CURRICULUM VITAE

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Education

2017 – 2021	University of Maryland School of Medicine, Baltimore
	Graduate Program in Life Sciences
	Department of Epidemiology and Public Health
	Doctor of Philosophy (Fall 2021)
2007-2010	University of Ilorin, Ilorin, Nigeria
	Post Graduate School
	Department of Epidemiology and Community Health
	Faculty of Clinical Sciences
	Master of Public Health
1998-2005	University of Ilorin, Ilorin, Nigeria
	College of Health Sciences
	Bachelor of Medicine, Bachelor of Surgery

Employment History

University of Maryland School of Medicine, Baltimore, MD

August 2017 to August 2021

Fogarty Fellow / Graduate Research Assistant

- Conducted literature reviews, conceptualized hypotheses, planned, formulated and executed statistical analysis plans
- Scientific writing, proof reading and publishing
- Conducted patient enrollment for a multicenter randomized non-inferiority trial of alcohol based hand- rub from University of Maryland Medical Center (PI Dr Thom Kerri)
- Conducted analytical queries for the severity of illness study
- Data validation using the University of Maryland Medical System patient database to run queries
- Peer reviewed for PLOS One(3) and BMC Infectious Diseases journals(4)
- Provide support to International Research Center of Excellence, Institute of Human Virology, Nigeria
- Provided support for grant writing (IMPART TRUST study)
- Dissertation Topic: Behavioral and Social Support Effects on Daily Oral Pre-exposure Prophylaxis use among men who have sex with men in Nigeria

Institute of Human Virology, Nigeria

February 2016 – August 2017

Senior Program Officer (Clinical)

Regional TB-HIV and Drug Resistant TB Coordinator

- Coordinated TB-HIV and Drug Resistant-TB (DR-TB) activities in the capital city (FCT), Nigeria where TB annual incidence was 219/ 100,000 persons
- Led weekly TB-HIV reports for all Quality Improvement Teams (QIT) in the FCT region
- Coordinated logistics of TB prevention, screening, diagnostics and treatment.
- Represented the region in TB-HIV and DR-TB stakeholders meetings
- Conducted needs assessment in TB-HIV/ DR-TB program and facilitated timely responses
- Supervised the activities of the TB-HIV referral coordinators in CDC priority local government areas (equivalence of US districts)
- Led the team that coordinated field activities of the Global fund supported DR-TB program in North central Nigeria at National Tuberculosis and Leprosy Training Centre (NTBLTC), Saye, Zaria.

Clinical Associate

- Directed the technical and administrative support of 18 facilities; 5 Comprehensive ART sites and 13 Primary Health Care Facilities in FCT region.
- Served as a quality of care ombudsman to ensure all patients in facilities supported gets high quality of HIV related services care
- Coached and mentored site staff, focal persons and IHVN staff to effectively address operational challenges
- Provided onsite clinical mentoring and technical assistance to facility staff
- Supervised site programmatic quality of care assessment
- Conducted clinical needs assessment for antiretroviral therapy
- Led didactic training for health care providers on antiretroviral therapy
- Performed quality improvement and program evaluation, monitoring and administrative support

Quality Improvement Team (QIT) Lead

- Planned and coordinated daily activities of the team that supervised 20 hospitals
- Allocated and followed up on timely delivery of work packages with teams
- Facilitated communication, collaboration and task sharing among the team
- Led weekly and adhoc meetings for the team
- Coached and mentored team members on and off- the jobs
- Coordinated, reviewed and edited weekly and monthly report submission
- Presented weekly project activities trackers for the team in regional meetings
- Coordinated site activities of team members

Institute of Human Virology, Nigeria

January 2013 – February 2016

Project coordinator, INSPIRE-MoMent PMTCT study

- Actively tracked and flagged deviations from research protocol implementation
- Developed and maintained study protocols and standard operation procedures.
- Ensured ethical conduct of study, including maintenance of participant safety
- Supervised and provided technical support to research assistants, data manager and data clerks
- Monitored progress towards study goals and reported the progress at routine study meetings
- Proposed and negotiated alternatives to improvement of protocol implementation
- Monitored and tracked project field activities including patient enrollment, follow up and documentation of all activities
- Actively trouble shot and provided pragmatic stopgaps for urgent challenges from the field
- Prepared periodic and ad hoc progress reports as required by Principal Investigator, funding agencies, and / or regulatory bodies.

- Attended research team meetings with national and international study stakeholders and actively participated in subject matter expert (SME) reviews
- Organized and facilitated weekly research team meetings with the principal investigators and all research staff
- Monitored study team compliance with Good Clinical Practice (GCP) standards and updates of all required ethical requirements
- Collaborated with data manager to develop case report forms and validated the completion of the forms by research assistants from the field
- Performed a random validation of data entry into database routinely to continuously assess the quality of data inputs
- Conceptualized, wrote, revised, edited and proof read and developed abstracts and published manuscripts

Excellence and Friends Management Consult Ltd (EFMC)

October 2011- December 2012

Project Manager; Clinical Care

- Coordinated the clinical care unit (ART, TB-HIV and Laboratory) activities of EFMC/ARISE Project
- Coordinated the overall antiretroviral therapy strategy and implementation of related activities within the project
- Provided technical direction in design and implementation of activities to supported clinical teams and facilities
- Participated and represented EFMC in stake holders ART/TB-HIV activities
- Set up high quality ART and TB-HIV services in line with laid down Government of Nigeria and partner expectation ensuring it's implemented effectively by the key stake holders
- Routinely provided supervisory mentoring visits to all EFMC supported comprehensive ART delivery facilities
- Provided technical support in areas of ART/TB- HIV for all EFMC supported sites
- Routine mentored and built the capacity of unit members
- Timely reported all unit activities to relevant stakeholders
- Coordinated regular supply of ARVs and relevant commodities to all EFMC supported facilities

