 21% believed it would be less painful, and 9% noted community experience with DMPA-IM.

3.2. Injection site preference, pain, soreness and irritation over time

At each visit, at least 90% of women selected the upper arm as their preferred injection site, largely because it was easily accessed or perceived to be less painful.

The majority of women reported little pain during the injection (75%–84%), and differences between groups were significant at baseline and at 6 months, with DMPA-IM reported in aggregate to be slightly less painful (Fig. 3). However, when individual women were asked at 3 months

Table 1
Characteristics of baseline sample

	SP n=179		DMPA-IM n=178		p value for differences between groups	Total N=357	
	n	Col %	n	Col %		N	Col%
Age group					**.73**		
18–24	17	9.5	21	11.8		38	10.6
25–34	96	53.6	90	50.6		186	52.1
35–45	66	36.9	67	37.6		133	37.3
Highest level of school					**.11**		
None	29	16.2	15	8.4		44	12.3
P1–P4	41	22.9	52	29.2		93	26.1
P5–P7	76	42.5	74	41.6		150	42.0
Postprimary	33	18.4	37	20.8		70	19.6
Marital status					**.64**		
Currently married	104	58.1	100	56.2		204	57.1
Previously married	67	37.4	66	37.1		133	37.3
Never married	8	4.5	12	6.7		20	5.6
Currently works for pay	87	48.6	86	48.3	**.96**	173	48.5
Number of previous pregnancies					**1.00**		
0–2	25	14.0	24	13.5		49	13.7
3–5	90	50.3	89	50.0		179	50.1
6+	64	35.8	65	36.5		129	36.1
Wantedness of most recent pregnancy					**.93**		
Wanted pregnancy then	92	51.4	88	49.4		180	50.4
Wanted pregnancy later	32	17.9	32	18.0		64	18.0
Did not want any more pregnancies	55	30.7	57	32.0		112	31.4
No previous pregnancies	0	0.0	1	0.6		1	0.3
Feelings about future pregnancy					**.63**		
Wants another child someday	45	25.4	51	28.7		96	26.9
Does not want another child	132	73.7	126	70.8		258	72.3
Don't know/missing	2	1.1	1	0.6		3	0.8
Time it takes to get to clinic on a typical day (min)	Mean	SD	Mean	SD	**.68**	Mean	SD
	94.7	55.9	97.5	61.4		96.1	59.1
Currently on ART					**.63**		
No	82	45.8	77	43.3		159	44.5
Yes	97	54.2	101	56.7		198	55.5
Ever used injectables					**.93**		
Never	52	29.1	53	29.4		105	29.4
Previously	94	52.5	90	50.6		184	51.5
Currently	33	18.4	35	19.7		68	19.1
Method client thinks she will prefer					**.89**		
Subcutaneous	105	58.7	99	55.6		204	57.1
Intramuscular	70	39.1	75	42.1		145	40.6
Not sure	4	2.2	4	2.2		8	2.2

which was the less painful injection, more women receiving SP noted that the DMPA-IM injection 3 months ago was more painful than the recent SP injection (49% vs. 33%, p≤.01). Most felt only a little pain or soreness *after* the injection (60%–83%), with no significant differences between randomization groups. When asked at 3 months which type of injectable caused less pain or soreness after injection, more women receiving SP noted that the DMPA-IM they received 3 months ago caused more pain (49% vs. 32%, p≤.01) and soreness (22% vs. 11%, p=.04). More skin irritation was reported by women receiving SP as compared to DMPA-IM at 3 and 6 months (Fig. 4), but very few women experienced "a lot" of irritation with either method (0%–5%). Women receiving SP at 3 months noted significantly more skin irritation as compared with receiving DMPA-IM 3 months ago (p≤.01).

