Perspectives on etonogestrel implant use in HIV-positive women in Cape Town, South Africa: a qualitative study among primary providers and stakeholders

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Abstract

Access to a range of safe and effective modern contraceptive methods enables women to make free and informed choices about their reproductive lives and broadly improves maternal and child health outcomes. Successful avoidance of unintended pregnancy and the corresponding ability to plan for pregnancy are especially valuable in the context of Human Immunodeficiency Virus (HIV) infection. Revised South African national guidelines seeking to expand overall contraceptive access were released in 2012 and, in response to the severity of the domestic HIV epidemic, specifically detailed the sexual and reproductive health rights and needs of HIV-positive women. Six years later, evaluation of the implementation and impact of these guidelines, as well as of more recent policy responses in this area, is necessary. This need for evaluation is outlined in Part A of this mini-dissertation in the form of a research proposal. A literature review (Part B) assesses what is currently known about considerations surrounding contraceptive decision-making in the context of HIV and antiretroviral therapy (ART). The use of the subdermal Long Acting Reversible Contraceptive (LARC) implant in HIV-positive women is explored in depth, given that the 2012 guidelines introduced the method as an entirely new option for South African women, as well as in light of recent controversy surrounding the implant's provision to women taking the first-line ART drug, efavirenz (EFV). A journal-style article structured for submission to *BMC Public Health* (Part C) then uses thematic qualitative methodology to explore primary family planning provider and other relevant stakeholder perspectives on the provision of implants to HIV-positive women clients attending Cape Town primary care facilities. The study adds to existing literature regarding implant provision in the context of HIV and ART, and offers new insight into the impact of a 2014 South African Department of Health decision to recommend against the then-newly introduced implant as an option for women taking EFV-based ART. This research finds that several converging factors may have lead primary providers to view the implant as broadly contraindicated in all HIV-positive clients regardless of their

exposure to EFV, namely: insufficient provider training; provider and community unfamiliarity with and scepticism about the new method; structural pressures on providers to keep up to date with and provide wide-ranging integrated services in busy clinical environments; and inadequate stakeholder consultation surrounding the wording and overall appropriateness of the implant/EFV guidance itself. Recommendations are provided in the article, including the need for: the retraining of primary healthcare providers in rights and choice-based family planning (particularly in implant provision and counselling); simplified counselling messages and user-friendly decision-making tools to help providers facilitate informed contraceptive choice for HIV-positive women; generalized beneficiary and community sensitization/education about implants including in the context of HIV and ART; and more comprehensive stakeholder/beneficiary consultation in future contraceptive policy-related endeavors.

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Plagiarism declaration

I, Anna Brown, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Contents

Abbreviations

ART	Antiretroviral therapy
(Cu-)IUD	(Copper) Intrauterine Device
DDI	Drug-drug interaction
DMPA	Depot Medroxyprogesterone Acetate
DTG	Dolutogravir
EFV	Efavirenz
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
MEC	Medical Eligibility Criteria
OB/GYN	Obstetrician/Gynaecologist
OC	Oral Contraceptive
UCT	University of Cape Town
WHO	World Health Organization

Part A: Protocol

Perspectives on etonogestrel implant use in HIV-positive women in Cape Town, South Africa: a qualitative study among primary providers and stakeholders

Summary

The following proposal is for a qualitative sub-study of a wider existing mixed-methods project, '*A formative study on the 2012 South African National Contraception Guidelines' implementation of new Long-Acting Reversible Contraceptive (LARC) methods in the Cape Town Metropolitan Area'* [1]. This sub-study, which will comprise a mini-dissertation in partial fulfilment of a Master of Public Health degree at the University of Cape Town, will be an in-depth investigation into primary provider and other stakeholder perspectives surrounding the provision of subdermal contraceptive implants to HIV-positive women using freely available public sector family planning services. The three-year single-rod etonogestrel implant, *Implanon NXT®,* was at the center of an extensive government provider training programme and promotional campaign beginning in February 2014, following the promotion of LARCs in general across the public sector as per the updated 2012 National Contraception Guidelines [2, 3]. During 2014, however, implants became directly associated with an already demonstrated drug-drug interaction (DDI) between certain enzyme-inducing agents and synthetic progestins, with the potential to reduce contraceptive efficacy [4, 5]. South Africa's first-line anti-retroviral drug, efavirenz (EFV) was implicated in the DDI, along with several other drugs used to treat tuberculosis (TB) and epilepsy. In response to the new findings, the National Department of Health issued guidance in October 2014 strongly advising against the use of

implants in HIV-positive women on EFV, including the recommendation of removal for women with implants already in situ. This removal recommendation was amended in a December 2014 technical brief to suggest women who already had implants may choose to keep them under the condition they receive 'proper counselling' [6, 7]. The appropriateness of this guidance has since been questioned, with more recent data showing even higher comparative 'typical use' failure rates of condoms, oral contraceptives (OC) and injectables [8], as well as in consideration of recognized barriers of access to intrauterine devices (IUDs) in many South African primary care settings [9]. Concerns have thus been raised as to the possibility that alternative contraceptive methods may not actually be preferable or accessible for some HIV-positive women, even when they are on EFV and the reduced efficacy of the implant is taken into account [8]. There is hence a need to understand current clinical practice with respect to HIV-positive women and contraceptive decision-making, and to develop supportive, clear counselling messages and tools, so that providers are able to convey the complexities of what is currently known about the issue to clients choosing between family planning methods. With a view to create an evidence base for such materials, semi-structured in-depth interviews will direct qualitative enquiry into primary providers' and other stakeholders' understandings of the issue of implant use among HIV-positive women at present, as well as examine current provider practice surrounding HIV and contraceptive provision and counselling in general. This enquiry will further contribute to the wider discussion about the recent scale-up of LARC provision in South Africa as the country moves towards the expansion of its contraceptive method mix.

Background:

Demographic and cross-sectional data suggest an unmet need for effective contraception in South Africa. The national contraceptive prevalence rate (CPR) among married and unmarried sexually active women was 58% in 2016 [10] yet estimates suggest that between 62% and 64% of pregnancies are still considered unwanted or mistimed [11, 12]. These figures are troubling, as enabling women and couples to

successfully avoid unintended pregnancy is a critical function of family planning and benefits public health by preventing abortions and myriad adverse health and socioeconomic outcomes associated with unplanned birth [13]. Relevant to the South African setting are a number of contextual factors that affect issues surrounding fertility and reproductive decision-making, including the need for services to cater to a significant portion of the population who are infected with HIV [14]. UNAIDs estimated that 23.8% of South African reproductive-aged (15-49) women were infected with HIV in 2016 [15].

High levels of unintended pregnancy in the context of high contraceptive prevalence may indicate that the methods South African women are choosing are often failing or are being incorrectly or inconsistently used [1]. The most recent government demographic survey in 2016 reported that, of the 58% of contraceptive users accessing freely available public sector services, two and three-month progestin-only injectables were the most widely used, followed by male condoms and the daily oral contraceptive (OC) pill [10]. Notably, these are all considered short-acting methods, associated with poor user adherence and high discontinuation rates [7]. In a move to reduce unintended pregnancy associated with short-acting methods, as well as to expand the contraceptive method mix available for women to choose from, the National Department of Health promoted the use of LARCs in public sector clinical facilities in its 2012 revision of the national contraception guidelines [2, 3]. The goal of providing greater choice for South African women is also well-supported by evidence that access to a range of contraceptive options is a key determinant of user acceptability and overall contraceptive coverage [16].

LARCs, including sub-dermal hormonal implants and intrauterine devices (IUDs), are becoming increasingly popular around the world [17]. They provide women with convenient, reliable and long-lasting protection from unintended pregnancy [17]. Depending on the method chosen, they last for three to ten years and, importantly, a lack of adherence concerns after insertion eliminates the discrepancy between ‘perfect use’ and ‘typical use’ [18]. Pregnancy avoidance on LARCs is thus not user-dependent in

the same way that shorter acting methods are. Trussell [18] reports failure rates of LARCs ranging between 0.2-0.8% unintended pregnancies within the first year of use for IUDs, and 0.5% for (etonogestrel) implants. When usage patterns are considered, these rates compare favorably to short-term methods including the OC (0.3% with perfect use; 9.0% with typical use) and the three-month injectable depot medroxyprogesterone acetate (DMPA) (0.2% with perfect use; 6.0% with typical use). LARCs also typically have the highest continuation rates of all reversible contraceptive methods, estimated to be between 78-80% at one year of use for IUDs and 84% for implants, compared with 67% for the OC and 56% for DMPA [17].

From a rights perspective, too, the relative discretion of having a LARC inserted means that women are able to retain high personal control over their family planning method, thus preserving reproductive autonomy [19]. As well as the benefits of convenience, reliability and discretion, LARCs also carry the potential to reduce unplanned pregnancies in HIV-positive women in South Africa, thereby reducing HIV-related maternal and child morbidity and mortality, including preventing vertical HIV transmission [20, 21]. For all of these reasons, the availability of LARCs in South African public sector facilities helps fulfil the wider public health objectives of catering to the sexual and reproductive health needs of South African women, including those who are infected with HIV, and ultimately ensuring that the majority of pregnancies occur only if and when women feel ready to have children [22].

As well as promoting already available copper IUDs (Cu-IUD) in public sector family planning services, the revised 2012 guidelines also introduced the subdermal contraceptive implant for the first time in South Africa [2, 3, 23]. Two brands of implants, the single-rod three-year etonogestrel *Implanon NXT®* and the double-rod five-year levornogestrel *Jadelle* were registered for use, but the initial provider training programme focused only on *Implanon NXT®* [23]. A match-stick sized implant that is easily inserted with an applicator just beneath the skin of the inner side of a woman's upper non-dominant arm, *Implanon*

NXT® has been demonstrated to be cost effective in low-resource areas, and its three-year life span is considered convenient for child spacing [24]. *Implanon NXT®* was rolled out country-wide in early 2014 [25].

An important caveat to the desirability of contraceptive implants in the South African setting, however, is a demonstrated cytochrome P450 3A-mediated DDI between synthetic progestins and certain enzyme-inducing agents, including the antiretroviral drug efavirenz (EFV) [26]. Pharmacokinetic (PK) evidence for the interaction comes from 2014 Brazilian [4] and Ugandan [27] data, which both showed progestin levels were reduced by more that 50% in women on EFV-based ART using etonogestrel and levonorgestrel implants respectively. With over a fifth of women of reproductive age in South Africa HIV-positive [28] and given that EFV-based ART regimens remain the first-line treatment for HIV recommend by the World Health Organization [29], the implications of this interaction for clinical care and contraceptive policy are significant.

While the actual clinical effect of the reduced bioavailability on pregnancy risk is still not fully known, there is considerable clinical data to suggest that EFV does impair the efficacy of the implant in some women. Clinical studies of contraceptive failure associated with concurrent implant and EFV use include a retrospective chart review in 2012 of 332 women using levonorgestrel implants on various combinations of ART in Swaziland [5], that reported 15 (12.4%) pregnancy events occurring in 121 women taking EFV, compared to none in the non-EFV based ART groups. A 2015 study combined three sets of longitudinal data to determine that implant users on EFV-based ART had a 6.0 incidence rate of pregnancy per 100 women-years, versus a rate of 1.4 in implant users not on EFV-based ART [30]. Confirming the findings of these smaller studies, rates of pregnancy among 25,000 HIV-positive women on multiple combinations of ART regimens and contraceptive methods were examined in a three-year retrospective cohort study in Kenya published in 2015 [8]. The adjusted pregnancy rate among implant users on EFV-based ART was 3.3

per 100 women-years, compared with 1.1 among implant users on nevirapine-based ART, and 1.3 in women not on ART. Although these figures demonstrate a three-fold higher likelihood of contraceptive failure in implant users on EFV-based ART compared with nevirapine-based ART, it is of considerable importance to note that the same study also showed that, of women on EFV-based ART who used various contraceptive methods, those who reported using the OC or DMPA were up to three times as likely to unintentionally fall pregnant as those who reported implant use.

Prospective cohort data is still needed to compensate for design limitations of the aforementioned studies and to determine exact failure rates, but what the current literature does suggest is the existence of the interaction between EFV and implants, and its potential to lead to contraceptive failure. Whether the potential for contraceptive failure in some cases justifies removing implants entirely as an option for women on EFV, however, especially in light of the Kenyan study, is unclear. In October 2014, the National Department of Health responded to the earlier data detailed above (i.e., the PK data from Brazil and the retrospective chart review data from Swaziland), with a national practice change circular advising that women taking enzyme-inducing agents, specifically EFV-based ART, should not be offered the implant [6]. Removal was recommended for those who already had the implant in situ. A somewhat less restrictive technical brief followed two months later in December 2014, which included the suggestion that women who wished to continue with an implant could do so with '*proper counselling*' [7]. There was no accompanying guidance regarding clear counselling messages for providers - undoubtedly since, at least at the time, the available evidence was limited.

While informing clients about the apparent reduced efficacy of the implant was crucial so that they could make informed personal decisions, the directives failed to consider that the implant, following the heavy promotional drive earlier that year and subsequent national roll-out, was and still is the primary LARC option available to women in South Africa; the only alternative being the IUD, which is more complicated

to insert and is not always accessible for many women [23]. Moreover, the importance of clients' contraceptive decision-making was not considered, especially in the case of women who had, prior to the new recommendations, already chosen the implant over other methods available to them. Compounded with what we now know from the Kenyan study [8], which was that some alternative methods may actually have higher typical-use failure rates than the implant for women on EFV, it is plausible that, in discontinuing the implant, some women may be switching to a method that may ultimately be less effective for them.