St Gerard Catholic Hospital, AIDSRELIEF Project

February 2008- September 2011

Antiretroviral Therapy (ART) Clinical Officer / Team lead

- Managed approximately 3,500 HIV patients in an AIDSRELIEF -supported ART clinic
- Challenged and improved the HIV knowledge base of my team by more than 50% with active learning on and off the job
- Mentored and supervised all newly engaged medical doctors
- Actively followed up on the supplies and logistics for clinic running
- Set up and expedited ART switch committee meetings
- Set up and executed a monthly continuous quality improvement plan targeted towards the weakest links of our clinics

Peer reviewed Publications (Reverse chronological order)

1. **Adeyemi OA,** Mitchell A, Shutt A, Crowell T, Ndembi N, Kokogho A, Ramadhani HO, Robb ML, Baral SD, Ake JA, Charurat ME, Peel S, Nowak RG, Hepatitis B virus infection among men who have sex with men and transgender women living with or at risk for HIV: a cross sectional study in Abuja and Lagos, Nigeria. *BMC Infect Dis*. 2021;21(1):654. doi:10.1186/s12879-021-06368-1

2. **Adeyemi OA,** Itanyi IU, Ozigbu CE, Stadnick N, Tsuyuki K, Olayiwola O. Ogidi AG, Eze C, Aarons GA, Onoka CA, Ezeanolue EE, Sero-prevalence and determinants of Hepatitis B among a cohort of HIV-infected women of reproductive age in Nigeria. *PLoS One*. (2020) doi:10.1371/journal.pone.0236456

3. Sam-Agudu NA, Aliyu MH, **Adeyemi OA,** Oronsaye F, Oyeledun B, Ogidi AG, Ezeanolue EE, Generating evidence for health policy in challenging settings: lessons learned from four prevention of mother-to-child transmission of HIV implementation research studies in Nigeria , *Heal. Res. Policy Syst.* 16 (2018) 32. https://doi.org/10.1186/s12961-018-0309-x.

4. Sam-Agudu NA, Isah C, Fan-Osuala C, Erekaha S, Ramadhani HO, Anaba U, **Adeyemi OA,** Obadiah GM, Lee D, Cornelius LJ, Charurat M, Correlates of facility delivery for rural HIV-psoitive pregnant women enrolled in the MoMent Nigeria prospective cohort study, *BMC Pregnancy Childbirth*. 17 (2017) 227. http://doi.org/10.1186/s12884-017-1417-2.

5. Al-Mujtaba M, Cornelius LJ, Galadanci H, Erekaha S, Okundaye JN, **Adeyemi OA,** Sam-Agudu NA, Evaluating Religious Influences on the Utilization of Maternal Health Services among Muslim and Christian Women in North-Central Nigeria, *Biomed Res. Int.* 2016 (2016) 1-8. https://doi.org/10.1155/2016/3645415.

6. Sam-Agudu NA, Cornelius LJ, Okundaye JN, **Adeyemi OA**, Isah HO, Wiwa O, Adejuyigbe E, Galadanci H, Afe AJ, Jolaoso I, Bassey E, Manhattan C, The Impact of Mentor Mother Programs on PMTCT Service Uptake and Retention-in-Care at Primary Health Care Facilities in Nigeria, *JAIDS J. Acquir. Immune Defic. Syndr.* 67 (2014) S132-S138. https://doi.org/10.1097/QAI.0000000000000331.

Abstracts

1. **Adeyemi OA**, Crowell T, Peel S, Ndembi N, Shutt A, Baral S, Charurat ME, Nowak RG: Hepatitis B virus and risk factors among HIV+ and HIV- Nigerian men who have sex with men. Poster presentation at the 20th International Meeting of the Institute of Human Virology, Baltimore, Maryland, United States. October 22- 25, 2018.

2. Fan- Osuala C, **Adeyemi OA,** Isah C, Sam-Agudu NA : Quality assessment of PMTCT data documentation among users and non-users data clerks in a Nigerian PMTCT program. Poster Presentation at the 8th annual CUGH Global Health Conference, Washington, DC, 7-9th April, 2017.

3. Isah C, Ogum E, **Adeyemi OA**, Yunusa F, Erekaha S, Sam- Agudu NA. Turnover Of Mentor Mothers In a Rural Nigerian PMTCT Program: Implications for HIV Peer Counsellors in Resource Limited Settings. Presented as a Poster in Pediatric Academics Society Conference, Baltimore, USA, April 30- May 03, 2016

4. **Adeyemi OA**, Erekaha S, Ogum E, Yunusa F, Swomen H, Barde H, Chime C, Ebagua I, Sam-Agudu NA. Viral load sample logistics for HIV positive women in rural settings: Experience from the INSPIRE MoMent Nigeria PMTCT study. Poster presentation at the 21st International AIDS conference, Durban, South Africa, 18 -22 July, 2016

5. Fan- Osuala C, Anaba U, Isah C, Obadiah GM, Bathnna M, Nta I, Erekaha S, **Adeyemi OA**, Omari H, Charurat M, Sam-Agudu NA. Health Facilty Delivery and Presence of Skilled Birth Attendant at Delivery among HIV- Positive Pregnant Women in a Mentor Mother Program. Poster Presentation at the 2nd Nigeria Implementation Science Alliance (NISA) conference, September, 15 -16, 2016.

6. Isah C, **Adeyemi AO**, Anaba U, Obadiah GM, Fan-Osuala C, Bathnna M, Nta I, Erekaha S, Omari H, Charurat M, Sam-Agudu N. The MoMent Study: Baseline Characteristics of HIV-Positive Pregnant Women Attending Antenatal Care Clinics in Rural North- Central Nigeria.Poster Presentation at the 2nd Nigeria Implementation Science Alliance (NISA) conference, September, 15-16, 2016.

7. Sam- Agudu NA, **Adeyemi OA** , Lufadeju Adejuyigbe E, Isah C, Swomen H, Yunusa F, Adamu G, Ajavu-Nyior J, Galadanci H, Isah H, Jolaoso I, Charurat M. Engaging Mentor

Mothers In a PMTCT Intervention Program In Rural North- Central Nigeria. Poster Presentation at 6th Annual Consortium Of University For Global Health (CUGH), Boston USA, March 25-28, 2015

8. Sam Agudu NA, Oyeladun B, **Adeyemi OA**, Bigirimana F, Oronsaye F, Oyelade T, Odoh D, Anyaike C, Newman N. The challenges of Conducting Implementation Research in a Highly Unstable environment: Experiences from the INSPIRE Nigeria PMTCT studies. Poster presentation at the International Conference Of STI and AIDS (ICASA), Harare, Zimbabwe, Nov 29- Dec 4, 2015.