3.3. Side effects

About 36% of women spontaneously reported experiencing any side effect when asked about the injection received 3 months earlier (Table 2), with marginally significant differences at 6 months, when 40% of women who received DMPA-IM 3 months ago reported any side effects, compared to 30% of women receiving SP 3 months ago (p=.06). We asked which side effects, if any, were experienced. The most common side effects at 3 months related to menstrual irregularity/spotting (11.8%) or more days

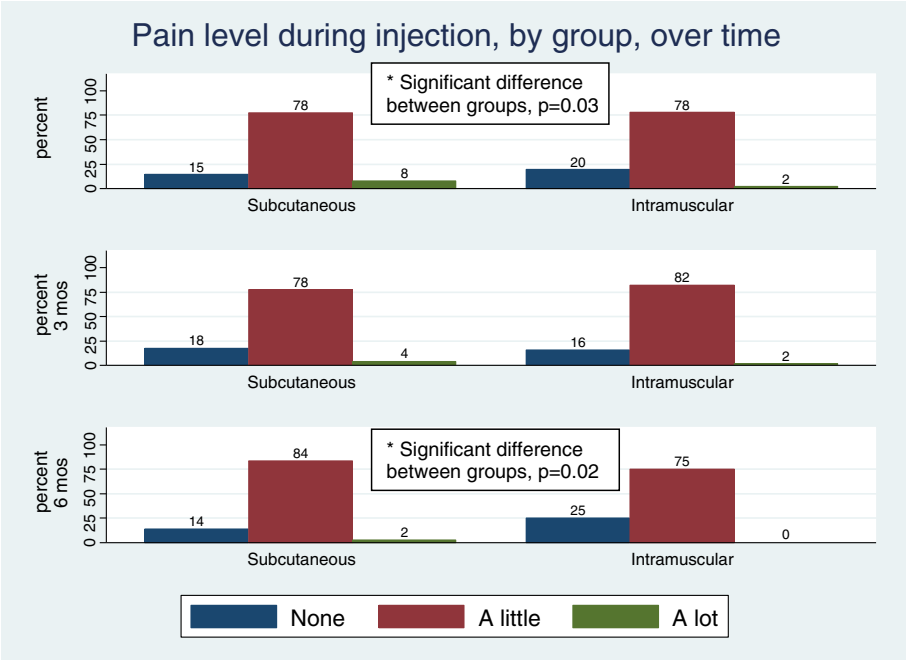

Fig. 3. Pain level during injection, by group, over time.

bleeding (11.2%). Significantly more women who received SP at baseline reported fatigue at 3 months (4.4% vs. 0%, p≤.01). At 6 months, the most common side effects were menstrual irregularity/spotting (7.6%), more days bleeding (7.3%) and amenorrhea (6.7%). Significantly more women who received DMPA-IM at 3 months reported menstrual irregularity/spotting at 6 months (4.4% vs. 10.9%, p=.03), while significantly more women who received SP at 3 months reported skin irritation at 6 months (3.8% vs. 0.0%, p=.03). All other reported side effects occurred in <5% of women. Few women (<5%) reported that side effects interfered with daily activities, and most (93%) reported "no" side effects or "very tolerable" side effects (data not shown).

3.4. Feelings about contraceptive injectables

At baseline, 3 months and 6 months, 100%, 99% and 96% of women, respectively, planned to use injectables again, and