With this growing and increasingly multifactorial body of evidence to consider, there is a need to understand current provider practice with respect to the provision of contraception to HIV-positive women as it currently stands in the wake of both the 2012 guidelines and the 2014 implant/EFV directives. By considering the perspectives of primary family planning providers, as well as of specialist providers and other stakeholders from government and academia, this study aims to provide preliminary insight into how the complexities of contraceptive care for HIV-positive women are presently understood by providers at the primary care-level. The data will ultimately be used to develop clearer, evidence-based guidance and counselling tools for providers, so that they will be better able to advise HIV-positive women who are choosing between contraceptive methods. More broadly, this study will produce further insight for its mixed-methods parent project [1], which aims to assess the uptake and usage patterns of LARCs in general, as their promotion in the public sector since the 2012 guidelines were released continues to make them more heavily utilized in the drive to reduce unintended pregnancy in South Africa.

Research Question and Objectives

The research question that this study seeks to answer is:

"What do primary healthcare providers and other stakeholders working in HIV and contraceptive care in Cape Town, South Africa know and understand regarding implant provision in the context of HIV and ART?"

In pursuing the answer to this question, investigators will:

I. Examine how primary providers and other stakeholders perceive and understand LARC provision in general, especially the implant, in the context of HIV and ART.

II. Determine primary providers' and stakeholders' levels of awareness of the National Department of Health's recommendations against offering the implant to women on EFV-based ART.

III. If they are aware of the above recommendations, explore:

a.) Primary providers' interpretation of this advice and its consequences for their own clinical practice.

b.) Stakeholders' understanding of the issue, how they believe it has been communicated to facilities and primary providers, and their perceptions regarding its consequences for clinical practice.

Findings will be analyzed with a view to develop appropriate, evidence-based counselling messages for providers regarding the use of the implant in the context of HIV/ART, as well as tools to support providers and clients in simplifying the decision-making process for HIV-positive women choosing between family planning methods.

Methods

Study Design

The proposed study will be qualitative in design. Data will include semi-structured in-depth interviews (based on interview guides) with providers and other stakeholders familiar with, or working at, Cape Town public sector primary healthcare clinics. The goal of conducting these interviews is to record a range of current perspectives about the provision of contraceptive implants in the context of HIV and ART from multiple vantage points. It is expected that, using this qualitative approach, investigators will succeed in identifying subtle influencing factors, such as cultural nuance and descriptive interpretations of issues, that it would not otherwise be possible to capture using quantitative data collection methods. Anticipated themes that may emerge from the data include: Patterns in the manner in which contraceptive options, including LARCs, are presented to HIV positive women; patterns in participant understandings of the interaction between the implant and EFV; and common misconceptions surrounding LARCs and particularly the implant in the context of HIV and ART.

Study sites

Primary healthcare provider interviews will take place at City of Cape Town or Western Cape Provincial public sector clinical facilities (to be determined by the Women's Health Unit, UCT). These will be HIV, family planning, or maternity services. Other stakeholder interviews will be conducted at a private space of the participant's choosing.

Study Population and Sampling

Participants will be purposively selected to include multiple perspectives, including primary providers from public sector family planning, HIV, maternity, and integrated services, as well as specialist providers

and stakeholders from government and academia. Participants will be recruited on the basis of their eligibility as per inclusion criteria on Table 1 below:

Group	**N =**	**Interview Location**	**Interview methodology**	**Inclusion Criteria**
Primary Providers	10-15	Private room at Western Cape or City of Cape Town public sector clinics (T.B.D.)	In-depth interview (IDI)	Must work in family planning, HIV, maternity or integrated services with a patient population that includes HIV-positive reproductive-aged women. May include Public Sector or NGO-based service providers.
Stakeholders	8-10	Private space of participants choosing	IDI	Must be a specialist provider or work in academia, civil society or government, in the areas of family planning and/or HIV services.

Table. 1 Study Populations Inclusion Criteria

Recruitment Procedures

Applying the abovementioned purposive sampling method, permission will be obtained to approach public sector family planning, HIV, maternity, or integrated service clinics. Investigators will recruit healthcare providers working at these clinics who render services to HIV-positive, reproductive-aged women. They will be informed about the study, their eligibility will be reassessed as per inclusion criteria, and, if they are interested in participating, an interview will be arranged.

Investigators will approach relevant stakeholders as per inclusion criteria (i.e. those working in the area of family planning and/or HIV services) via telephone or email. They will be informed about the study and invited to participate. Interviews will be subsequently arranged.

Data Collection procedures

Interviews with stakeholders will be conducted in English by the student investigator using in-depth, semi-structured interviewing techniques. Upon reading and signing consent forms, these interviews will last approximately 30 minutes to one hour. Participants will be provided with the investigators' contact details should any follow-up questions or concerns arise and will be notified upon completion/publication of results.

All interviews will be digitally recorded, and detailed field notes will be kept. Specificities as to how data from each of the study groups will be collected are as follows:

1.) Primary providers: In-depth provider interviews will take place at the provider's place of work and will follow the format of an interview guide that will be developed. Written informed consent will be obtained prior to the interview and some basic relevant demographic details will be recorded (e.g. sex, place of work, education/training).
2.) Other stakeholders: After reading and completing informed written consent stakeholders will be interviewed in-depth with aid of an interview guide that will be developed. The setting will be a private room at a location of the participant's choosing, and basic relevant demographic characteristics will likewise be recorded.

Data Analysis and Management

Interview data will be transcribed for analysis verbatim. Qualitative data comprising field notes and interview transcripts (in Microsoft Word format) will be gathered and processed into a study database using a software programme such as NVIVO or Atlas Ti. No identifiable participant data will accompany

field notes or transcripts, though interviewee demographic data elements will be recorded. The data will be coded for themes, and the research team will then conduct a thematic analysis.

Ethical and legal considerations

Ethical approval for the parent project associated with this study has been granted from the Human Research Ethics committee, Faculty of Health Sciences at the University of Cape Town (HREC REF 718/2015) and the Research Ethics Committee at the University of the Western Cape (Registration no: 15/4/27). Accordingly, this sub-study has been designed to fulfil the following specific objectives of the wider study:

> *2.V: "To explore among public sector contraceptive and HIV care service providers in the Cape Metropole area" … "Whether they are aware of the International and National Department of Health recommendation not to provide implants to women living within the context of HIV and HIV medications and if so their understanding of it and the impact this may have had on discontinued provision/ removal and use."*

Investigators on the parent project will provide full oversight in the form of dissertation supervision (Dr. Chelsea Morroni) and co-supervision (Professor Jane Harries). Permission to conduct interviews with providers will be obtained from the management of the relevant health facilities.

Reasonably Foreseeable Risks or Discomforts to Human Subjects

No substantial risks to participants are anticipated. If for any reason the interviews cause any discomfort or distress to participants, participants will have the option to terminate the interview. To avoid unintended privacy violations, all data collected will be kept confidential and only accessed by the

researchers for the purposes of this study. Storage of all data, transcripts and files related to the study will be stored securely (password-protected) on a hard-drive, and access to it restricted to those working on the research project. Monitoring and oversight will be provided by the Women's Health Research Unit at the University of Cape Town. Once data collection is complete, the investigator will keep no record of personal identifying information in the retrieved data set. Individual transcripts will be alpha-numerically coded and anonymized, and no identifiable information from any individual beyond demographic characteristics will be used in the dissemination or possible publication of this study. Data will be destroyed once the analysis has been sufficiently conducted and approved by principal investigators in the larger project. Any physical paper copies of transcribed data will likewise be shredded.

Informed consent

Informed consent will be sought before commencement of interviews. The purpose of the study will be clearly outlined, confidential treatment of all records and data will be ensured, and it will be stressed that the participant's decision to participate or not to participate will carry no consequences for them professionally. It will be made clear that participation is voluntary, and the participant has the right to refuse to answer questions and discontinue the interview at any time. Coercion will be avoided by ensuring that all administrators of consent are properly trained in relaying the above information. Along with verbal explanation, consent forms will be provided for the participants to read and sign. Copies of the consent forms for participants to take home will contain the South African contact information of investigators, should any concerns, clarifications or complaints arise subsequent to participation in interviews.

Possible Benefits to Participants and to Society

Primary providers will potentially gain personal benefit from the study in the form of enhanced clarification about the use of implants in the context of ART. Wider societal benefits anticipated will be a

greater understanding of how the current policy has been conveyed to providers and implemented, which will go on to create an evidence base for developing clear guidance and counselling tools aimed at resolving present confusion surrounding this issue.

Dissemination of Findings

The results of this study will be compiled in mini-dissertation format and submitted to the Faculty of Health Sciences at the University of Cape Town in partial fulfilment of Master of Public Health degree. We hope to further use the results to develop and publish clear counselling messages and tools that providers can use to relay accurate information about implant use in the context of HIV and ART to their clients.

Timeline

This research will be conducted in the first half of 2017, as predicted in the table below. This schedule is flexible and can be extended to February 2018 if necessary in case of fieldwork delays or other unforeseen interruptions.

Activity	**Late 2016**	**Jan 2017**	**Feb 2017**	**Mar 2017**	**Apr 2017**	**May 2017**	**Jun 2017**	**July 2017**	**Aug 2017**
Ethics permission granted									
Literature review conducted									
Finalization of study instruments									
Fieldwork conducted									
Data analysis conducted									
Writing of report									
Thesis submitted									

Financial resources

Labor costs for this study are not applicable due to this research being conducted by a master's student. Any additional costs associated with financing the study will be derived from the parent project's funding, which includes a National Research Fund (NRF) rated researcher's incentive grant, as well as a Centre For AIDS Research pilot and feasibility project grant awarded to Dr Chelsea Morroni.

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PART B: Literature Review

Contraceptive counselling and decision-making in the context of HIV and ART: available evidence and South African policy and practice implications

Introduction

All women, regardless of HIV status, similarly benefit from gaining control over their fertility. This includes the ability to prevent or delay pregnancy according to individual needs and preferences and to enjoy coitus without pregnancy-related anxiety [1, 2]. Rising global modern contraceptive coverage has also helped reduce maternal and infant mortality rates, as well as broadly improve social, educational and economic outcomes for women and their families [3]. With family planning also playing a critical role in the prevention of vertical HIV transmission, as well as of other HIV-related maternal and child morbidities, further benefits exist in ensuring that HIV-positive women have access to effective and acceptable contraception [1, 4-6]. Such access is especially important in sub-Saharan Africa, where some 24 million HIV-positive individuals (or 71% of all people living with HIV) reside, and where women in general disproportionately carry 58% of HIV infections [7, 8]. In South Africa, UNAIDS estimated in 2016 that, compared with a prevalence of 14.2% in reproductive-aged men (15-49), 23.8% of reproductive-aged women were HIV-positive [9]. With the number of HIV-positive persons in the country now exceeding seven million, 2017 mid-year population estimates imply that this figure represents at least three million reproductive-aged women [10]. Although men and boys face their own distinctive and important barriers

to testing and treatment services [11], the nature and scale of the structural, socio-cultural, and physiological challenges faced by HIV-positive women of reproductive age in South Africa demands a responsive, evidence-based policy-making environment that realizes their nationally and internationally recognized family planning rights and needs [12]. The purpose of this literature review is to assess for the South African setting what is currently understood about contraceptive counselling and decision-making in the context of HIV and ART. South Africa's current contraceptive and HIV policy-making environment is considered with respect to a range of available global, regional and local data and perspectives, including: HIV's epidemiological features in reproductive-aged women populations; issues surrounding unmet need for effective contraception generally and in the context of HIV; the various barriers HIV-positive women face in accessing contraception and in realizing their legally recognized family planning rights and needs; as well as additional concerns and practice implications specific to HIV-positive women, including recent controversies surrounding drug-drug interactions (DDIs) between certain hormonal and antiretroviral agents.

Methods

A scoping review method was applied to broadly map for the South African context what is currently understood about meeting the contraceptive needs of HIV-positive women. Recent policy responses in this area were first contextualized by extracting regional and local demographic data that describe the magnitude and significance of how the HIV epidemic and levels of unmet need for contraception affects reproductive-aged women populations. Publications by the World Health Organization (WHO), associated United Nations agencies, and South Africa's national statistical service, Statistics South Africa, were preferred sources for demography information. Other background literature concerning the history of contraceptive service provision in South Africa was also utilized to situate the most recent national contraception guidelines, released in 2012. Subsequent government directives specifically concerning

contraceptive provision to HIV-positive women were reviewed, including a 2014 South African National Department of Health decision to recommend against sub-dermal hormonal implant provision to women taking the first-line anti-retroviral drug, efavirenz (EFV) [13-18]. Commentary published in the Journal of the International AIDS Society in 2017, which presents perspectives on the literature and present controversies surrounding this particular topic, was closely considered [16], as was a 2017 systematic review of 46 studies broadly regarding DDIs between antiretroviral and hormonal contraceptive agents [19]. The WHO's continuously updated advice regarding Medical Eligibility Criteria (MEC) for contraceptive use [20], as well as rights-based approaches to family planning in the context of HIV and ART, were also drawn upon to synthesize an appraisal of evidence-based, best-practice contraceptive counselling and decision-making for HIV-positive women clients attending South African public sector family planning services.