9. Sam-Agudu NA, Cornelius LJ, Okundaye JN ,**Adeyemi OA**, Isah CA, Isah HO, Lufadeju F, Adejuyigbe E, Charurat M. The MoMent Study: Acceptability of Mentor Mothers as a PMTCT Intervention In Rural North- Central Nigeria. Poster presentation at International Workshop on HIV Treatment, Pathogenesis in Resource Setting, (INTEREST), Lusaka, Zambia, May 5-6 2014.

10. **Adeyemi OA**, Isah HO, Al-Mujtaba M, Isah C, Adeniyi T, Okundaye JN, Llewellyn LJ, Sam-Agudu NA. Determinants of PMTCT Service Uptake In Northern Nigeria: Family Unit As a Focal Point. Poster presentation at International Conference Of AIDS and STI in Africa (ICASA) Cape Town, South Africa, December 7-11, 2013.

Honors and Awards

Jan 2017

Fogarty International Scholar Award For Excellence In Academics And Employment Records by the Institute of Human Virology, School of Medicine University of Maryland, Baltimore

May 2018

Renee Royak-Schaler Memorial Endowment Award For Excellence In Academic Work and Research In Underserved Population And Women's Health Behavior by the department of epidemiology and public health, University of Maryland, Baltimore

Professional Society Membership

2005- Present	Medical and Dental Council of Nigeria
2005 –Present	Nigeria Medical Association
2010- Present	International AIDS society
2013- Present	American Academy of HIV Medicine (AAHIVM)

Services

Project development:

2012	Pioneered Comprehensive HIV/ AIDS portfolio in an indigenous PEPFAR implementing partner (Excellence and Friends Management Consult, Ltd)

Administrative Service

2011	Team Lead, AIDSRELIEF PEPFAR Project
2012	Team Lead, Clinical Unit, EFMC
2012	Board Member, Excellence and Friends Management Consult, Ltd
2013	Project Coordinator, INSPIRE-MoMent study
2016	QIT Lead / TB-HIV FCT Regional Lead

Institutional

2011-2102	Interviewer, Excellence and Friends Management Consult Ltd
2013-2016	Interviewer, INSPIRE-MoMent Study, IHVN.
2016-2017	Clinical Associate, Institute of Human Virology, Nigeria (IHVN)
2017- 2021	Graduate Research Assistant, Institute of Human Virology, School of Medicine, UMB.
2018- 2021	Teaching Assistant, Graduate Program in Life Sciences, UMB.

Voluntary

2019-Present	Peer reviewer, PLOS One and BMC Infectious Diseases journals.
2021-Present	Development of curriculum learning modules for AAHIVM

Teaching Service

Fall 2018	Teaching Assistant, PREV 621 – **Bio statistical Methods**
	Weekly office hours for students
	Graded weekly Assignments
	Proctored Mid- Semester and Final Exams
	Managed course grading on blackboard
Fall 2019	Teaching Assistant, PREV 723 – **Survival Analysis**
	Graded Weekly assignments
	Organized weekly office hours to meet with students
	Managed course grading on blackboard
Spring 2020	Teaching Assistant, PREV 801- **Analysis of longitudinal and clustered data**
	Graded Weekly assignments
	Organized weekly office hours to meet with students
	Managed course grading on blackboard

Fall 2020	Teaching Assistant, PREV 701 – **Cancer Epidemiology and Prevention**
	Graded Weekly mid-semester and finals
	Provided feedback to students on graded
	Organized weekly office hours to meet with students
	Managed course grading on blackboard
	Set up invitation for guest lecturers
	Managed Grade tracker for in-class student activities performance
Spring 2021	Teaching Assistant, PREV 803 – **Clinical Trial and Experimental Epidemiology**
	Provided technical assistance to student as they developed their concept sheet
	Provided technical assistance to student as they developed their protocols
	Provided guidance for students during weekly workshops

Software Skills

Statistics:	SAS, STATA
Microsoft office:	Word, Excel, Power Point, Outlook

Abstract

Dissertation Title: Behavioral and Social Support Effects on Daily Oral Pre-exposure Prophylaxis use among men who have sex with men in Nigeria

Olusegun A. Adeyemi, Doctor of Philosophy, 2021

Dissertation directed by:

Man Charurat, Ph.D, MHS
Min Zhan, Ph.D
Nadia Sam-Agudu, MD
Sylvia Adebajo, MD, PhD
Daniel Morgan, MD, MS
Rebecca Nowak, Ph.D, MPH
Jaih Craddock, Ph.D MSW

Introduction: HIV incidence among men who have sex with men (MSM) in Nigeria was 5.8-23.1/100 person years (PY) in 2019, exceeding the ≥ 3/100 PY recommended by the WHO for initiation of HIV pre exposure prophylaxis (PrEP).

Objectives: To estimate the correlation between self-reported PrEP adherence (SRPA) and PrEP biomarkers (assay), to assess the association between perceived social support (SS) with protective PrEP adherence (PA), and to estimate the effect of PrEP use on behavioral outcomes.

Methods: In this open-label, one-year follow-up, prospective cohort study, MSM living in Abuja were introduced to PrEP in clinic or community based setting for five scheduled visits (baseline, months 1, 3, 6, and 9). Clinical information and sexually transmitted infection (STI) samples were collected at each study visit. PrEP biomarker assays were conducted at month 3 and 9. The correlation between SRPA and assay results was estimated with

Spearman's correlation. Logistic regression estimated adjusted odds ratio (aOR) between SS (informational, instrumental and informational) and PA. A conditional logistic regression estimated aOR of STIs (Rectal and urethral Gonorrhea [NG] and Chlamydia) of behavioral outcomes (Condomless anal intercourse [CAI] and concurrent sex partnerships) comparing pre-PrEP versus Post-PrEP period.