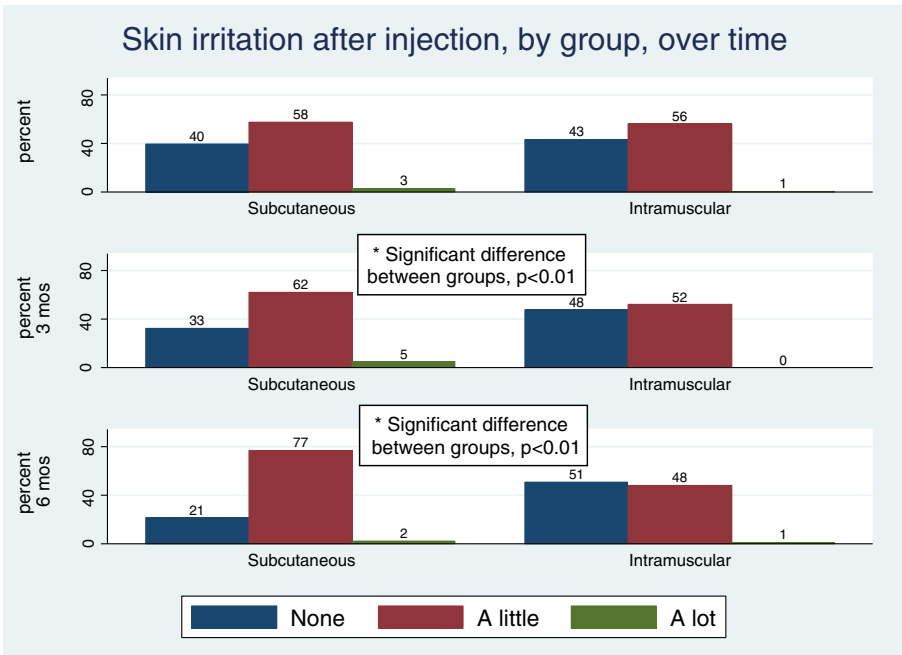

Fig. 4. Skin irritation after injection, by group, over time.

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Table 2
Side effects (any and top 10) as reported at 3- and 6 month-follow-up visits

Total w/ visit	Side effects as reported at 3 months							Side effects as reported at 6 months						
	Injection received at enrollment							Injection pattern from baseline to 3mos						
	SubQ		IM		p value[b]	Total		Baseline IM, 3 months SubQ		Baseline SubQ, 3 months IM		p value[b]	Total	
	161		162			323		158		156			314	
Reported side effect in last 3 months	*n*	Col %	*n*	Col %		*N*	Col %	*n*	Col %	*n*	Col %		*N*	Col %
Experienced any side effect from injection received at enrollment[a]	55	34.2	62	38.3	**.44**	117	36.2	48	30.4	63	40.4	**.06**	111	35.4
Menstrual irregularity/spotting not present before getting the shot	17	10.6	21	13.0	**.50**	38	11.8	7	4.4	17	10.9	**.03**	24	7.6
More days bleeding than before getting the shot	18	11.2	18	11.1	**.98**	36	11.2	8	5.1	15	9.6	**.12**	23	7.3
Larger amount of menstrual blood	8	5.0	7	4.3	**.78**	15	4.6	4	2.5	3	1.9	**1.00**	7	2.2
No menstrual bleeding at all	10	6.2	4	2.5	**.11**	14	4.3	9	5.7	12	7.7	**.48**	21	6.7
Dizziness	5	3.1	9	5.6	**.41**	14	4.3	3	1.9	7	4.5	**.22**	10	3.2
Headaches	6	3.7	6	3.7	**1.00**	12	3.7	6	3.8	4	2.6	**.75**	10	3.2
Fatigue	7	4.4	0	0.0	**<.01**	7	2.2	3	1.9	4	2.6	**.72**	7	2.2
Decreased wetness during sex	3	1.9	3	1.9	**1.00**	6	1.9	5	3.2	3	1.9	**.72**	8	2.6
Decreased interest in sex	2	1.2	1	0.6	**.62**	3	0.9	3	1.9	5	3.2	**.50**	8	2.6
Injection site pain	0	0.0	0	0.0	–	0	0.0	3	1.9	7	4.5	**.22**	10	3.2

[a] Participants could report multiple side effects.
[b] Pearson χ^2, unless any cell has <5 participants, in which case Fisher's Exact Test was used.