Key Search Topics:

Search terms and variations thereof entered into Pub Med, JSTOR, and Google Scholar via UCT Library's online electronic journal subscription service included: *'HIV in women of reproductive age'; 'unmet need for effective contraception in South Africa'; 'HIV related barriers of access to sexual and reproductive health services in South Africa'; 'contraceptive decision-making and rights-based family planning in the context of HIV and ART'; 'drug-drug interactions between synthetic hormones and enzyme-inducing agents'; 'efavirenz and contraceptive implants'*

Results/Findings

HIV in women of reproductive age: South Africa's global, regional, and national context:

Despite no as yet available cure or effective vaccine, there is reason for optimism as the global HIV pandemic matures into its third decade. With record rates of sero-status knowledge, initiation of ART and

achievement of viral suppression, as well as incidence of new infections declining in most regions, world-wide estimates indicate that substantial progress is being made towards the goals of improving the lives of those already infected with HIV and eventually containing the spread of the virus [7]. Improvements overall should not divert attention from key populations where significant gaps remain, however. In sub-Saharan Africa, women disproportionately bear 58% of the HIV burden [7], and those aged 15-24 are up to eight times as likely in some areas to be infected as males the same age [21]. Women in general and adolescent girls and young women in particular have thus been identified as a group not only at heightened vulnerability to infection, but whose needs must be prioritized if the trajectory of the regional HIV epidemic is to be stabilized and eventually reversed [7, 21]. Local estimates in South Africa indicate that reproductive aged women (15-49) are 1.6 times as likely to be HIV-positive as their male counterparts, while this risk increases to 3.9 times as likely for adolescent girls and young women in the 15-24 age bracket [8-10, 22]. Factors exacerbating the link between gender and increased HIV risk regionally and in South Africa are thought to include age-disparate heterosexual relationships; exposure to gender-based violence; inability to negotiate safe sex; heightened physiological susceptibility; educational disadvantage; financial hardship; inadequate political representation; and inaccessibility of appropriate and non-judgmental sexual and reproductive healthcare services [7, 12].

Past and Current Estimates of Contraceptive Prevalence Rate and Unmet Need for Effective Contraception in South Africa

As well as benefiting individuals, couples, and their families, public programmes that encourage modern contraceptive use have helped catalyze profound global societal change in terms of economic development, improved maternal and child health outcomes, gender equity, and demographic transition [23]. As the world's societies move towards industrialization and urbanization, and away from agrarian and subsistence lifestyles, the desire for large families has tended to diminish [24]. Likewise, investment

in children's education has increased the cost of raising them, and improved rates of child survival to adulthood have allayed parental and cultural fears of producing fewer offspring in many contexts [23]. Longitudinal demographic data show that the pace of fertility decline has been slower in sub-Saharan Africa compared with Latin America and Asia, however, though patterns across the region are nonetheless heterogeneous - reflecting distinct and complex social, cultural, religious, economic and political settings between and even within countries [23, 25, 26]. South Africa's particular historical profile thus warrants independent evaluation.

South Africa's first National Family Planning Programme was implemented in 1974 under the *apartheid*[1] regime, supported by government trepidations that unregulated population growth in segregated black African and 'Coloured' (mixed-race) communities would serve both to overwhelm the white minority as well as undermine the centralized economic interests of the country [27]. Notwithstanding the racially-motivated nature of this political agenda, many non-white women purportedly voluntarily received family planning services during this period, perhaps in large part on account of preserving their own and/or their families' survival [27]. Women were often rendered the sole caretakers and breadwinners in their families, as the migrant labor system frequently made the presence of men in households sporadic, thus prospective childbearing in the face of poverty and other converging structural, political, and domestic hardships was daunting, and family planning options became attractive [27]. By end of the 1980's, records[2] suggest that contraceptive coverage had reached 44% among black African women [27]. Relevant

[1] Apartheid was a political system of social, legal, economic, and spatial segregation on the grounds of race that existed in South Africa between 1948-1991 [27]

[2]Kaufman (1998) in an overview of apartheid era contraception use notes that: 'The use of demographic data from South Africa warrants considerable caution. The lack of documentation on methodology, the highly politicized nature of demographic information, and the complexity of geography under apartheid produced a number of ambiguities and uncertainties.' [27].

to historical considerations of the current South African context is the legacy of injectable hormonal methods, which were promoted during *apartheid* for their ease of administration and cost-effectiveness, and in 2016 remained the most popular choice of method for women overall [28-30].

Since the introduction of human and reproductive rights-centric law and policy after democratic transition in 1994, South African fertility rates have continued to steadily decline and remain among the lowest in sub-Saharan Africa, at 2.6 live births per woman in 2016 [30-33]. Amid an increasingly multi-faceted and resource-intensive disease burden, however, including extremely high rates of HIV, tuberculosis (TB), gender-based violence, and non-communicable diseases [34], present levels of unmet need for effective contraception also remain unacceptably high. The South African national contraceptive prevalence rate (CPR) among married and unmarried sexually active women stood at 58% in 2016 [30], yet cross-sectional estimates have reported that 62-64% of pregnancies are still considered unwanted or mistimed [35, 36]. Data showing that incidence of abortion is also rising in all age groups in South Africa further highlights the importance of investigating and addressing shortcomings in access to effective contraception and family planning services [26].

Estimates of and Reason for Failure of Contraceptive Methods Available to South African Women

High CPR relative to high rates of unintended pregnancy indicates that the methods South African women are choosing may often be failing, or else are being incorrectly or inconsistently used [29]. It is important to note that no modern contraceptive method, even sterilization, has been shown to be completely infallible, but some have considerably higher failure rates than others [37]. Shorter acting methods such as injectables and the oral contraceptive pill (OC) are more user dependent and thus tend to be associated with poorer patterns of use and higher incidence of contraceptive failure [37]. Long-Acting Reversible Contraceptive (LARC) methods, however, such as intra-uterine devices (IUDs) and subdermal hormonal implants, have been shown to be consistently effective for three to ten years, and a lack of adherence

concerns after insertion essentially eliminates the discrepancy between 'perfect use' and 'typical use' [38, 39]. Trussell [38] reports failure rates of LARCs ranging between 0.2-0.8% unintended pregnancies within the first year of use for IUDs, and 0.5% for implants. When usage patterns are considered, these rates compare favorably to short-term methods including the OC (0.3% with perfect use; 9.0% with typical use), and injectables (0.2% with perfect use; 6.0% with typical use). Local estimates of typical-use failure rates in South Africa and Zimbabwe have been reported as 1.1 unintended pregnancies per 100 women-years for LARCs, 6.5 for injectables, and 7.3 for the OC [18]. LARCs also typically have the highest acceptability and continuation rates of all reversible contraceptive methods, estimated to be between 78-80% at one year of use for IUDs and 84% for implants, compared with 67% for the OC and 56% for injectables [29, 38].

As mentioned above, a high unintended pregnancy rate in the context of freely available contraceptive services and a relatively high CPR, suggests problems with both correct use of and access to effective contraceptive methods in South Africa [2, 29, 40]. Statistics South Africa Demographic and Health Survey data indicate that injectables were the most frequently used by married and unmarried sexually active women in 2016 (25% in total; 18% for the three-month depot medroxyprogesterone acetate (DMPA) and 7% for the two-month norethisterone enantate) [30]. The male condom was also prevalent at 15%, while the OC and sterilization made up 7% and 6% of preferred methods respectively. Notably, all of these more popular methods, except for the irreversible option of sterilization, scale towards the lower end of relative contraceptive efficacy – largely due to abovementioned poor patterns of use and high discontinuation rates [7, 8]. Highly effective LARC options currently available in the South African public sector include contraceptive implants and copper IUDs (Cu-IUD), and were used by 3.9% and 1.2% of women respectively in 2016 [30].

The Current South African Policy Environment: Contraceptive Guidelines and Method Mix

A concerted effort to attend to the broader unmet need for effective contraception in the South African public sector was made in 2012, with the release of the updated National Contraception and Fertility Planning Policy and Service Delivery Guidelines [41], along with a companion document, the National Contraception Clinical Guidelines [42].

Reflected in 'Objective 1: Expanded Choice' of the new guidelines, under the premise that offering women a range of methods forms the basis of tailoring fertility control to their individual needs, the policy revisions were designed to provide women with multiple safe and effective options suitable for varying lifestyles and preferences. Highly effective, 'fit and forget' LARC options were also promoted for more widespread use, under the rationale that these would provide more convenient, reliable and long-term alternatives to the more popular shorter-acting methods with higher typical-use failure and lower continuation rates. As well as listing '*incremental expansion*' of Cu-IUD usage as a key indicator in Objective 1, sub-dermal hormonal implants were also listed as a LARC option entirely new to the South African public sector. Perceived advantages of implants were their cost-effectiveness in South Africa's limited resource, high disease burden setting, their documented acceptability overseas and elsewhere on the continent, their three to five-year lifespan, and the simple and time-efficient procedure required for their insertion by trained providers [43-45].

As well as expanding the method mix available to South African women, the 2012 contraceptive guidelines also introduced explicit reference to WHO's medical eligibility criteria (MEC) [20]. The MEC is a means of determining different methods' suitability for women according to their medical conditions and other characteristics. The MEC categorizes contraceptive eligibility from 1-4: 1 - '*Use the method in any circumstance'*; 2 - '*Generally use the method*'; 3 - '*Use of the method not usually recommended unless other, more appropriate methods are not available or acceptable*'; 4 - '*Method NOT to be used*'. In the

context of HIV infection and ART, it was intended that the MEC should be used to determine which methods would be suitable for women based on factors such as their disease stage and ART regimen. The guidelines also made specific stipulations surrounding the use of contraception in the context of HIV/ART.

South African Contraceptive Policy with regard to HIV and ART

In consideration of South Africa's high HIV burden setting, the 2012 guidelines sought to address the '*dual challenges of HIV and [unintended] pregnancies, through the promotion of condom use and dual contraception as well as through the active promotion of integrated HIV and sexual and reproductive health services'* [42]. Given that the contraceptive efficacy of condoms is generally less than many other modern methods, it was emphasized that, despite the broad recommendation that barrier methods be used correctly and consistently by sero-discordant and sero-concordant couples alike, the concurrent use of other female-controlled methods was also a key strategy for protecting HIV-positive women against unintended pregnancy [12, 46]. Alongside synchronized government and civil society efforts to integrate the country's ART programme into additional primary-level services – particularly tuberculosis (TB) treatment, but also other priority areas including family planning [47], the guidelines instruct that the full range of contraceptive options be made equally available to HIV-positive women in conditional alignment with WHO's MEC. For reproductive-aged HIV-positive women, both this increased availability of methods to choose from (particularly LARCs) and the convenience of integrated contraceptive and HIV/ART services may have been particularly valuable, as using ART adherence to stabilize CD4 counts and contraceptives to effectively plan for pregnancies ahead of time is considered an important strategy for improving HIV-related maternal and child health outcomes, including the prevention of vertical HIV transmission [4-6].

The Introduction of the Contraceptive Implant and Implications for HIV-positive Women

The contraceptive implant's rollout in South Africa began in early 2014 and included substantial provision to HIV-positive women both on and not on ART [16]. During that year, however, preliminary anecdotal,

pharmacokinetic and clinical data emerged to support existing findings that the concurrent use of some enzyme-inducing agents may lower the contraceptive efficacy of implants and most other hormonal contraceptives [13, 15, 17]. The enzyme-inducing agents implicated in this DDI include certain TB medications, anti-epileptics, and, significantly for HIV-positive women, the non-nucleoside reverse transcriptase inhibitor (NNRTI), EFV, upon which the WHO's (and South Africa's) recommended first-line ART regimen was then and is still based. It was suggested that increased metabolic activity in the liver in the presence of these drugs would reduce the bioavailability of the hormones released by implants, thereby heightening the likelihood of breakthrough pregnancies occurring.

In October 2014, the National Department of Health issued a nation-wide circular advising against implant provision and recommending its removal among users of the category of drugs in question, and specifically suggested HIV-positive women on EFV-based ART should instead be offered an IUD, the three-month injectable DMPA, or, as a second-line option due to concerns over potentially similar drug-drug interferences, the OC [49]. A more detailed technical brief followed two months later in December 2014, which noted a demonstrated reduction in etonogestrel concentration among efavirenz-based ART users and reiterated that the IUD or DMPA should be offered instead of the implant [50]. '*Other hormonal methods*' (i.e. two-month injectables and the OC) were also '*not recommended as their contraceptive efficacy can be reduced by strong enzyme-inducing medicines*' [50]. The final recommendation in the December brief advised that, if an HIV-positive woman on EFV already had the implant in situ, she need not have it removed under the condition that she be '*properly counselled about the increased risk of pregnancy because of drug interactions*' and about *'the importance of using additional non-hormonal contraceptive measures'*. Evidence and perspectives surrounding the appropriateness of these recommendations are investigated in detail later in this review but are first contextualized by considerations of the contraceptive needs and rights of HIV-positive women, and the barriers they often encounter in accessing services that facilitate informed contraceptive choice.

Fertility Intentions and the Contraceptive Needs and Rights of HIV-positive Women

With the advent of prevention of mother-to-child transmission programmes (PMTCT), highly active antiretroviral therapy (HAART) and other successful interventions, the impact of sero-status on women's childbearing prospects has been drastically reduced in the last two decades [51]. This means that, with proper planning through the use of contraception and ART adherence, there is no longer any medically defensible reason that the presence of an HIV infection in and of itself should impede a woman's desire for children [6, 52]. The WHO's Consolidated Guideline on the Sexual and Reproductive Rights of Women Living with HIV suggests that women accessing HIV treatment and management services should be supported in realizing their fertility intentions, in their pursuit of healthy and satisfying sexual relationships, as well as be provided with a range of contraceptive options accompanied by appropriate counselling to facilitate informed choice [12].