Results: Of 400 that initiated PrEP between April 2018 and May 2019, 219 had ≥1 assay, with median age 23 (interquartile range 20-27) years. Of this 219, sixty-six (30%, 95% CI: [0.24, 0.36]) had ≥1 PA. A total of 206 were eligible for pre-post-PrEP period analysis. In multivariable analysis, participants with perceived emotional SS had 42% increased odds (aOR: 1.42, 95% CI: [1.00, 2.00]) of PA. In the post-PrEP period, compared with pre-PrEP period, participants had 3.5 times increased odds (OR: 3.53, 95% CI: 1.10, 11.35) and 51% decreased odds (aOR: 0.49, 95% CI: 0.28, 0.84) of rectal NG diagnosis and reporting CAI, respectively, but no significant changes in prevalence of all STIs.

Conclusion: There was no association between SRPA and assay; perceived emotional SS was a facilitator of PA. We demonstrated trends of PrEP associated sexual behavioral modifications but further studies are required. Our study findings have implications for PrEP implementation in Nigeria and similar settings.

Behavioral and Social Support Effects on Daily Oral Pre-exposure Prophylaxis use among Men who have Sex with Men in Nigeria

by
Olusegun Adewale Adeyemi

A dissertation submitted to the Faculty of Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2021

DEDICATION

To my Lord and Savior for His grace bestowed upon me

To my family

To the ones we have lost

To the ones that have made it thus far

ACKNOWLEDGMENTS

I want to thank all my dissertation committee members for sticking through this with me. I want to start with the committee co-chair who doubles as my academic advisor, Dr. Charurat, thank you for your direction, guidance, and making time for me whenever I came calling. More particularly, thank you for not giving up on me when it looked like the chips were falling apart. Dr. Morgan, thank you for accepting to serve on this committee and even when the unexpected pandemic (SARS-CoV-2) struck and made this decision tougher for you because of your involvement at the forefront fighting for us all, you still showed up. Dr. Zhan- I am grateful for your patience with me all through our very many meetings. Thank you for the guidance and effort invested in this product, from drawing up a statistical plan to the point of execution. Even when things appeared tough, you had a way of diffusing the tension and making me see the bright side, at the end of every call or meeting with you, it felt like therapy- Thank you for imparting your expertise with such kindness and warmth. Dr. Nowak, committee co-chair – I cannot thank you enough for your relentless efforts on my dissertation and for being my research mentor from practicum classes. I really want to appreciate you for all the learning curves you have guided me through. I particularly want to thank you for always responding in a timely fashion to all my emails, dissertation drafts, etc., despite your busy schedules. Thank you for taking the time to read every line of my work and, more importantly, for your comments and edits; they made this dissertation and me better. Dr. Sam-Agudu- Thank you for giving me my very first lessons in formal research. My meeting and interaction with you since 2013 from the days of INSPIRE- MoMENT PMTCT study was the foundation on which my research

interest was built. Thank you for always being there for me through it all. Your words of encouragement when the going was tough meant a lot to me. Dr. Craddock- Thank you so very much for always being responsive to my email and requests for one on one meetings (which were quite a lot). Thank you for being my guide through the "Aim 2" (social aspect) of my dissertation, it would have been much tougher without you. Dr. Adebajo- It was not easy playing catch-up with the rest of the committee, given you joined them last, but you did it and I must say, with such grace. The wealth of experience and depth of knowledge you added to this dissertation in such a brief time on the committee is admirable. Thank you for all your responses and comments, they challenged and brought the best out of me.

I will like to acknowledge and appreciate the management and staff of the National Institutes of Health for the Fogarty HIV Research Training program (Epidemiology Research Training for Public Health Impact in Nigeria [Epi-Nigeria]), as well as the United States Government for the opportunity, afforded me for this study.

The staff of Institute of Human Virology, division of epidemiology. Professor Abimiku – Thank you (and Professor Charurat) for the vision you had to invest resources in availing platforms for this opportunity. I would not have been here without you. Professor Adebamowo- Thank you for stepping in on my behalf when I least expected, I have no words to thank you enough. Mrs. Johnson (Joyce) - Thank you for making this journey quite smooth and ensuring I had the provisions, I needed to succeed. Sheri – Thank you for always having my back and making sure "everything" worked – you have such magic, and I have no idea how you do it. Ashley- Thank you for assisting me when I came calling especially with the assay logistics. Dr. Jumare- Thank you for believing in me and for your patient and astute guidance all through my Ph.D. journey. I am glad I had you to call on

for this. Dr. Ramadhani, thank you for allowing me to see the world through your eyes, they provided clarity beyond words for me.

I am grateful to Dr. Marzinke and the John Hopkins Pharmacology laboratory unit staff for technical assistance and expertise with running the study assays. I will also like to acknowledge all the co-investigators of the TRUST study for the work they have put into this since 2013.

The Maryland Global Initiative Corporation, Nigeria / TRUST study staff. Ruxton Adebiyi and Blessing Kayode; words fail me to express my gratitude to you. Thank you for all the marvelous work you did in real-time on the field to implement the TRUST-PrEP study despite all the challenges. Ruxton, thank you for working and improving the quality of the data with every merge. Dr. John Chama, Mr. Uchenna Ononaku, and the team, I am so grateful for your work- without your commitment and hard work, this dissertation would not have been possible. To every participant in RV 368/ TRUST and TRUST-PrEP study since 2013, thank you for trusting the team with your care.

The Institute of Human Virology Nigeria: Dr. Dakum - Thank you for the opportunity availed unto me as a staff in the first place. I took your fatherly advice offered in 2019 during your Baltimore trip to heart, and I can only hope I have made you proud. Dr. Mensah – Thank you for your support on this journey. Dr. Ndembi – Thank you for opening your doors and arms unto me all through this journey. Dr. Sunny Phillips- Thank you for your encouragement and preparation for this journey. Mrs. Petronilla Nwadike and all the biorepository lab staff - Thank you for assisting with the logistics of study assays.