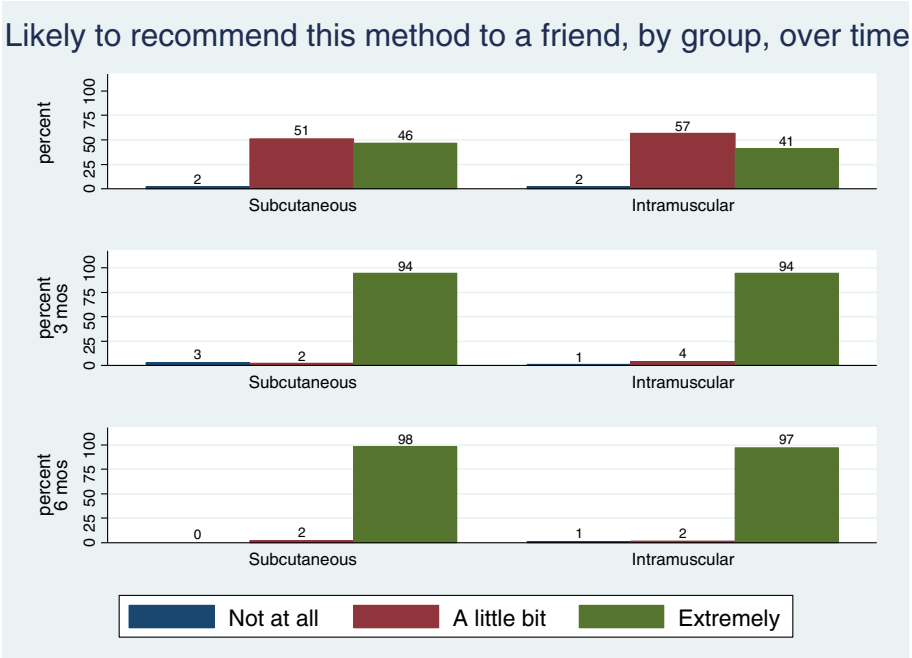

Fig. 5. Likelihood of recommending this injectable method to a friend, by group, over time.

95%, 88% and 97% of women had no concerns about using the method again, with no differences between injection types. Fear of side effects was the most common concern reported. Willingness to recommend the injection to a friend did not differ by group at any time, but being "extremely likely" to recommend it increased from 43% to 94% to 98% (Fig. 5). Satisfaction with the injection received that day did not differ by group, but complete satisfaction increased from 53% to 71% to 91% over time (Fig. 6).

3.5. Type of injection preferred

At 6 months, 64% of women opted to receive SP, while 36% chose to receive DMPA-IM; these proportions differed significantly from 50% ($p \leq .01$). Acceptability was similar regardless of injectable use experience: 63% of "never users," 65% of "previous users" and 63% of "current users at baseline" preferred SP. Nearly all women (98%) had a specific preference. Among 202 women who selected SP,

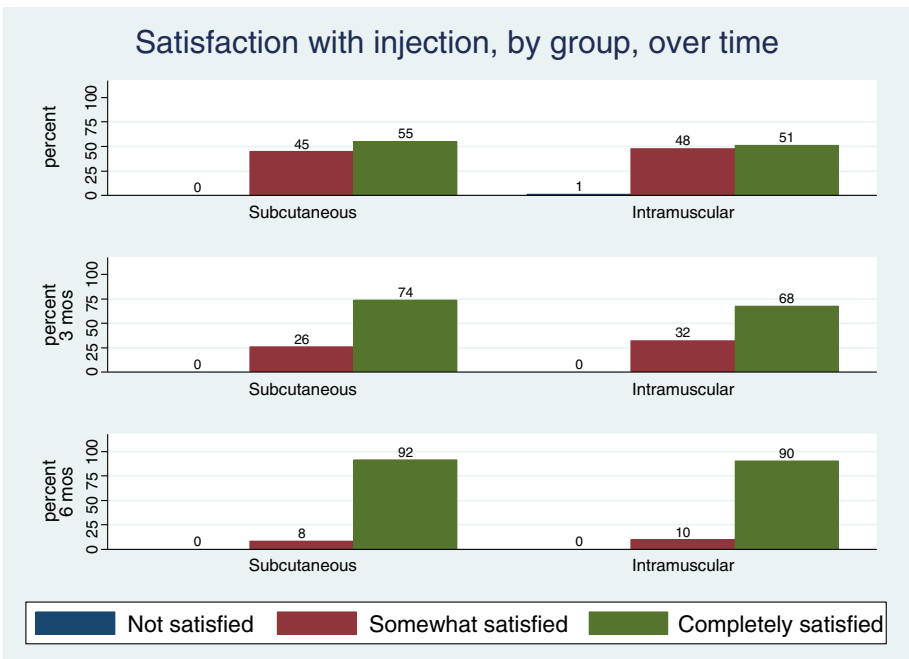

Fig. 6. Satisfaction with injection, by group, over time.