Studies from sub-Saharan Africa have produced mixed results as to the influence of HIV status over women's fertility intentions. Longitudinal data from Malawi suggests HIV-positive women tend to have lower fertility intentions than HIV-negative women [53, 54]. HIV status was not found to be a significant factor in the desire for at least one child in several studies from Zambia, Zimbabwe, and South Africa, as it is often offset by societal and cultural expectations surrounding women and fertility [55-57]. Another study from South Africa found an almost equal proportion of HIV-positive women open to planning pregnancies compared with those against the idea [51], with an additional finding, supported by still other data from Uganda and South Africa, that time from diagnosis and health status, particularly in women without children and stabilized on ART, are associated with increased fertility desire [51, 57, 58]. These variations suggest that observed patterns in fertility intentions, though informative, are likely to be contextually dependent and of course not universal. In fact, they are broadly representative of the diverse fertility intentions of women in general; HIV-positive women, like all women, benefit from access to

evidence-based information and services that enable them to safely make choices according to their personal circumstances and preferences [52].

Barriers to informed and effective contraceptive use in HIV-positive women in South Africa and Regionally:

Despite the explicit intentions of the 2012 contraceptive guidelines to remove general barriers to access in South Africa, many related to resource scarcity, supply chain management, and provider training remain [2, 59]. Ensuring clinics are able to offer women a reasonable enough number of modern methods to constitute real choice is a challenge, and this is especially true for implants, IUD insertions and sterilization procedures [2]. A lack of trained providers at primary clinics often means women are either pressured to use whichever method is immediately available or 'preferred' by their provider, or else the unavailable service is referred on to a higher-level facility [2, 59]. Referral presents a problem particularly for women living in rural and remote areas, where attending higher-level facilities may require long distance travel and prohibitive time and transport costs [2]. Research from sub-Saharan Africa has demonstrated that HIV-positive women continue to have poorer access to family planning services and contraception than their HIV-negative counterparts [21-23]. Delivering access to good quality, non-judgmental contraceptive counselling is a particular difficulty. Being young (especially adolescent), unmarried, and/or HIV-positive all increase a woman's risk of being offered a limited choice of contraception, and in some cases of being refused services entirely, due to provider bias, stigma, misinformation, or discrimination [2, 59].

With such a disproportionate (and large) number of women across the sub-Saharan African region experiencing HIV infection during their reproductive years, it is also important to examine the gender divide and its implications as a barrier to preserving women's contraceptive needs and rights. A 2014 assessment of cross-sectional demographic data from 12 sub-Saharan African countries determined 'consistent and strong associations between HIV infection in women and physical violence, emotional

violence, and male controlling behavior' [60]. Heterosexual relationship power inequity was also found to increase young women's HIV acquisition risk in a 2010 longitudinal analysis of randomized controlled trial data collected in South Africa between 2002-2006 [61]. The design characteristics of most existing barrier method technologies, including female and male condoms, require more direct agreement between sexual partners. In the context of unequal power relations between women and their male partners, HIV-positive women could be driven to take a more submissive stance during such negotiations [62]. In light of these and other findings demonstrating more generalizable associations between intimate partner violence (IPV) and incidence of sexual and reproductive coercion [63], it could be argued that the importance of ensuring access to discreet, female-controlled contraception including LARCs may be compounded in the presence of HIV infection, given heightened intimate partner violence (IPV) risk.

Contraceptives in context of HIV infection and ART

In 2016, the WHO recommended that all diagnosed HIV-positive individuals be eligible for ART regardless of CD4 count or clinical stage [64, 65]. This 'test and treat' approach is supported by evidence that, not only does early ART intervention improve HIV progression outcomes, but viral load suppression in relevant bodily fluids also substantially decreases transmission risk [64]. South Africa was an early adopter of this universal treatment strategy and has pledged to meet the targets of UNAIDS '90-90-90' testing and treatment cascade, whereby 90% of HIV-positive individuals will know their status, of whom 90% will receive ART services, and a further 90% of those on ART will achieve viral load suppression [66]. UNAIDS estimated that in 2016 South Africa's progress towards meeting the '90-90-90' targets for its approximately 7 100 000 HIV-positive individuals were [9]: 86% knew their status; 56% of those who knew they were infected were on ART; and 46% on ART had achieved viral suppression.

Consequently, while ART has formally been made available to all HIV-positive reproductive-age women, it is important to acknowledge that many are still not receiving or have chosen not to yet receive ART, but

nonetheless will invariably have contraceptive needs to be met. The WHO's 2017 Consolidated Guideline on Sexual and Reproductive Health and Rights of Women Living with HIV recommends that women in Preliminary and Clinical Stages 1 or 2 of HIV progression can use most methods including implants without restriction (MEC Category 1) and can generally use IUDs (MEC Category 2). If a woman's HIV has progressed to Clinical Stage 3 or 4, MEC Category 1 still applies to most hormonal methods, but initiation of an IUD is generally recommended against (MEC Category 3) until/unless her condition improves. It need not be removed if already in situ, but she should be monitored for signs of pelvic inflammatory disease [12].

When women do initiate ART, the WHO's current recommendations vary according to treatment regimens[3], due to the potential for DDIs between certain hormonal contraceptives and antiretroviral agents [12]. All are currently listed with a 'low-to very low-quality evidence' caution. Importantly for this review regarding South African contraceptive policy and practice implications, those on first-line ART regimens containing EFV can use DMPA without restriction (MEC Category 1), though can generally use all other hormonal methods, including implants (MEC Category 2). IUDs in the presence of ART carry the same recommendations as for women not on ART (MEC Category 2-3), and likewise depend on HIV clinical stage and pelvic condition[13].

[3] In summary, hormonal methods may be used without restriction (MEC Category 1) in clients on ART regimens containing nucleoside/nucleotide reverse transcriptase inhibitors, the newer non-nucleoside/nucleotide reverse transcriptase inhibitors (including etravirine and rilpivirine) and the integrase inhibitor, raltegravir. Women on protease inhibitors and the NNRTI's EFV or nivirapine can use DMPA without restriction (MEC Category 1), and can generally use all other hormonal methods (MEC Category 2) [12].

Overview of Evidence Regarding Drug-Drug Interactions between Hormonal Contraceptives and ART

While considerable gaps remain in our understanding of hormonal contraceptive use in the context of HIV and ART, there has been substantial recent investigation into DDIs between progestin-based hormonal methods and antiretroviral agents. A 2017 systematic review of 50 published reports from 46 separate studies found that EFV is the only anti-retroviral that seems to be implicated in lowering hormonal contraceptive efficacy [19]. The cytochrome P450 enzyme-inducing action of EFV reduces the bioavailability of synthetic progestins in the body, making suppression of ovulation less likely [39]. This reduced contraceptive efficacy applies to all hormonal methods except for the high-dose 3-month injectable, DMPA [19]. Given that implants, at least for many South African women, may be the only accessible LARC option in their setting, and that EFV-based ART regimens remain the first-line treatment for HIV in South Africa, as well as in consideration of the 'test and treat' approach and '90-90-90' targets, the potential implications of this interaction for HIV-positive reproductive-aged women in the country are unquestionably significant.

Pharmacokinetic (PK) evidence for EFV's interference with the implant's metabolic pathway began to gain greater attention in 2014 following the publications of two studies from Brazil [13] and Uganda [14], which, despite limited sample sizes, both showed greater than 50% reductions in hormone bioavailability in women on EFV using etonogestrel and levonorgestrel implants respectively. More recently published findings from 58 Ugandan women (divided into three study groups) in 2016 demonstrated 82% lowered etonogestrel concentrations at 48 weeks post implant insertion in women exposed to EFV when compared to ART-naïve women [67]. No significant effect on serum hormone levels was found in women in the third group, who took nevirapine-based ART. Early clinical studies of contraceptive failure associated with concurrent implant and EFV use include a retrospective chart review in 2014 of 332 women using levonorgestrel implants on various combinations of ART in Swaziland [15], that reported 15 (12.4%)

pregnancy events occurring in 121 women taking EFV, compared with none in the non-EFV based ART groups. In an attempt to further describe the effect of observed etonogestrel reduction on clinical outcomes, another 2015 study combined three sets of longitudinal data to put together a relatively small sample of implant-using HIV-positive women from East and Southern Africa [17]. Implant users on EFV-based ART were found to have a 6.0 incidence rate of pregnancy per 100 women-years, versus a rate of 1.4 in implant users not on EFV-based ART.

These smaller clinical studies were substantiated in 2015 by a large, three-year retrospective cohort review that looked at pregnancy rates among 25,000 HIV-positive women on multiple combinations of ART and contraceptive methods in Kenya [18]. The adjusted pregnancy rate among implant users on EFV-based ART was 3.3 per 100 women-years, compared with 1.1 among implant users on nevirapine-based ART, and 1.3 in women not on ART. These figures clearly demonstrate a higher likelihood of contraceptive failure in implant users on EFV-based ART. It is also of considerable importance however, that, relative to the implant's reduced efficacy in the presence of EFV, the same study also found that women on EFV-based ART using different, shorter-acting methods recorded failure rates of 5.4 and 9.3 per 100 women years for DMPA and the OC respectively. Thus, while IUDs and sterilization were retained as the most effective options overall (0.93 per 100 women-years), the implant was nonetheless a more effective option than both the injectable and the OC for women on EFV-based ART.

Various limitations related to study designs and sample sizes mean that the above-mentioned findings still need to be clarified by prospective cohort data, but such investigations will be resource intensive and require long periods of follow up [16]. Suggested strategies for improving contraceptive failures associated with EFV's propensity to reduce serum levels of progestin have included increasing hormone dosages (i.e. by inserting two implants instead of one or by commissioning a higher dose implant). One such randomized trial is currently scheduled in Uganda [68], but study results are not expected before

2022. Whether or not an anticipated dosage reduction of EFV (600mg to 400mg) - which, according to recent results from the ENCORE1 trial, may be non-inferior in terms of virological failure and also reduce drug toxicity risk, as well as being cost effective in developing settings [69] - will correspond with changes to etonogestrel or other progestin concentrations in women concurrently using hormonal methods, is also a question that warrants answering [26]. In the meantime, it is important to consider the available evidence from a rights-based family planning perspective, supported by domestic and international legal and policy framework.

Rights-based Family Planning for HIV-Positive Women: Informed Choice, Service Quality, and Method Range Considerations

It is generally recognized that informed contraceptive choice is integral to tailoring fertility control to women's needs, and also to ensuring maximum contraceptive coverage, effectiveness and acceptability [12]. HIV-positive women need to be counselled by their providers not only about the respective efficacies, usage considerations and side effects of the various contraceptive methods available to them in their settings, but also about any implications in terms of possible changes to HIV progression rate or transmission risk, and any evidence of DDIs involving their ART or anything else they take concomitantly with their method [70]. Additional factors, such as the importance of dual protection with both barrier and non-barrier methods, sero-status disclosure, relationship dynamics, desire for method discretion, and comorbid medical conditions, also need to be considered and discussed in the family planning setting as these may affect contraceptive choice [70]. Services that allow HIV-positive women to contemplate their own circumstances and choose freely from a range of methods, as well as support them to plan a safe and healthy pregnancy if they wish, are well supported by South Africa's contraception guidelines and wider legislative framework [2].

Providing HIV-positive women with an understanding of considerations surrounding their sero-status, ART, and fertility desires, also aligns with the 'woman-centered' approach recently endorsed by the World Health Organization (WHO) in the Consolidated Guideline on Sexual and Reproductive Health and Rights of Women Living with HIV [12]. This approach sees women 'as active participants in, as well as beneficiaries of, trusted health systems that respond to women's needs, rights and preferences in humane and holistic ways'. These principles enhance reproductive agency, bodily autonomy and self-determination as well as improve clinical and livelihood outcomes of women and their families [12]. WHO's women-centered approach represents a shift away from traditional, more paternalistic styles of practice towards an emphasis on shared decision-making between women and providers. As well as aligning with the ethical imperatives of the WHO, the current South African policy-making environment is designed to rebuild historical mistrust in the healthcare system and is thus in direct and deliberate contrast with apartheid-era focus on population-control via coercion [2]. Maintaining an open dialogue in a supportive clinical environment is critical to ensuring women are comfortable enough to discuss their personal needs with their providers, which is particularly true for HIV-positive women as they may fear judgement or reprimand due to embedded stigma surrounding HIV and sexual activity [57].

Conclusion

HIV-positive women have a similar need for effective contraception as women in the general population, and similarly benefit from the ability to choose between different methods according to their own lifestyles and preferences. Avoidance of unintended pregnancy may be particularly important for HIV-positive women, however, due to the role of family planning in preventing vertical transmission and improving other HIV-associated maternal and child health outcomes. It is therefore critical for health systems to allow HIV-positive women to choose a method that will be most effective and suitable for them. With the goal of expanding contraceptive choice in mind, the South African National Department

of Health's 2014 decision to deviate from WHO MEC guidance and recommend against the implant as an option altogether for HIV-positive women on EFV-based ART may have been inappropriate. With IUDs not always accessible or appropriate for many women and given that other hormonal methods, including the OC and the two-month injectable, are also currently recommended against in the context of EFV, it is not unreasonable to foresee that, in practice, the only method available to many HIV-positive women on EFV may be the-three month injectable, DMPA. Aside from the implant/EFV directives severely limiting the contraceptive choices for women on EFV-based ART, recent evidence also suggests that DMPA may potentially be even less effective than the implant for some women even when the higher contraceptive failure rate associated with the DDI between implants and EFV is taken into account. Moreover, generations of South African women and providers are very accustomed to injectables such as DMPA, and whilst these should of course remain an option in the current method-mix, sufficient education about other methods, especially LARCs, is important if the maxim of informed contraceptive choice is to be achieved.