The University of Maryland Baltimore, department of epidemiology staff. I am grateful to each one of my professors. Particularly, I appreciate Professor Gruber- Baldini and Dr. Albrecht who have been of tremendous assistance and guidance to me. Professor Harris- Thank you for taking me on allowing me to rotate with you. I loved working with you and the team. Dr. Stafford – Thank you for the guidance and open-door access you granted all through my study. Dr. Sarah Jackson – Thank you for being my practicum-teaching assistant; in the short time we had together, you imparted me with so much that I have carried forward to date.

I would like to acknowledge my very first mentors on this path- Dr. Ayodotun Olutola and Dr. Bola Gobir, thank you for the seeds you sowed in me. My friend and brother who stood by me when I had it rough – Dr. Olakune Alonge, thank you. My long-standing friend who welcomed me into Baltimore and encouraged me on this path – Dr. Victor Popoola, Thank you.

I could not ask for a better cohort than as course colleagues- Florence, Timileyin, Jimmy, Christina, Krystal, Lydia, and Gulam. Thank you for the opportunities to bring the best out of one another.

To my family- My parents – Mr. Bola Adeyemi and Mrs. Adedoyin Adeyemi, thank you for being my first teachers and instilling discipline very early in me. The world's best siblings – Damilola, Kayode, and Seyi, you guys brought the best out of me from childhood and you still push me to date. To my darling wife – Bukola, I can only imagine what I had put you through this past four years, and I am truly grateful for your sacrifice and love. Oluwaloni and Oluwatoni, you are priceless.

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List of Abbreviations

ART	Antiretroviral Therapy
AUC	Area Under the Curve
aOR	Adjusted Odds Ratio
BLQ	Below limit of quantification
BRC	Behavioral Risk Compensation
CAI	Condomless Anal Intercourse
CDC	The U.S. Centers for Diseases Control and Prevention
CT	Chlamydia Trachomatis
CI	Confidence Interval
DAG	Directed Acyclic Graphs
FDA	Food and Drug Administration
FTC	Emtricitabine
GEE	Generalized Estimating Equations
HIV	Human Immunodeficiency Virus
IHV	Institute of Human Virology
IHVN	Institute of Human Virology, Nigeria
IRR	Incidence Rate Ratio
IQR	Interquartile range
LCMS	Liquid Chromatography Tandem Mass Spectrometry
MSM	Men who have sex with men
NG	Neisseria Gonorrhea
OR	Odds ratio
POL	Popular Opinion Leader
PrEP	HIV Pre Exposure Prophylaxis
MSM	Men who have sex with men
QQ	Quantile quantile

RDS	Respondent Driven Sampling
ROC	Receiver Operating Characteristic
SS	Social Support
STI	Sexually Transmitted Infections
TDF	Tenofovir Disoproxil Fumarate
TGW	Transgender Women
UNAIDS	Joint United Nation Programme on HIV and AIDS
WHO	World Health Organization

CHAPTER I: INTRODUCTION AND BACKGROUND

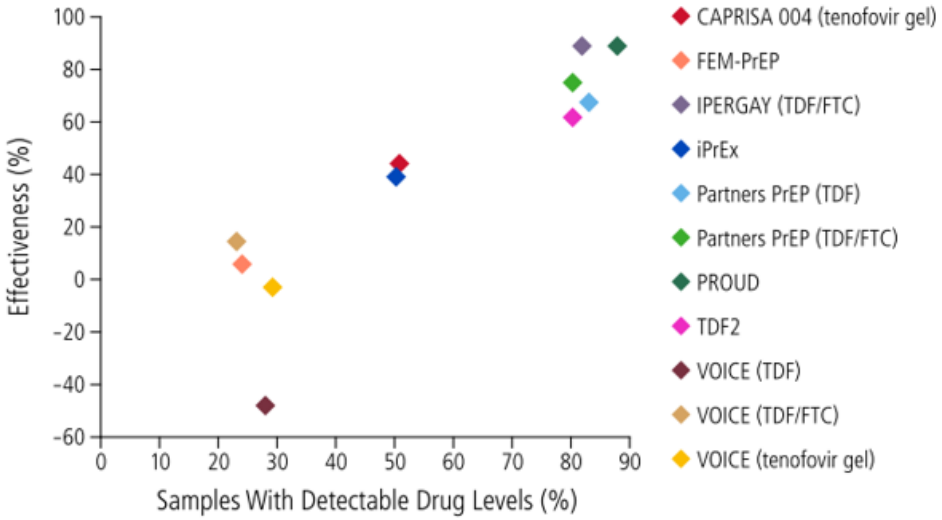
HIV incidence among men who have sex with men (MSM).

HIV disproportionately impacts MSM globally[1,2]. Although global HIV incidence among other populations has been trending downwards, it remains stable or comparatively higher among MSM[1]. In most countries, MSM constitute less than 3% of the population, but reportedly bear between 15 to 70% of all new HIV infections annually across a range of countries[3]. For example, in the United States, MSM were 2% of the population and accounted for 69% of new HIV diagnoses in 2018[4]. To further provide context, the risk of HIV transmission per 10,000 sexual exposures is approximately 8, 63 and 138 for condomless receptive penile-vaginal intercourse, needle sharing, and condomless receptive anal intercourse, respectively[5]. According to the 2019 Joint United Nations Programme on HIV/AIDS (UNAIDS) report[6], Nigeria has the second-largest HIV epidemic globally. This is of particular concern, as HIV incidence among MSM in Nigeria was recently reported as 5.8-23.1 per 100 person-years (cumulative 95% CI:3.6 -33.1)[7]. Of note, the World Health Organization (WHO) recommends offering daily oral pre- exposure prophylaxis (PrEP) in settings at or above an HIV incidence of 3 per 100 person- years[8].