48% noted that it was less painful than DMPA-IM, 48% noted fewer side effects, and 4% gave another reason. Among 112 women who selected DMPA-IM, 56% noted fewer side effects, 21% noted less pain, 15% noted that SP had irritated their skin, and 8% gave another reason.

3.6. Chances of selecting SP based on baseline factors

We constructed a modified multivariate Poisson regression model, stratified by never or ever use of injectable contraception, to assess which baseline factors predicted selection of SP at 6 months (Table 3). Among naïve injectable users, an ordering effect was observed; women who received SP at baseline were 39% more likely to select SP at 6 months as compared to women who received DMPA-IM at baseline. Compared to women who responded at baseline that they would not be willing to (hypothetically) self-inject, naïve users who were slightly or very willing to (hypothetically) self-inject at baseline had 68% and 77%, respectively, higher chances of selecting SP at 6 months. Among women who were previously or currently using injectables at baseline, Muslim women had 37% higher chances of selecting SP than Catholic women. Ever-users who were "very willing" to (hypothetically) self-inject at baseline had 41% increased chance of selecting SP at 6 months.

3.7. Severe adverse events and discontinuations

In total, 43 women discontinued by the 3- (n=34) or 6-month (n=9) visit (Fig. 2). Thirteen women (30%) discontinued (n=10), declined to cross over (n=2) or failed to adhere to the protocol (n=1). Among 10 discontinuers, four discontinued due to side effects, three due to no longer having a sex partner, one for both of these reasons, one because her husband complained about side effects, and one did not provide a response. Twenty-three women (6.4% of those enrolled) either were lost to follow-up (n=19) or returned past the 13-week reinjection window (n=4). There were two deaths, one in each randomization group. One death was due to febrile illness of unknown etiology, possibly due to immune reconstitution inflammatory syndrome following ART initiation; the other was due to severe anemia, possibly due to zidovudine use or malaria. Five women (12%) became medically ineligible due to either switching to a non-first-line ART regimen (n=1) or pregnancy (n=4). All pregnancies occurred between baseline and 3-month visit, with two in each randomization group. We could not rule out the possibility of an early pregnancy at enrollment undetected by the urine hCG test. Women who became pregnant were referred to the government health unit for antenatal care and followed to assess outcomes.

Table 3
Multivariate modified Poisson regression model with robust error variances

	Characteristic	Crude			Adjusted		
		IRR	95% CI	p value	adjIRR	95% CI	p value
Never used injectables before baseline	Randomization pattern						
	Received DMPA-IM at baseline and SP at 3 months	Ref	–	–	Ref	–	–
	Received SP at baseline and DMPA-IM at 3 months	1.40*	1.00–1.97	.05	1.39*	1.02–1.90	.04
	Religion						
	Catholic	Ref	–	–	Ref	–	–
	Protestant	0.94	0.64–1.36	.74	1.08	0.76–1.56	.66
	Saved/Pentecostal	0.45	0.17–1.19	.11	0.56	0.23–1.38	.21
	Muslim	1.31	0.94–1.84	.11	1.12	0.82–1.54	.48
	Interest in hypothetical self-injection at baseline						
	Not willing to self-inject at baseline	Ref	–	–	Ref	–	–
	Slightly willing to self-inject at baseline	1.70*	1.15–2.52	<.01	1.68*	1.12–2.51	.01
	Very willing to self-inject at baseline	1.85*	1.32–2.60	<.01	1.77*	1.26–2.48	<.01
Previous or current injectable use	Randomization pattern						
	Received DMPA-IM at baseline and SP at 3 months	Ref	–	–	Ref	–	–
	Received SP at baseline and DMPA-IM at 3 months	1.12	0.92–1.36	.25	1.12	0.93–1.35	.25
	Religion						
	Catholic	Ref	–	–	Ref	–	–
	Protestant	1.01	0.79–1.29	.97	1.02	0.81–1.30	. 85
	Saved/Pentecostal	1.06	0.70–1.61	.79	1.09	0.71–1.66	.69
	Muslim	1.38*	1.09–1.74	<.01	1.37*	1.10–1.71	<.01
	Interest in hypothetical self-injection at baseline						
	Not willing to self-inject at baseline	Ref	–	–	Ref	–	–
	Slightly willing to self-inject at baseline	1.21	0.93–1.57	.16	1.21	0.93-1.57	.16
	Very willing to self-inject at baseline	1.41*	1.16–1.72	<.01	1.41*	1.16–1.71	<.01

3.8. Provider preferences

We asked the 22 study providers which method they preferred to administer. Seventy-three percent (n=16) chose SP, with the most common reasons being that providers felt it was less painful for their clients or easier to provide. Details on provider preferences will be the subject of a separate analysis.