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PART C: Article

Perspectives on etonogestrel implant use in HIV-positive women in Cape Town, South Africa: a qualitative study among primary providers and stakeholders

Target Journal: BMC Public Health

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Abstract

Background: This study explored primary provider and other stakeholder perspectives regarding South African public sector provision of contraceptive implants to HIV-positive women in 2017, and in particular investigated the impact of a 2014 South African National Department of Health recommendation concerning the concurrent use of implants and the antiretroviral drug, efavirenz (EFV).

Methods: Thematic analysis was used to identify emerging themes from qualitative data, which included semi-structured interviews and a focus-group discussion with 10 family planning providers at four primary care clinics, and semi-structured interviews with 10 other stakeholders working in the fields of HIV and/or contraceptive care in or around Cape Town, South Africa.

Results: None of the providers at the clinics visited offered the contraceptive implant to HIV-positive women, regardless of their exposure to EFV. This was consistent with patterns of family planning service delivery at primary care facilities across Cape Town as observed by local stakeholders. Inadequate provider training, growing provider and community scepticism about implants general, ambiguous wording of government communiques, provider unwillingness to cause harm, and pressure to provide integrated services in busy clinical environments, all appeared to contribute to providers' unwillingness to offer the implant to HIV-positive clients in general.

Conclusions: To ensure government directives regarding the family planning needs and rights of HIV-positive women are clear, guided by evidence and interpreted as intended, future recommendations should be written in full consultation with primary providers, beneficiaries of services and other stakeholders. Memoranda need to be accompanied by simplified counselling messages and tools designed to assist primary providers to facilitate informed contraceptive choice for their clients. These materials would be especially useful in busy integrated service environments. Generalized retraining of providers in rights and choice-based family planning, and in particular implant provision and counselling, is also recommended.

Key words

HIV; contraceptive implants, South Africa; long-acting reversible contraceptives, LARC, qualitative methods

Background

Providing women with access to modern contraception reduces the risk of negative health and socioeconomic outcomes associated with unintended pregnancy [1]. Offering a range of different method options also heightens the ability for women to make informed and personal choices, which in turn has

been shown to optimize contraceptive acceptability and efficacy [2, 3]. Improving contraceptive service quality may have added benefits in settings with high Human Immunodeficiency Virus (HIV) burdens, as ensuring HIV-positive women are able and supported to plan their childbearing is an important strategy for reducing HIV-associated maternal and child morbidities, including preventing vertical HIV transmission [4, 5].

Efforts to meaningfully meet the contraceptive needs of women generally in South Africa, including among the 21%-23% of reproductive-aged women in the country who are currently HIV-positive [6-8], were made in 2012, with the release of the revised National Contraception and Fertility Planning Policy and Service Delivery Guidelines [9], and the National Contraception Clinical Guidelines [10]. These updated guidelines were specifically designed by the South African National Department of Health to expand contraceptive access and method choice, and to align freely available public sector services closely with the World Health Organization's (WHO) continuously updated Medical Eligibility Criteria (MEC). The MEC is a numerical system for categorizing contraceptive eligibility (from 1-4) and allows for the tailoring of an appropriate method range for individual women based on their medical conditions and other characteristics [11].

Among the key indicators listed in the updated guidelines was the 'incremental expansion' of access to highly effective, 'fit and forget' Long Acting Reversible Contraceptives (LARCs), which include intrauterine devices (IUDs) and sub-dermal contraceptive implants [9, 10, 12]. LARCs require no action on the part of users once inserted, meaning that adherence concerns are eliminated [12]. Once in situ, LARCs have contraceptive lifespans of three to ten years from insertion, making their durations of use significantly longer than other reversible methods including two and three-month injectables and the daily oral contraceptive pill (OC) [12]. Discontinuation rates for implants and IUDs also tend to be the lowest of all

reversible methods [12]. These factors combined make LARCs among the most effective, user acceptable, and cost-efficient forms of contraceptive technology currently available [13, 14].

Along with upscaling access to copper IUDs (Cu-IUDs), the 2012 guidelines also introduced a new LARC option into the South African public sector method-mix: the subdermal contraceptive implant. An extensive provider training programme made Merck MSD's etonogestrel implant, *Implanon NXT®,* widely available to women from early 2014, and the new method's technological innovation, ease of use and high efficacy generated considerable public enthusiasm [15, 16]. Uptake records suggest that initially high demand for *Implanon NXT®* dropped unexpectedly within a year of its launch, however, and has continued to decline steadily each year since [15]. Although available data is currently very limited, reasons for this decline point towards an inadequate provider training programme, which resulted in poor pre-counselling for potential users. Early reports suggest that client dissatisfaction with the implant centered around unanticipated side-effects that providers had not adequately counselled users to expect, provider resistance to removal, and community apprehension about the new method [15, 17].

Another controversial aspect of the implant's introduction in South Africa was a government recommendation issued in late 2014 that advised against implant provision to users of certain enzyme-inducing agents, including rifampicin, used to treat tuberculosis (TB), several antiepileptics, and efavirenz (EFV), the drug upon which the country's first-line antiretroviral therapy (ART) regimen was and is presently based [18]. Evidence for the recommendation came from pharmacokinetic [19] and some clinical [20] data demonstrating a drug-drug interaction (DDI) between EFV and the synthetic progestins in implants such as *Implanon NXT®*, with the potential to reduce contraceptive efficacy and lead to method failure. Although the presence of this DDI is established, the exact contraceptive failure rate associated with the interaction between EFV and implants and the clinical unintended pregnancy rate due to concomitant use are not fully known. A practice change circular issued in October 2014 advised against

the implants provision and recommended its removal among users of EFV and the other drugs in question [18]. A slightly less restrictive technical brief followed two months later in December 2014, which suggested women using these medications may keep their implants if already in situ, provided they were given 'proper counselling' about the interaction [21]. The details of what constituted proper counselling were not specified.

The strong recommendation against implant use in the context of EFV-based ART has since been a subject of debate within the HIV and women's health fraternities in South Africa, especially given that the WHO has retained the implant's MEC category 2 status ('can generally use the method') among users of EFV [22]. Expert commentaries have expressed concern that comparative failure rates of other methods available to women were not sufficiently considered when the South African government took its stance and, crucially, that the importance of women's personal method choice considerations was not taken into account [23, 24]. Recent retrospective cohort data from Kenya has since suggested that other shorter-acting methods, including those most widely used by South African women, injectables and the OC, may be even more likely to fail than the implant, even when the reduced efficacy associated with EFV exposure is taken into account [25]. These higher failure rates are likely due to adherence issues commonly observed among users of short-acting methods in typical-use settings [26].

While the appropriateness of removing implants from the contraceptive method mix available to HIV-positive women on EFV-based ART because of reduced effectiveness concerns has been discussed elsewhere in published literature [23, 24], there has been no assessment of the directives' impact on contraceptive choice and decision-making in South African primary care settings. This article reports on qualitative data documenting the perspectives of family planning providers at four primary care clinics in Cape Town, as well as of various specialist providers and other relevant government and academic stakeholders in South Africa's Western Cape Province. The purpose of the study was to ascertain what

family planning providers and relevant stakeholders knew, understood and practiced regarding implant provision in the context of HIV infection and ART, and specifically their levels of awareness about associated policy and research output since *Implanon NXT®'s* introduction in South Africa. Participants were also asked for their suggestions to potentially improve contraceptive choice and service delivery to HIV-positive women in their daily practice and in future South African policy-making initiatives.

Methods

Study design

This study was qualitative in design, and utilized in-depth, semi-structured interview and focus group discussion data collected from family planning providers at primary clinics, specialist providers, and other relevant government or academic stakeholders working in HIV and/or contraceptive care. It was a sub-study of a wider, existing mixed-methods project: '*A formative study on the 2012 South African National Contraception Guidelines' implementation of new Long-Acting Reversible Contraceptive (LARC) methods in the Cape Town Metropolitan Area'* [27].

Study sites

Study participants were divided into two groups; Group A participants were family planning providers based at primary care clinics, and Group B participants were specialist providers and relevant stakeholders from government and/or academia who worked in HIV and/or contraceptive care.

Group A interviews were conducted at four public sector primary care facilities managed by the City of Cape Town (Table 1). All of the Group A facilities provided *Implanon NXT®* on site, although there was significant variation in terms of clinic size, services and contraceptive methods offered, and client demographic profiles.

Clinic type	Setting	Client population	Relevant Services Offered
Large youth clinic, also functioning as a community centre and meeting space for youth	Peri-urban, low income area with high HIV burden	Mostly black African, isiXhosa speaking, school-aged and young adult clients	HIV diagnosis, treatment and support services Full range of contraceptive services including injectables, the OC, *Implanon NXT®* and IUDs
Large, generalized primary care clinic	Urban, low income area with high HIV burden	Mostly black African, isiXhosa speaking clients of all ages	HIV diagnosis, treatment and support services Contraceptive services included injectables, OC and *Implanon NXT®;* providers were trained but not certified to provide IUDs, so these were referred to a higher-level facility
Small generalized primary care clinic	Urban, low-middle income with medium HIV burden	Mostly Afrikaans speaking, "Coloured" (mixed-race) clients	HIV testing services but not ART Contraceptive services included injectables, OC and *Implanon NXT®;* providers were trained but not certified to provide IUDs, so these were referred to a higher-level facility
Medium-sized generalized primary care clinic	Urban, middle income area with low HIV burden	Mixed demographics; Clients mostly from Afrikaans speaking Coloured or African migrant backgrounds.	HIV diagnosis, treatment and support services Full range of contraceptive services including injectables, the OC, *Implanon NXT®* and IUDs.

Table 1. Group A interview sites: Characteristics of primary facilities and services offered

Group B participants were interviewed at their places of work, which included hospitals, academic research units, and government offices.

Participants and Sampling

A total of 20 participants were included in the study, with 10 participants each in Groups A and B respectively. Sampling for both groups was purposive.

Group A interviews focused on providers at primary care facilities pre-approved by the City of Cape Town for utilization by the parent study. All primary providers met the study inclusion criteria of being professional nurses trained in family planning. Eight Group A participants were female, and two were male. Six were interviewed individually and four participated in a focus-group discussion.

Group B interviewees were selected for their expertise as specialist providers and as government/academic stakeholders involved in HIV and/or contraceptive care. The sample included obstetricians/gynaecologists (OB/GYN's), family planning trainers, an HIV clinician, a clinical researcher, a pharmacologist, as well as women's and HIV/TB health managers. Nine participants in Group B were female and one was male. All participants in Group B were interviewed individually.

Data Collection and Study Instruments

Data collection took place between May and August 2017. Interviews were conducted in English by the student investigator and averaged 45 minutes (20-90 minutes) in duration. Interviews were recorded in audio format and transcribed verbatim.

Separate interview guides were developed for groups A and B in collaboration with the supervisor and co-supervisor and were pre-tested. Participants in both groups were asked for their overall perspectives on the implant and its use in the context of HIV and ART generally. All participants were asked for their recommendations for improving contraceptive choice, care and service provision for HIV-positive women in primary care settings.

With the intention of capturing the chains of communication between government authorities, specialist providers, and family planning providers based at primary clinics, Group A and B interview guides differed in the nature of the questions they posed about the implant/EFV directives (see Appendices D and E). Group A interviews focused on primary providers' interpretations of the implant/EFV directives and consequent impacts for their own practice. Group B interviewees were asked for their opinions about the implant/EFV directives at the policy-making level, and how they believed the directives had been received and interpreted at the primary care level. Perceived influencing factors that may have contributed to these interpretations were probed in both groups.

Data Analysis and Management

The student investigator transcribed each interview shortly after recording, along with voice memos and handwritten field notes, in Microsoft Word format. An inductive thematic approach was used to analyze data, with the student investigator identifying emerging themes and discussing them with the supervisor and co-supervisor during the course of the fieldwork. Upon completion of data collection, audio files were destroyed, and all transcripts were then reviewed manually and processed through the qualitative software programme, NVivo, which assisted in further developing and refining codes and themes by visually mapping 'word trees', showing semantic patterns of associations between key words and their respective contexts.

Once themes had been finalized, results were organized to construct a sequence of perspectives regarding the release of the 2012 updated contraceptive guidelines, *Implanon NXT®'s* early 2014 introduction in South Africa, the late 2014 implant/EFV directives, and consequent impacts these policy events had, and continue to have, on primary contraceptive care provision to HIV-positive women. Finally, recommendations for improving outcomes in future policy implementation initiatives were gathered. The student investigator maintained frequent communication with the supervisor and co-supervisor

throughout data collection and during analysis, who provided critique, cross-checking and generalized guidance regarding findings.

Ethical Considerations

Ethical approval for this study was granted by the Human Research Ethics Committee (HREC) at the University of Cape Town (see appendix F). Permission to conduct interviews at primary facilities was granted by the relevant health authorities. Participation in the study was voluntary and written informed consent was obtained from all interviewees (see Appendix C). Written invitations were distributed at primary clinics prior to Group A interviews being arranged (see Appendix A). Group B participants were sent email invitations (see Appendix B). Anonymity and confidentiality were assured and maintained throughout data collection and analysis, with names removed from transcripts and each participant assigned alpha-numerical codes.