The effectiveness of PrEP depends on adherence

Four placebo-controlled clinical trials have demonstrated the effectiveness of Tenofovir Disproxil Fumarate (TDF) and Emtricitabine (FTC) in decreasing HIV acquisition among high-risk groups including MSM[9,10]. The "*IPREX"* (Iniciativa *Profilaxis Pre- Exposicion translated "Pre-Exposure Prophylaxis Initiative"*) study randomly assigned MSM and transgender women (TGW) from North and South America, South Africa, and Thailand to receive daily dosing of TDF-FTC or placebo[11]. In the United Kingdom, the "*PROUD"* (Pre-exposure Option for Reducing HIV) study randomly assigned MSM to receive either daily dosing of TDF-FTC or a deferral one-year period[12,13]. Furthermore, the *"IPERGAY"* study[14](Action to Prevent Risk Exposure By and For Gay Men) had an event-driven placebo-controlled trial PrEP study in France and Canada. In this study, all participants were asked to take 2 pills of TDF-FTC between 2 to 24 hours before sexual intercourse, a third and fourth pill 24 and 48 hours after sexual intercourse respectively[15]. Finally, in the *"Partners PrEP"* study[16] among sero-discordant couples in Uganda and Kenya, the HIV negative partners were assigned in a randomized trial to one of the following regimens; a once-daily TDF, once-daily combined TDF-FTC or a matching placebo. All studies demonstrated that oral PrEP's adherence strongly correlated with its effectiveness. Figure 1.1 shows the correlation of percentage of samples with detectable drug levels and their effectiveness from eleven PrEP studies.

Figure 1. 1: Relationship between adherence (as measured by drug level) and effectiveness of PrEP[9]



Methods of daily oral PrEP Adherence Measures

Adherence to daily oral PrEP is measured and reported in various ways [17–19]. A common way of assessing PrEP adherence is self-report[20–22]. Self–report of daily oral PrEP adherence has generated concerns about its validity[17,23] and several studies have conflicting findings of the use of self-report as an adherence monitoring tool for daily oral PrEP[17,18,24,25]. Nonetheless, self-reported PrEP adherence remains the most common method of PrEP assessment[26], especially in lower-income countries, where the more objective measures are either not available or affordable[27]. Pill counts, pharmacy records, and medication event monitoring systems may improve adherence data accuracy compared to self- report, but do not record the actual dose-taking event[28]. The quantification of serum

analytes for adherence prevents patients' manipulation and objectively shows proof of medication use [28].

Analytes concentrations (surrogate biomarkers) in specimens such as serum, plasma, dried blood spot, hair follicles, and urine samples have been measured as means of verification of daily oral PrEP adherence[17,18,25,29,30]. The analyte of TDF-FTC measured depends on the method of choice. After a steady-state of the analyte level is attained in serum, a protective level for study participants is reached when at least four daily doses of TDF-FTC are used in a week[28]. This level of doses per week equaled to the minimum protective levels of serum TFV and FTC are 5.9 (4.6-6.4 ng/ml) and 6.7(5.4 – 7.6 ng/ml), respectively[28]. These protective levels were obtained from serum quantification of directly observed use of once weekly, twice weekly, two tablets twice weekly (4 doses/week), and once daily (7 doses/week) fixed dose of TDF-FTC for 5 weeks in 49 HIV negative healthy individuals randomized to one of the four arms of the HPTN066 study[28]. The dose proportionality is traditionally assessed using peak concentrations (Cmax) and area under the concentration curve (AUC), but these parameters are challenging to capture in real-life settings. This is because the time dependent pharmacokinetics of the analytes cannot be monitored effectively when study participants are not under direct observation from oral PrEP pill intake to excretion of the TDF-FTC metabolites.

Figure 1.3 shows the receiver's operating characteristic curve displaying the area under the curves for serum TFV doses ranging from 1 to 7 per week. The threshold concentrations indicating a minimum number of doses per week or greater were selected to optimize the sensitivity and specificity of >90% respectively. This curve shows that for each serum analyte measured, there is at least a 95% probability of correctly predicting the number of

days TDF was used by the study participant. Table 1.1 shows the steady-state TFV and FTC pharmacokinetics summary by analytes in serum.

Figure 1.2: Receiver Operating Characteristic (ROC) curves for serum tenofovir (TFV) indicating dose frequency ranging from one to seven doses per week and the associated area under the curve (AUC)[28]

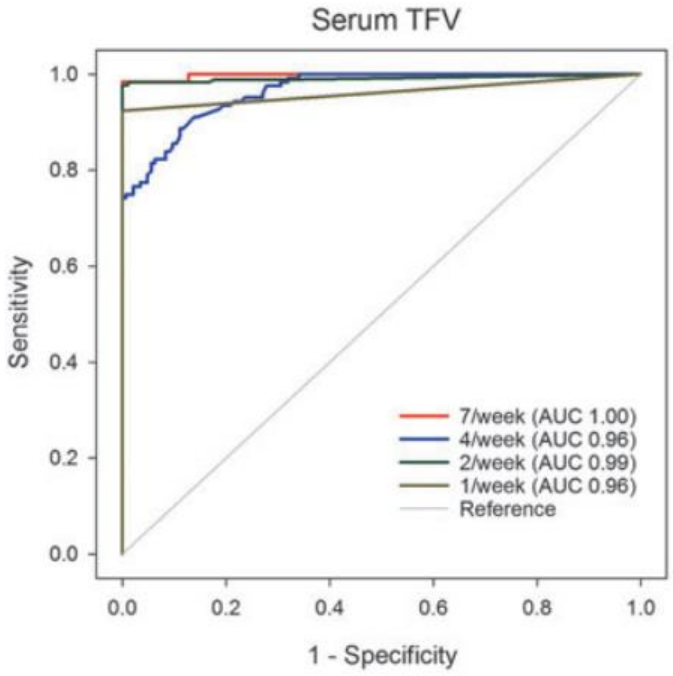


Table 1.1: Steady-State TFV /FTC Pharmacokinetics Summary

Matrix	Analyte	LLOQ	1 tab/wk	2tab/wk	4tab/wk	7tab/wk
Serum	TFV	0.31ng/ml	0.5 (0.5-0.6)	3.6(2.6-3.7)	5.9(4.6-6.4)	52.2(49.0-55.6)
Serum	FTC	0.31ng/ml	0.8(0.4-0.9)	5.4(3.7-6.0)	6.7(5.4-7.6)	70.9(67.7-81.9)

(LLOQ: Lower Limit of Quantification| tab: tablet)

Bottlenecks of PrEP implementation

The transition of daily oral PrEP studies from clinical trials to real-world implementation has had its challenges. A key recurring issue is the incidence of breakthrough HIV infections among PrEP users[31]. Although the majority of these breakthrough HIV infections occurred in patients with an objectively ascertained sub-optimal serum concentration of TDF-FTC analytes, a few cases of seroconversions secondary breakthrough infections in persons with demonstrated adherence have been reported [25,31,32]. These, however, are exceptions, not the rule in the use of daily oral PrEP. Poor adherence remains a major bottleneck in daily oral PrEP implementation[24], hence the justification for ongoing clinical trials for alternatives such as long-acting injectable or implants[33].