4. Discussion

A substantial proportion of women (64%) and health care providers (73%) reported preferring SP over DMPA-IM after experiencing both methods in this randomized cross-over trial.

This study has several strengths. Our randomized cross-over design allowed women to directly compare the two types of injectables over time. We included injection-naïve participants since information on SP acceptability among injection-naïve women is important, particularly if SP introduction strategies intend to recruit new injectable users. We found that "never" or "previous" contraceptive injectable users were more likely than "current" users to predict at baseline that they would prefer SP at 6 months, but that stated preference for SP at 6 months did not differ by prior injectable experience.

A limitation is that we assessed HIV-positive women attending clinical HIV care, so our results may not be applicable to HIV-negative women, women in whom HIV status is unknown, or women without regular clinical contact. However, 99% of participants stated that they did not feel that their HIV status affected their preference for type of injection.

Half of previous pregnancies were reported as unintended, and many women (73%) reported wanting no more pregnancies. Analyses related to the feasibility of community-based distribution and/or self-injection of injectables are of interest, and possibilities for expanding use of longer-acting and permanent methods, such as implants, IUDs and sterilization, should be examined.

While not an efficacy study, our data suggest equivalent contraceptive efficacy of DMPA-IM and SP, consistent with previous studies [3–5]. One percent of women became pregnant, but we could not rule out the possibility of undetected early pregnancy at enrollment. No pregnancies occurred between months 3 and 6.

SP is currently labeled for injection in the upper thigh and abdomen. In 2011, FHI 360 evaluated the pharmacokinetic profile of MPA during 120 days following injection of DepoSubQ Provera 104 in the upper arm. Experts concluded that this injection site provided adequate contraceptive protection for 3 months (13 weeks) plus a 2-week window for reinjection [22]. In our study, over 90% of women chose to receive their injection in the arm, highlighting the need to ensure labeling for use at this site.

In our study, participants at baseline appeared to believe that SP would result in fewer side effects. Most specific reported side effects did not differ by injection type, but fatigue may have been higher for SP, though we are unaware of a plausible mechanism to explain this finding. On the other hand, menstrual irregularly/spotting or "any reported side effect" may have been lower for SP. Consistent with other studies, we found more skin irritation with SP, but it was lower than reported elsewhere [4]. Overall, reported pain, soreness and skin irritation was minor, but data regarding which method caused more pain during injection was inconsistent. Satisfaction and likelihood of recommending an injectable method to a friend increased over time in both groups, suggesting that women became increasingly more comfortable with both types of injections.

Few baseline factors were associated with selection of SP at 6 months. While we observed an ordering effect among new injectable users, women preferred SP regardless of being randomized to SP (70%, $p \leq .01$) or DMPA-IM (59%, $p=.03$). Muslim women displayed a strong preference for SP (87%, $p \leq .01$). Women open to the idea of self-injection preferred SP more strongly; these individuals may be more open to innovation in general or may view SP as a necessary component for the possibility of self-injection.

DMPA, delivered either intramuscularly or subcutaneously, is not expected to interact with ART [23]. Some studies suggest a potential for lower contraceptive efficacy with combined oral contraceptive pills, and possibly contraceptive implants, when coadministered with certain ART regimens [23]. Thus, while it is critical to balance concerns around a potential increased risk of female-to-male HIV transmission with use of injectables by HIV-positive women not on ART [11], easier access to injectable contraception may be a particularly important contraceptive option for HIV-positive women on ART.

In summary, SP appears to be acceptable to HIV-positive women and their care providers in Rakai, Uganda, and strategies for appropriate rollout of this innovative technology should be explored.

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