Results

Overview of Key Findings

Thematic analysis of interview data returned findings that broadly conformed to the following narrative:

At the time of data collection, none of the primary facilities visited were offering the implant to HIV-positive women at all, regardless of whether or not they were currently taking EFV-based ART. A set of converging factors appeared to drive primary providers to interpret the 2014 implant/EFV directives in this way.

First, the directives were received by providers in the wider context of insufficient training and relative unfamiliarity with the implant, given the method's recent introduction in South Africa. Substantial provider and client uncertainty surrounding side-effects, as well as concerning community perceptions

about the implant, fostered a general sense of suspicion about and distrust of the method amongst providers.

Second, the directives were perceived by some participants to be ambiguously worded, in that, it seemed to imply additional harm associated with the drug-drug interaction between the implant and EFV, rather than just reduced contraceptive efficacy. In the context of suspicion about and unfamiliarity with the implant generally, providers were reluctant to risk harming their clients and wished to avoid potential legal ramifications of being seen to support their clients in making poor clinical decisions.

Third, structural pressures on providers, including heavy workloads, time constraints, and difficulty keeping up to date with all policies, protocols and directives associated with the wide range of integrated services they were expected to deliver, also contributed to the decision to apply the directives to all HIV-positive women. Rather than contend with the nuances of a policy update about an unfamiliar new method, providers perceived that the safest and simplest interpretation was to view implants as broadly contraindicated in the context of HIV.

Recommendations to improve contraceptive services and facilitation of contraceptive choice and informed decision-making for HIV-positive women clients included: retraining providers, especially in implant counselling and provision but also in more foundational, rights and choice-based family planning concepts; developing user-friendly, time-efficient, evidence-based decision-making tools; as well as more comprehensive stakeholder/beneficiary consultation in future contraceptive policy-related decision-making.

Impressions of the 2012 Contraceptive Guidelines and the Implant's Introduction and Rollout

There was a consensus among all stakeholders in Group B that the 2012 guidelines were '*a step forward for South Africa'* (OBGYN), in that they were comprehensive, closely aligned with the WHO MEC, and aimed to improve contraceptive access, especially to LARCs. Both stakeholders and family planning

providers at primary clinics recalled widespread enthusiasm and anticipation surrounding the implant as a welcome new option for South African women. As one stakeholder, who had worked for several decades in family planning training at an HIV-focused NGO, remembered, '*When Implanon [NXT®] came here… Wow! Here is something that is going to save, and which does not need the clients to come to the clinic very often. It was a savior, in our eyes'* (family planning trainer). Primary providers likewise remembered the initial optimism surrounding the implant, describing it as '*revolutionary when it came*' (professional nurse).

Despite recalling this initially positive reception, the South African National Department of Health's decision to present the implant as a wide-reaching solution to the country's high rates of unintended pregnancy was criticized by some stakeholders: '*the method was sold to the public, and to the staff, as if this is going to be the solution for all the family planning woes that we've had until now. Which of course it isn't*' (Health Manager).

Stakeholders involved in provider training before and during the initial *Implanon NXT®* rollout described feeling that the process had been rushed, not well coordinated, and, ultimately, a poor reflection of the 2012 guidelines' original intentions to expand contraceptive choice. It was perceived that the unfamiliarity of the new method, combined with a lack of comprehensive training under time pressure, left many providers unable to counsel women about or provide the method optimally.

As one OB/GYN remembered, *'the implant was completely foreign to [providers], so I think the training on its provision was quite rapid, and the focus was insertion - to train them how to put it in, but the training on how to counsel women about their options was lacking'* (OB/GYN). Verifying this sentiment, another specialist provider involved in the national provider training programme acknowledged that, '*whilst everyone denies it, I think there was very much a cascading of, 'See one, do one, teach one'* (family planning trainer).

Confirming stakeholders' perceptions that the rollout had not been well executed, family planning providers at primary clinics invariably reported that, while the implant had been very popular when it was first introduced, the number of insertions at their clinics had declined quickly thereafter. Despite what most providers described as their best efforts to counsel women and allay their fears about the method, many perceived that a large number of clients requested their implants be removed soon after insertion. In these cases, providers felt ill-equipped to manage women's concerns about the method appropriately and in an evidence-based way, often being unsure of whether particular side effects were likely to be linked to the implant and/or how to appropriately manage them. Side-effects mentioned by multiple providers as leading to early removals included irregular bleeding, weight changes, headaches, and hair loss.

It was also observed by some participants in both Groups A and B that clients were often weary of the method, seeing it as a '*foreign thing*' or a '*chip*' inside their bodies. Further concerning information, in particular anecdotes involving implants being violently removed from women's arms by gang members, to be 'crushed' and smoked as a recreational drug, had also circulated widely in communities and deterred women from receiving or retaining the method.

Circumstances surrounding the Implant/EFV Directive

Stakeholders and providers at primary clinics reflected that the timing of the recommendation against concurrent EFV-based ART and implant use was such that it was received just as initial enthusiasm surrounding the implant had waned; providers were feeling overwhelmed and unable to manage clients' growing and multidimensional concerns about the new method, removal requests were increasing, and insertion rates had already started to decline.

Stakeholders recalled an inadequate consultation process prior to the issuing of directives, criticized the wording of the distributed documents, and were concerned that the department had not taken sufficient

time to consider women's personal method choices, especially given that they considered absolute efficacy to be only one aspect of why women choose to use certain contraceptive methods. The result of the directive, which most stakeholders interpreted as effectively withdrawing the implant as an option for women on EFV-based ART, was variously described as '*unusual*', an '*overreaction*', '*dogmatic*', '*rushed*', lacking '*perspective*' (with respect to the concern that other methods were later suggested to have even higher rates of contraceptive failure), and worded such that providers might interpret that '*Implanon [NXT®] is actually not [physically] safe – not [in terms of efficacy] as a contraceptive method, but safe for the individual*' (OB/GYN).

In not consulting primary providers and service beneficiaries, it was suggested that policymakers had failed to consider how the wording of the recommendation might be interpreted in the primary care setting: *'[The directives were] interpreted as, 'There is something wrong with the implant', and I think that has had really very serious consequences for the rollout and has done reputational harm to the intervention'* (clinical researcher). Stakeholders therefore generally felt that the National Department of Health's decision to recommend against the implant as an option for women on EFV-based ART was premature, not in the best interest of HIV-positive women and may have caused significant unintentional auxiliary damage to the implant's already compromised reputation at primary clinics and in communities.

Interpretation and Impact of Implant/EFV Directive on Clinical Practice

Regardless of whether or not clients were on an EFV-based ART regimen, all the family planning providers interviewed had interpreted the 2014 circular and technical brief to mean that implants were broadly contraindicated in the context of HIV infection. This confirmed stakeholders' general perceptions of restricted provision of the implant to HIV-positive women across Cape Town primary clinics. An HIV/TB coordinator, who had observed the widespread exclusion of the implant as an option for HIV-positive women in her area, suggested that providers were hesitant to offer a method they perceived might harm

clients, with concerns over the implants unanticipated side effects also seen as a motivating factor: '*No one is being offered – no HIV-positive woman is being offered Implanon [NXT®]. I think they're just playing safe'* (Sub-district HIV/TB coordinator).

Levels of understanding among primary providers as to the rationale behind the directives ranged from a vague notion that the implant should simply not be used on '*chronic*' clients (including those infected with HIV), to, *'I'm not sure which one, exactly, the ARV that is contraindicated with this [Implant] …*' to, '*We were told the efavirenz, it lowers the effectiveness - we were told, but how? I never went through it, or understood it quite clearly',* to*, 'They say, it's contraindicated with the drugs that they're using, and that person can still fall pregnant when they are using the Implanon [NXT®], because it is not stronger than the three-months injection'.* While some providers had recently observed HIV-positive women coming from maternity units with implants newly inserted, or otherwise had awareness of the WHO's MEC recommendations, all were reluctant to provide implants in the context of HIV infection pending clear, updated instructions from the National Department of Health. Fear of legal issues was a concern, especially if any increased risk of harm to the client was perceived. One nurse outlined his apprehensions: *'It's not that I'll find it difficult to insert, but at the end of the day I'll be held accountable. Anything bad that may happen… some may lay charges, you know?*' (professional nurse).

In contrast with primary providers, specialist providers and other stakeholders had greater awareness of the evidence surrounding the National Department of Health's recommendations, and viewed it in accordance with their own understandings of the risks and benefits of providing implants in the context of HIV and ART. Specialist providers generally endorsed explaining increased risk of contraceptive failure and the importance of dual protection using condoms in addition to the implant, rather than denying the implant as an option altogether for clients on EFV-based ART regimens. In justifying this, they cited the WHO's MEC, the original 2012 guidelines which emphasize the importance of giving all women (including

HIV-positive women) choice, and evidence indicating higher comparative failure rates of most other available methods. One specialist provider had written letters for her clients to take along to their primary providers once the decision to keep or initiate the implant had been made: *'Ultimately, I've written letters for clients, so they can carry it with them, because they go to the clinic and clinic says, 'No, you must have that out!'* (Specialist family planning provider).

Family planning services offered to HIV-positive women

The three-month depot medroxy progesterone acetate (DMPA) injection was considered by primary providers at three of the four clinics to be the only appropriate contraceptive method for HIV-positive women, while DMPA was offered alongside the Cu-IUD to HIV-positive women at the fourth. Although one of the three clinics only offering DMPA did have providers certified to insert IUDs (the other two did not), providers there were nonetheless reluctant to insert them, as '*most people are not suitable for IUDs'* (professional nurse). Another provider at one of the two other clinics had received training but had deliberately not pursued certification, deciding that, after seeing clients experience severe pain and infection, and insertion procedures taking up to an hour and a half, *'I said, 'no, man – not for me. It's fine, the doctor will do that*' (professional nurse). All facilities recommended the correct and consistent use of condoms to HIV-positive women regardless of the non-barrier method used.

Provider Capacity and Integrated Service Delivery

Some participants in Group A observed that primary providers in the public sector did not always have the time nor the capacity to provide comprehensive counselling and choice of contraceptive methods to their clients, especially LARCs, in the context of rendering integrated services: *'The family planning sister must do everything… it's more like a one stop shop that we're currently busy doing. So, there are some services that you are going to neglect… When you're there, and I must put in an Implanon [NXT®], and I know there's a sick child – I must still see the sick children. I'm not going to put in the Implanon [NXT®],*

I'm going to opt for something else. It won't be the client's choice, it will be the provider's choice, because of the clients that must still be seen' (professional nurse).

This issue with integrated service delivery was also acknowledged by several stakeholders, with one OB/GYN concerned that primary providers were over often overburdened by the responsibility to *'understand every single detail about every single condition that they're dealing with'* (OB/GYN). He believed it was '*impossible*' to expect providers to properly retain and convey that all necessary information to clients during single consultations, and still make time to facilitate something like informed contraceptive choice.

Some stakeholders also noted that, particularly in areas where there was limited provider training, they had observed a culture of simplified rule-following sometimes developing as a means of alleviating the burden of wide-ranging responsibilities, thereby enhancing the ability for providers to make efficient decisions: '*So, a lot of the clinicians are doing things that they aren't necessarily fully trained and equipped for, particularly the nurse clinicians, and so, they adopt one rule, and that's just the way it happens*' (clinical pharmacologist). In the specific case of the implant/EFV directives, *'I do think it's probably easier just to take out the implant – you just learn the rule and then you follow it'* (HIV clinician).

Participant suggestions for future contraceptive policy-making and service delivery initiatives

During interviews, stakeholders and primary providers made various recommendations for improving contraceptive choice and service delivery to HIV-positive women in South Africa.

Policy-making recommendations

At the policy-making level, participants emphasized the need for taking more time to consult with different stakeholder groups, particularly in less urgent circumstances where available evidence does not indicate there is any immediate physical danger associated with an intervention or service. Summarizing

this sentiment, one clinical researcher thought it was necessary to 'first, make an assessment of… how quickly do we need to move on this?' then, if time allows, *'put a good task team together that includes both international – perhaps WHO – as well as local stakeholders, as well as the core beneficiaries and healthcare workers who are at the rock face. Bring them in, have a conversation around not only, 'what does the data show?' and 'what do we need to do?', but, 'what are the alternatives?', and, finally, 'what would our various intervention scenarios turn into?' So, a good appraisal of what the unintended consequences are'* (clinical researcher).

In line with this was advice from another stakeholder to put in place a system of policy 'panel-beating', a strategy she used in her own work as a health manager to help ensure distributed information was interpreted and implemented as intended: *'Policymakers must be very careful about how they word their warnings and guidelines, et cetera. They would improve a lot if they had things read and interpreted by somebody else. Sometimes, I get something, and I see it one way, and then somebody else reads it another way… so, I frequently call on the secretary, the cleaner, the clerk, and say, 'Okay, read this for me, what did you understand?'* (health manager).

Provider training recommendations

Several stakeholders perceived significant gaps in primary provider knowledge about family planning in general, as well as particularly inadequate implant training. Retraining should start with revisiting the foundations of the menstrual cycle and go on to cover informed choice-centered contraceptive provision and counselling. With regard to eliminating misunderstanding surrounding the implant and HIV, this advice was directed at both nurses and physicians, including HIV clinicians: '*So the recommendation, it's basically to train your healthcare providers who provide family planning again. Also, HIV clinicians, because a lot of the people who get referred to the family planning clinic to take the implant out come from the HIV clinics'* (OB/GYN).