Globally, significantly more people need to take PrEP to meet the UNAIDS timeline to end new HIV infections [34]. Access to PrEP is a global challenge irrespective of socio-demographic peculiarities[35]. In middle and low-income countries, daily oral PrEP coverage is inadequate for all those eligible[35]. The WHO recommended "test and start" treatment as prevention for HIV-positive patients still faces scale-up challenges[36]. One of the major reasons for this is apathy from the governments of high HIV burden countries [37]. "Donor fatigue" is also setting in as most of the support for antiretroviral medications in resource-limited countries is from donor agencies[38].

In higher-income countries, for example, the United States, inequitable access is the major challenge. Several studies[23,39] have reported an overwhelmingly disproportionately high HIV incidence among younger, African American MSM, however, they are the least likely to receive a prescription for daily oral PrEP. This typifies the inverse care law[40]. "The

inverse care law [is the principle that] the availability of good medical [or social] care tends to vary inversely with the need " [40] of the population served. In addition, studies have shown that when daily oral PrEP is equitably available, such as in clinical trial settings, younger African American MSM are the least likely to be adherent[30]. The non-adherence may have potential implications on the resistance mutation patterns of the antiretroviral (ARVs) use for treatment after seroconversion [41].

Background for study Aims

Since PrEP approval by the FDA in 2012[42,43], dried blood spots[28,30,44], hair follicles[44–46], urine[29,47,48], and self-report[17,22,44,45,49,50] amongst others have been studied for adherence measures in different global settings. Several investigators have combined at least two methods[22,49] typically including a less invasive, more cost-effective screening for PrEP adherence (or lack thereof) which may be routine (e.g., self-reported adherence) and a more rigorous,typically more invasive objective method (e.g. TDF and FTC serum quantification assay). Based on this model, some previous studies[17,51,52] have shown that self-reported PrEP adherence may overestimate the protective equivalence, for example, participants of the ATN-110 / ATN-113 over reported adherence by 40% (95% CI: 31- 49%). In contrast, other studies[25,30,53] have shown that self-reported PrEP adherence is a good proxy for PrEP adherence. The debate about correlations between self-reported PrEP adherence and the PrEP biomarkers is still ongoing.

While most of the studies[17,28,44] that have investigated the objective assessment of self-reported PrEP adherence among MSM have been done in high-income, relatively low HIV burden settings, there have been very few in Sub-Saharan Africa, where most of the HIV

epidemic burden lies. Therefore, the previous studies' generalizability to low-middle income and high HIV burden settings like West Africa may be limited.

To optimize self-reported PrEP adherence, social support has been shown to be helpful, especially for vulnerable populations[54]. Previous studies show that both actual and perceived social support have played key roles in medical, behavioral and psychological outcomes for patients with different health conditions[55–58]. Social support has been associated with positive psychological and behavioral outcomes of patients [56,59] and has been demonstrated to benefit health-buffering stress, influence states of minds, and modify behaviors[60] of patients. Only a few studies[54,61,62] have examined the role of actual or perceived social support on medication adherence among MSM and other persons living with HIV, and even fewer studies [63,64] evaluated the role of perceived social support among MSM taking PrEP, in particular. Support from friends and peers has been observed to promote patients' adherence by encouraging optimism, self-esteem and giving practical assistance (instrumental social support)[57].

The quantitative measurement of perceived social support entails measuring the functional type of perceived support. Functional social support has been categorized[55,63] into instrumental (pertains to support with tangible aids and services), informational (supports with advice, suggestion, or information) and emotional (support with the expression of empathy, love, trust and care) social support. Most of the literature[63,65] that has examined the role of social support in adherence among MSM have paid more attention to the structural component of social support, which investigates the strength and number of their social network parameters[55], with little attention to how effectively the network participants relate with one another.

A much-debated question is whether the use of PrEP among MSM has resulted in increased risky behaviors[66] (e.g., condomless anal intercourse), a concept generally referred to as behavioral risk compensation[67] (BRC). BRC theory suggests that people typically adjust their behaviors in response to their perceived risk level; in this context, PrEP treatment has been implicated in risk perception adjustment among MSM[68]. Previous studies[14,68–71] have examined BRC among MSM on PrEP, and there have been conflicting results. In a Seattle STD clinic, Montano et al[72] examined sexual behaviors and sexually transmitted infections (STIs) prevalence among 183 MSM, who initiated PrEP between 2014 and 2017. At 12 months post-PrEP initiation, they found a 46% increased risk of MSM reporting *"never using condoms in the last 30 days"* compared with the initial PrEP visit (aRR:1.46, [95% CI: 1.13, 1.88]). Similarly, the percentage of patients diagnosed with any STI with and without PrEP was 49.2% and 35.0%, respectively, culminating in a significant difference in mean STI cases diagnosed per person before PrEP compared with after PrEP use (0.5 vs 1.1; $p < 0.01$). Likewise, a multi-site, open-label Australian PrEP study[51] recruited 114 MSM and presented a one-year interim analysis reports. Reported condom use among study participants significantly decline, with a significant increase in the diagnosis of STIs. Compared to baseline, there was a 2.8 fold increase (aIRR: 2.77, [95% CI: 1.52, 5.56]) of any STI (syphilis; anal and pharyngeal gonorrhea; and anal and urethral chlamydia).