Stakeholders also noted an issue that complicated the initial implant rollout out whereby, '*there was an assumption that doctors don't need training'* (women's health director), and, when it came to incorrect insertions, '*doctors are worse than nurses'* (specialist provider). Nurses who had received training to become implant trainers themselves had also reportedly been forbidden from training doctors. A women's health director mentioned that, *'I'm talking about Heads of Gynae[cology], especially at one of the hospitals, that decided, no, a nurse will not train a doctor',* before adding*, 'the bureaucracy and hierarchy of this whole thing doesn't benefit the client in any way*' (women's health director). Aware of the respect doctors that command in the community, professional nurses in Group A also raised similar concerns: '*The doctors need to be educated because our people have faith in them… What is said by the doctors, they believe it. Who is a nurse compared to a doctor?*' (professional nurse).

Counselling recommendations

Counselling was viewed as more important than meeting government numerical targets for method coverage, with both stakeholders and primary providers expressing frustration that '*pushing for numbers*' in the case of the implant rollout had ultimately compromised the ability for clients to choose the method for themselves. It was advocated that patient-provider contraceptive decision-making, especially in the context of HIV infection, should be centered around facilitating mutual trust. In the words of one family planning trainer, *'the client should not be forced to take any type of contraception. You open the shop, educate the patient, and let the client choose what she thinks would suit her'* (family planning trainer).

Another specialist provider observed that, '*sometimes there's this distrust of the healthcare provider, like, they are trying to infringe on [HIV-positive women's] reproductive rights* (OB/GYN). To remedy this, she recommended explaining to clients that contraception was not just about preventing pregnancy, but about assisting women to achieve the family size they desire, however large, while safeguarding both

their own and their children's health: '*If you want to have 10 kids, you can have 10 kids, but I want you to have 10 planned kids with the best possibility of survival. And that you are healthy.'*

The theme of building trust and facilitating choice also emerged as a necessary area for improvement in primary provider interviews, especially when it came to offering long-acting options such as the implant. One primary provider explained that, *'we [providers] have this way of, you know, subtly forcing them to take something, and ultimately, they walk out and they're angry with you as a nurse, as a facility. They're angry because you've given them something that they didn't want, and a three-year device is…it's a three-year device. So, irrespective of if they have HIV or they don't have HIV, I think if the client has the knowledge and consent – we need to treat clients as if they were adults'* (professional nurse).

The majority of primary providers interviewed did, however, emphasize that they wanted to and tried to put time and effort into fully and appropriately counselling their clients. One primary provider, who counselled mostly adolescent girls and young women, liked to ensure her clients were not only fully informed about the advantages and disadvantages of different methods, including potential side effects, but also asked them about their short, medium and long-term goals in life. She and her young clients would write these down together, so that they could then discuss how an unintended pregnancy might disrupt their chances' of achieving their goals: *'if you're not taking control of your body, you won't be able to reach these things, because there will be too many obstacles'* (professional nurse).

For determining a client's method options, participants favored the MEC wheel (when it was known to them, which wasn't the case for several primary providers), which was seen as a user-friendly and time-efficient equivalent to reading an '*entire text book'* (family planning trainer). Other recommended tools for explaining the efficacy, side effects, advantages and disadvantages of different available methods included language appropriate pamphlets, posters and videos in clinic waiting rooms and at ART adherence clubs. In order to overcome the difficulty of explaining comparative efficacy rates to those with

limited skills to interpret probability, one specialist provider had found success using a table that listed available methods alongside small icons of pregnant women to represent the number of pregnancies that might occur if 100 women were to use a method for one year. She suggested developing a similar visual aid to show comparative failure rates in the context of EFV-based ART.

Recommendations for restoring the implant's reputation and addressing community misinformation

There was a consensus among primary providers and stakeholders that there was a pressing need to address the implant's broader negative reputation amongst women and in communities. As one stakeholder cautioned, '*If we do not educate the public, then there is somebody who is going to educate, because life doesn't allow for a vacuum or a void'* (family planning trainer). With regard to the community response to the implant/EFV directives in particular, a health manager highlighted the importance of engaging HIV activist groups, who *'play a very important role in whether a method or system, or drug, or whatever, is going to be adopted or not. They are very strong activists, and most of them were scared that they had an Implanon [NXT®] inserted and they were on ARVs. They were first to rush, 'Please! Take it away, take away! What do you think they are going to tell the rest of the community?*' (health manager).

Discussion

This study adds to an existing body of literature about the provision of contraceptive implants to HIV-positive women, and also offers the first direct insight into the primary-care level implications of the South African National Department of Health's decision to recommend against implant provision to women taking EFV-based ART. Discussions with primary family planning providers revealed that, at all four clinics visited during the study, implants were not offered to HIV-positive women at all. Providers implemented the directives this way despite varying levels of awareness that the recommendation against implant use only concerned clients exposed to EFV. Providers responses corresponded with stakeholders' wider impressions of how the directives had been implemented in primary care settings across Cape Town.

Thematic analysis of the interview data suggested that a number of composite factors may have come together to lead primary providers to implement the directives as they did. Stakeholders who had been involved in the initial implant provider training programme recalled a process that had been rushed and poorly coordinated, and felt that it did not appropriately equip providers with the skills to counsel women about the new method. This sentiment surrounding training is reflected in available literature regarding the 2014 implant roll-out in South Africa [15, 17]. As is likewise described in the available literature [15, 17], early removal requests were reported by providers to have ensued not long after the first insertions took place, as many clients returned with concerns about side-effects, and fears regarding theories and anecdotes about the implant that had circulated in communities. Providers had thus already developed considerable scepticism about the suitability of the method for their clients in general by the time the implant/EFV directives were issued.

When the directives were received, the strength of their wording was also perceived by some participants to imply the possibility of physical harm associated with the implant's interaction with EFV, rather than just reduced contraceptive efficacy. Several participants also expressed doubt that many primary providers, under considerable pressure to provide integrated services in busy public sector clinical environments, could have realistically gained a nuanced understanding of the directive, given that it was just one update among many that they were expected to read, interpret, and implement. Adopting the simple and 'safe' rule that implants were broadly contraindicated with HIV infection was hence considered by some stakeholders to be in line with a strategy occasionally used by providers in integrated primary care settings, especially in areas where there was any perceived risk of harming clients or where provider training was limited.

A prominent concept in sociology theory suggests that the behavioral patterns of 'street-level bureaucrats', or civil servants who interact directly with members of the public, often fundamentally

shape the way policies associated with public services are implemented [28]. In the presence of structural pressures such as heavy workloads, time constraints, resource limitations, high client turnover, and training deficiencies, the capacity for individuals working on the ground to precisely interpret and implement incoming policies and updates may be compromised [29]. This predicament tends to result in the street-level bureaucrat implementing an informal, often simplified version of a policy as a 'coping strategy' [29]. Such coping behavior may have been particularly pronounced in the case of the implant/EFV directives, where it was perceived that a 'judgement call' may risk harm to a patient, or perhaps even result in legal action against providers, and also considering that providers already had doubts about the suitability of implants in general for their clients.

The potential these findings suggest for eroding contraceptive choice for HIV-positive women in South Africa is concerning. With over a fifth of reproductive-aged women in the country currently HIV-positive [6-8], a figure that in 2017 represents at least three million women [8], it is important to re-emphasize that the size of the population for which the implant/EFV directives may possibly have had consequences for is significant. It is also worth reiterating that the revisions made to the national contraception guidelines in 2012 specifically sought to be responsive to the sexual and reproductive needs and rights of all women, including HIV-positive women, and thus guard against such erosions of choice [2, 9, 10, 30]. South Africa's implant/EFV stance is currently unique among countries in its deviation from the present WHO MEC guidance [11]. Given impending changes to first-line ART regimens (such as the medium to long-term strategy to eventually replace EFV with dolutegravir (DTG) [31], which is a differently classed drug to EFV and is unlikely to be implicated in similar drug-drug interactions), it is critical that the South African policy environment is receptive to newly available literature on the topic, and is open to taking appropriate, evidence-based action where indicated to update guidance and to train healthcare providers accordingly.

Suggestions for improving the quality of contraceptive counselling and service provision to HIV-positive women were given at different levels and were objectively similar to recommendations made in existing literature [2, 15, 17]. From a policy-making perspective, it was suggested that, especially in circumstances where there is no indication of immediate physical harm associated with an intervention, sufficient time should be taken to conduct a full appraisal of evidence, stakeholder input, and possible unintended consequences of recommendations. Stakeholders at all levels, including primary providers and beneficiaries of services, should be consulted to ensure a policy has the best chance of being interpreted as intended. It was also suggested by stakeholders that primary providers, including clinicians, essentially be retrained – particularly in implant provision and counselling, but also at the foundational level in rights and choice-based family planning. For making counselling more time-efficient in busy clinical settings, standardized messages and decision-making tools, as well as user-friendly materials for clients to absorb at home and in clinic waiting rooms, were recommended. Combined with further engagement of community groups, the undoubtedly important message of reduced implant efficacy in the presence of EFV could be potentially be redelivered in a way that might be easier for providers and clients to understand, and that would still make room for informed client choice.

Limitations

This study was limited by its small sample size and containment within the Cape Town Metropolitan Area. However, participating primary clinics catered to a relatively broad cross-section of society, and specialist providers and government/academic stakeholders were deliberately chosen to represent a diversity of expertise and experience pertaining to HIV and/or contraceptive care and service delivery. Further investigations are nonetheless necessary to verify findings, in particular the suggestion that the implant may have been informally removed from the method-mix offered by primary providers to HIV-positive women in general. All interviews were conducted in English, which was not the first language of most

participants. A final but important limitation was that HIV-positive contraceptive users were not included in the study due to time and logistical constraints, and it is therefore strongly recommended that future research considers data collected from reproductive-aged HIV-positive women themselves.

Conclusions

The findings of this study suggest that the South African National Department of Health's 2014 recommendation against concurrent implant and EFV use may have had unintended consequences at the primary care level, including potentially depriving HIV-positive women generally of a safe, convenient and effective contraceptive method option. With the appropriateness of the recommendation against implant use in the context of EFV-based ART already under debate, these results underscore an urgent need for further investigation and evidence-based action on behalf of the South African National Department of Health. Thematic analysis of qualitative interview data found that the decision primary providers made not to offer implants to HIV-positive women likely did not occur in a vacuum: It was against a backdrop of earlier pitfalls in the implant provider training and launch phase, the implants increasingly negative reputation among women and in communities, as well as broader structural pressures on providers, that the 2014 practice change circular and technical brief were received, interpreted, and implemented. To ensure that the perceived possibility of client harm would be minimized, and under pressure to keep up to date with policies associated with the wide range of integrated services they offered, providers derived a simple and 'safe' rule from the implant/EFV directives that implants were generally contraindicated in the context of HIV, regardless of EFV exposure. It is possible that this was symptomatic of a 'coping behavior' traditionally observed among 'street-level bureaucrats' attempting to implement top-down policies in busy, stressful, and often under-resourced public sector service environments. A challenge for future research and policy output will be to develop training programmes and counselling tools that simplify and standardize the facilitation of informed contraceptive choice, particularly in busy integrated

service environments, as well as to adequately consult services beneficiaries and stakeholders at all levels during decision-making and policy development processes, such that distributed documents have the best chance of being interpreted as originally intended.

List of Abbreviations

ART	Antiretroviral therapy
(Cu-)IUD	(Copper) Intrauterine Device
DMPA	Depot Medroxyprogesterone Acetate
DTG	Dolutogravir
EFV	Efavirenz
HIV	Human Immunodeficiency Virus
MEC	Medical Eligibility Criteria
OB/GYN	Obstetrician/Gynaecologist
OC	Oral Contraceptive
TB	Tuberculosis
WHO	World Health Organization

Declarations

Ethical approval and consent to participate

Ethical approval to conduct this sub-study was granted by the University of Cape Town's Human Research Ethics Committee (HREC REF:654/2016). Ethical approval for the parent study, which included permission

by the City of Cape Town to conduct interviews at City-managed study sites, was also granted from the Human Research Ethics Committee at the University of Cape Town (HREC REF 718/2015) and the Research Ethics Committee at the University of the Western Cape (Registration no: 15/4/27). Written informed consent was obtained from all participants.

Consent for publication

Not applicable

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Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding authors upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

Anna Brown (AB) undertook data collection and conducted the analysis and drafted the manuscript under the supervisory guidance of Chelsea Morroni (CM) and Jane Harries (JH) as part of an Master of Public

Health dissertation. CM and JH contributed to study design and conceptualization and reviewed the drafted manuscript. All authors read and approved the final manuscript.

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Appendices

Appendix A: Primary Provider Research Invitation Flyer (Group A)

Research Invitation

May 2017

Dear Respected Healthcare Provider,

I would like to invite your voluntary contribution to the City of Cape Town-approved UWC/UCT collaborative research project: *'A formative study on the 2012 South African National Contraception Guidelines' implementation of new Long-Acting Reversible Contraceptive (LARC) methods in the Cape Town Metropolitan Area'* (6644) (Project ID 10560; Investigators: Prof Di Cooper, Prof Jane Harries and Dr Chelsea Morroni).

As a provider involved in HIV and/or contraceptive care, your input in particular would be highly valued for a sub-study associated with the project: *'Patient-provider decision-making in uptake, retention and discontinuation of etonogestrel implant in HIV-infected women in the Cape Metropolitan Area'*. The over-arching goal of this study to develop supportive, clear counselling messages and tools, so that providers like you are able to convey appropriate, evidence-based information in a time-efficient manner to your HIV-infected clients choosing between family planning methods.

Thank you for considering this invitation to participate in this project. Your contribution would take the form of a confidential 30-45 minute recorded interview and would take place from mid-May to June 2017 at your place of work at a time of your choosing (likely after 2pm during the quieter clinic hours).

I look forward to hearing from you and kind regards,

Anna Brown
Master of Public Health Candidate, UCT

On behalf of

Dr Chelsea Morroni,
Senior Lecturer, Women's Health Research Unit, School of Public Health and Family Medicine, UCT

PHONE/WHATSAPP EMAIL
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Appendix B: Sample Stakeholder Research Invitation Email (Group B)

Subject: **Invitation to participate in a sub-study of 'A formative study on the 2012 South African National Contraception Guidelines' implementation of new Long-Acting Reversible Contraceptive (LARC) methods in the Cape Town Metropolitan Area'**

Dear_____

I am writing to invite your contribution to the City of Cape Town-approved UWC/UCT collaborative research project '*A formative study on the 2012 South African National Contraception Guidelines' implementation of new Long-Acting Reversible Contraceptive (LARC) methods in the Cape Town Metropolitan Area*' (6644) (Project ID 10560; Investigators Prof Di Cooper, Prof Jane Harries and Dr Chelsea Morroni). Ethics approvals have been obtained from UCT and UWC.

As a policy-maker, stakeholder or provider involved in HIV and/or contraceptive care, your input in particular would be highly valued for a sub-study associated with the project: '*Patient-provider decision-making in uptake, retention and discontinuation of etonogestrel implant in HIV-positive women in the Cape Metropolitan Area'.* The over-arching goal of this study to develop supportive, clear counselling messages and tools, so that providers are able to convey appropriate, evidence-based information in a time-efficient manner to HIV-positive clients choosing between family planning methods.

Thank you for considering this invitation to participate in this project. Your contribution would take the form of a confidential 30-45 minute recorded interview to be conducted by myself, or my research associate Anna Brown (UCT masters candidate) and would take place in early 2017 at a time and location of your choosing.

I look forward to hearing from you and please do not hesitate to contact me for further information. It may be easier to speak by phone, so I am happy to phone you at your convenience to discuss and arrange.

Yours sincerely,
Chelsea

Dr Chelsea Morroni
Senior Lecturer, Women's Health Research Unit
School of Public Health and Family Medicine
University of Cape Town

Appendix C: Participant Consent Form

CONSENT FORM

Title of Research Project: *'THE SOUTH AFRICAN CONTRACEPTION AND HIV STUDY (SACHOICE): PATIENT-PROVIDER DECISION-MAKING IN UPTAKE, RETENTION AND DISCONTINUATION OF ETONOGESTREL IMPLANT IN HIV-INFECTED WOMEN IN THE CAPE METROPOLITAN AREA.'*

The University of the Western Cape and the University of Cape Town are currently talking to policy-makers and providers attending health centres/organisations to improve our knowledge and understanding of HIV+ women's use of Long Acting-Reversible Contraception methods, in particular the implant (*Implanon*). The over-arching goal of this study to develop supportive, clear counselling messages and tools, so that providers are able to convey appropriate, evidence-based information in a time-efficient manner to HIV-infected clients choosing between family planning methods. We have received permission from the Western Cape and City of Cape Town Departments of Health, and the managers at this centre to approach Health Care Providers and clients for interview in this study. We would like to ask your permission to interview you as one of those working in this policy area.

What is this research about?

We are talking to policy-makers, providers and their HIV+ clients about women's use of contraception, especially Long Acting-Reversible Contraception methods such as the implant (*Implanon*), and their use of contraceptive services. This is to improve our understanding of how contraceptive services that best meet clients' needs can be provided. We will use the information you give us to make some recommendations about implementing the guidelines for providing *Implanon*.

If you take part in the study

If you agree to take part in in this research, a trained researcher will ask you if are willing to be asked some questions and discuss your role in contraceptive provision and/or policy making including implant provision to HIV+ women. Our discussion will take up to an hour. The researcher will speak to you on your own. The interviews will be tape recorded with your permission, so that researchers can listen to it afterwards and write down everything you have said.

What could be some risks of taking part

You do not have to answer any questions or discuss any subject or issue that you are not comfortable discussing.

Taking part and withdrawing

Even if you have signed and agreed to take part in the study, you have a right to say that that you no longer want to take part in the study at any time. Also, if you choose not to take part in the study or if you decide that you no longer want take part in the study once you have agreed, it will not affect your work as a provider or policy maker.

What some of the benefits of the research may be

You may not benefit directly from taking part in this study; but, by doing this study, we hope to understand better women's needs for contraceptive methods. We will use the information you give us to make some recommendations about implementing the guidelines for providing *Implanon* to HIV+ women. Hopefully we will be able to make it a little easier and faster for providers to render good quality family planning services to these clients.

Keeping this private and with no names

If you give your permission to take part in this study, we would like you to know that:

(a) You will be given a number rather than your name being use in the research

(b) Your name and all other personal information will be stored under that number, so that no one knows the information is about you as a person by name

(c) We will use your views, feelings, opinions and so on in the research only

(d) Only the researcher and those interviewing you will know any individual information we get from you and this will be kept private in a safe place at all times.

Who are we if you need to contact us

If you have any questions or worries about the research, please feel free to contact or the persons leading this study at UCT.

Anna Brown

Tel: +27 (0) 60 731 2035
Email : annaihbrown@gmail.com

Dr Chelsea Morroni
Email: chelseaamorroni@gmail.com

Prof Jane Harries
Email : jane.harries@uct.co.za

If you have questions or worries about your rights while you are taking part in the study, please contact:

School of Public Health and Family Medicine
Faculty of Health Sciences
University of Cape Town
Anzio Road, Observatory, Cape Town, 7925
Contact:+27 (0) 21 406 6300

This research has been approved by the University of Cape Town's Human Research Ethics Committee

SIGNATURES

The study has been described to me in language that I understand. My questions about the study have been answered. I understand what my participation will involve and I agree to participate of my own choice and free will. I understand that my identity will not be disclosed to anyone. I understand that I may withdraw from the study at any time without giving a reason and without fear of negative consequences or loss of benefits.

Participant's name.....

Participant's signature..... **Date**.....

Researcher

I have read this document to the participant, in Isi-Xhosa, Afrikaans or English or given this to them to read. I have tried to answer her /his questions to the best of my knowledge.

Date:_____ Signature of Researcher:_____

Appendix D: Primary Provider Interview Guide (Group A)

Question Guide: In-depth interviews with healthcare workers

The aim of this interview is to build an understanding of how providers perceive their role in ensuring effective delivery of contraceptive care to HIV-positive women clients, and to extract ideas and recommendations as to how such guidelines and care might be improved in the future. The questions will explore providers' perspectives on current clinical guidelines and practice with respect to Long-Acting Reversible Contraceptive (LARC) provision the context of HIV care and are designed to elicit responses that will first demonstrate the interviewee's understanding of the LARC options available to women in general, and their knowledge and views as to their use in HIV-positive women in particular. The questions will further go on to explore the more specific issue of implant provision in the context of HIV and the first-line anti-retroviral drug efavirenz. We would like to capture interviewees' perceptions of how the 2012 guidelines and subsequent policy-directives have translated into their practice, whether they believe that the relevant information has been adequately disseminated, and if they have noticed any shortcomings or confusion surrounding the recommendations - whether personally, among their colleagues, or amongst their clients.

The interview will be administered flexibly to ensure that relevant aspects that the participant feels to be important are discussed.

For interviewer: The questions below are a guide to relevant topic areas and do not represent definitive questions to be asked.

Appendices

1. Consent forms administered and signed

2. Let's first discuss your role as a health care provider. Can you briefly describe your job and the contraceptive and/or HIV services you offer your women clients?

3. What do you think about the Long Acting Reversible Contraceptives, like Implanon and IUDs, that introduced in the Contraceptive Policy and Clinical Guidelines that were launched in 2014? What are your general impressions of them and how were they introduced to you and other staff?

4. Which LARC options have you been trained to provide in this clinic? Do you believe these options have been successfully introduced in your practice?

5. What advice have you been instructed to give HIV-positive women with regard to Implanon and IUDs?

6. Can you describe for me your view of how this information was communicated to you? Did you or any of your colleagues experience any confusion or misinterpretation surrounding the advice about Implanon and IUDs?

7. We are interested in your suggestions as to ways to potentially streamline and simplify the contraceptive decision-making process for women with HIV. Do you have any suggestions for tools that might help providers give good quality and time-efficient family planning advice regarding Implanon to women with HIV?

Appendix E: Other Stakeholder Interview Guide (Group B)

Question Guide: In-depth interviews with stakeholders

The aim of this interview is to explore stakeholders' perspectives on current clinical guidelines and practice with respect to Long-Acting Reversible Contraceptive (LARC) provision the context of HIV care. The questions are designed to elicit responses that will first demonstrate the interviewee's understanding of the LARC options available to women in general and their knowledge and views as to their use in HIV-positive women in particular. The questions will then go on to explore the more specific issue of implant provision in the context of HIV and the first-line anti-retroviral drug efavirenz. We would like to capture interviewees' perceptions of how the 2012 guidelines and subsequent policy-directives have translated into practice, whether they believe that the relevant information has been adequately disseminated to providers, and if they have noticed any shortcomings or confusion surrounding the recommendations.

The interview will be administered flexibly to ensure that relevant aspects that the participant feels to be important are discussed.

For interviewer: The questions below are a guide to relevant topic areas and do not represent definitive questions to be asked.

1. Consent forms administered and signed

2. First could you briefly describe your job for me, and specifically your role in contraceptive provision and/or HIV care?

3. Did you personally have any involvement in the development of the revised Contraceptive Policy and Clinical Guidelines that came out in 2012 and were launched in 2014? If so, what was your involvement?

4. What were your general impressions of the guidelines and how do you think they have since translated into clinical practice?

5. What is your understanding of the new Long-Acting Reversible Contraceptive methods that were made available to women as per the new guidelines, and do you believe the rollout of these options has been successful in the Cape Metropolitan Area?

6. What are the implications, if any, that you believe the guidelines have had for LARC provision to HIV-positive women in particular?

7. *(If not already discussed)* Are you aware of the 2014 recommendations by the Department of Health surrounding a demonstrated drug-drug interaction between the contraceptive implant and certain enzyme-inducing agents, including the anti-retroviral drug efavirenz? If so, what is your understanding of this interaction and its implications for HIV-positive women choosing between family planning methods?

8. Can you describe your view of how this information has been communicated to providers such as yourself, and also subsequently to HIV-positive women clients? Specifically, are you aware of any provider or client confusion or misinterpretation surrounding the advice?

9. We are interested in your suggestions as to ways to potentially streamline and simplify the contraceptive decision-making process for women with HIV. Do you have any suggestions for tools that might help providers give good quality and time-efficient family planning advice regarding Implanon to women with HIV?

Appendix F: Ethical Clearance

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

11 October 2016

HREC REF: 654/2016

Dr C Morroni
WHRU
Public Health & Family Medicine
Falmouth Building

Dear Dr Morroni

PROJECT TITLE: THE SOUTH AFRICAN CONTRACEPTION AND HIV STUDY (SACHOICE): PATIENT-PROVIDER DECISION-MAKING IN UPTAKE, RETENTION AND DISCONTINUATION OF ETONOGESTREL IMPLANT IN HIV-INFECTED WOMEN IN THE CAPE METROPOLITAN AREA (Masters' candidate-A Brown)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the proof of concept for phase 1 of the above-mentioned study.

Approval is granted for one year until the 30th October 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

We acknowledge that the student A Brown will be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

pp T Burgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Appendix G: Journal Style Guide

BMC Public Health Research article

Criteria

Research articles should report on original primary research, but may report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research will not be considered.

BMC Public Health strongly encourages that all datasets on which the conclusions of the paper rely should be available to readers. We encourage authors to ensure that their datasets are either deposited or in publicly available repositories (where available and appropriate) or presented in the main manuscript or additional supporting files whenever possible. Please see Springer Nature's information on recommended repositories.

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
    - or for non-clinical or non-research studies a description of what the article reports
- list the full names, institutional addresses and email addresses for all authors
    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed, and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and material
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval.

See our editorial policies for more information.

If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

See our editorial policies for more information on consent for publication.

If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

Appendices

All manuscripts must include an ‘Availability of data and materials’ statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analyzed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognize it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

- The datasets generated and/or analyzed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
- All data generated or analyzed during this study are included in this published article [and its supplementary information files].
- The datasets generated and/or analyzed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current

study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].

- Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

More examples of template data availability statements, which include examples of openly available and restricted access datasets, are available here.

BioMed Central also requires that authors cite any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier (such as a DOI) and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs. For example:

Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analyzed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]

Competing interests

All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

Please use the authors initials to refer to each author's competing interests in this section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies.

Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

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Authors' information

This section is optional.

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. The reference numbers must be finalized, and the reference list fully formatted before submission.

Examples of the BioMed Central reference style are shown below. Please ensure that the reference style is followed precisely.

See our editorial policies for author guidance on good citation practice.

Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link (e.g. for blogs) they should be included in the reference.

Example reference style:

Article within a journal

Smith JJ. The world of science. Am J Sci. 1999;36:234-5.

Article within a journal (no page numbers)

Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. BMC Med. 2013;11:63.

Article within a journal by DOI

Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement

Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Book chapter, or an article within a book

Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.

OnlineFirst chapter in a series (without a volume designation but with a DOI)

Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Complete book, authored

Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Online database

Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

Supplementary material/private homepage

Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

Organization site

ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.