In contrast, some studies[11,66,70] have refuted the association between BRC and increased risky behaviors or STI prevalence. The EPIC study[66] was a randomized control trial with the objective to evaluate the impact of a bi-directional text messaging intervention on PrEP retention and adherence; it reported that the overall risk of STIs and risky behaviors

declined in both arms from baseline. Similarly, a modeling study[66] simulated the PrEP use following the CDC's guidelines. In their reference scenario of "*40% PrEP coverage and 40% reduction in the per-act probability of condom use"*, they found that 42% and 40% of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* respectively will be prevented in the next 10 years[66]. Because PrEP associated STI screening led to the increased treatment of asymptomatic STIs, the incidence of STIs decreased[66].

In addition, there have been concerns about the increase in risky sexual behaviors and consequently STIs among those taking PrEP. These concerns are mostly due to the public health challenges resulting from multi-drug resistant gonorrhea as well as the potential facilitation of HIV infection by recurrent STIs following behavior modification due to PrEP-related BRC[73].

Study Aims

This study estimated the correlation between self-report PrEP adherence and PrEP biomarkers, as well as, assessed the role of perceived social support in adherence to daily oral PrEP among MSM in Nigeria. The study also assessed if daily oral PrEP use led to the modification of risky behavioral outcomes (condomless anal intercourse and concurrent sexual relationships) and laboratory diagnosis of STIs, i.e., *Neisseria gonorrhea* and *Chlamydia trachomatis*.

The specific aims for this study were:

1) To estimate the correlation between the daily oral PrEP adherence by self- report and by surrogate biomarkers among MSM in Nigeria

a. Hypothesis: Compared with the month 3 study visit, there will be increased discordance

between daily oral PrEP self-reported adherence and biomarker measures at the month 9 study visit.

Sub –Aim 1: To explore the association between self-reported PrEP adherence and protective PrEP adherence.

2) To assess the association between perceived social support and the protective pre-exposure prophylaxis (PrEP) adherence among MSM in Nigeria

a. Hypothesis: Those with perceived social support, compared with those without, will have different odds of protective adherence to daily oral PrEP among MSM in Nigeria.

3) To estimate the effect of daily oral PrEP use on risky behavioral outcomes (i.e., condomless anal intercourse and concurrent partnerships, as well as laboratory, diagnosed rectal and urethral *Neisseria gonorrhea* and *Chlamydia trachomatis*) among MSM in Nigeria.

a. Hypothesis: Compared with pre-PrEP period, MSM will have different odds of behavioral outcomes and sexually transmitted infection diagnosis post-PrEP period.

Importance of Study

Nigeria, a country with a 220 million population, has the second-largest HIV epidemic burden globally[74]. Within the country, HIV incidence is highest among MSM and key populations[75]. It is therefore of both national and global health relevance that daily oral PrEP adherence be investigated in this population. The incidence of HIV in Nigeria has implications for the United Nations' goals of ending the global AIDS epidemic by 2030[76,77].

MSM in Nigeria face structural, constitutional and psychological barriers that keep an already "hard to reach" population even further away from the mainstream, publicly available health care services[78]. In a study[79] that examined the prevalence of internalized

homophobia among MSM in Nigeria from Lagos and Ibadan, approximately 33.3% of all respondents reported internalized homophobia, which has been associated with poor outcomes in the uptake of health care services[80]. Furthermore, in 2014, Nigeria signed a same-sex marriage criminalization bill into law, further resulting in increased fear of seeking health care[81] by the MSM population.

Despite the challenges faced by MSM in Nigeria's highly homophobic setting, daily oral PrEP provides a unique and discrete method of biomedical chemoprophylaxis whereby, well-informed MSM can have improved HIV prevention strategies compared to the traditional behavioral methods (condom use during sex, preventing concurrent partnerships).

Furthermore, there is a paucity of studies on PrEP adherence in low middle-income settings and this study will add to the body of knowledge and potentially provide more insight to improve PrEP adherence among MSM. In addition, findings from this aim will shed light on the possibility of engaging self-reported PrEP adherence as a potential cost-effective, PrEP adherence evaluation method in a resource-limited setting like Nigeria.

Social support has been identified to have played important roles in patients' medication adherence since the middle of the twentieth century[55,58]. Surprisingly, only a handful of studies[63,65] have examined the roles of social support in medication adherence among MSM, and even fewer studies have investigated its roles in PrEP adherence. An understanding of the nature of social support with the best positive impact on PrEP's adherence in the context of this study's settings may provide a guide to the support systems and services needed for a successful PrEP implementation, not just in Nigeria but similar settings as well.

In Nigeria, like many other resource-limited African countries, there is a need to establish if daily oral PrEP use among MSM is feasible and sustainable. A crucial step towards achieving this is evaluating potential fallouts of PrEP as a biomedical HIV prevention method; one of them being PrEP-associated BRC. This study's findings on BRC evaluation will contribute evidence to inform policies that will guide the implementation of PrEP in the future.

CHAPTER II. STUDY DESIGN AND METHODS

Study Design

TRUST-PrEP was an open-label, non- randomized, prospective study. It leveraged an ongoing prospective HIV prevention and treatment study, TRUST/RV368 abbreviated TRUST study, in Abuja. The TRUST study was a partnership between the Institute of Human Virology (IHV) at the University of Maryland, John Hopkins University, IHV-Nigeria (IHVN) and the US Military HIV Research Program. The TRUST study has been enrolling MSM since March 2013 using a respondent driven-sampling method.

The TRUST study group had previously reported that compared with MSM recruited earlier, those in later waves are characterized by a low proportion of uptake of HIV voluntary counseling and testing, high rate of newly diagnosed HIV infection, low uptake of clinical services, and a high viral load [82]. This informed the need for identification and engagement of key influential MSM among the early wave recruitment (called popular opinion leaders "POL") for didactic training on PrEP introduction and peer-to-peer recruitment from their networks.

In the TRUST-PrEP study, there were two approaches for PrEP introduction to prospective study participants; the clinic approach and the community approach. The clinic approach utilized a health care provider initiated PrEP introduction for all MSM who were already enrolled in the parent TRUST study and attending the clinic. On the other hand, the community approach utilized a peer-to-peer driven PrEP introduction facilitated by the trained POLs. The POLs introduced PrEP to peers within their community and network, while offering them study enrollment coupons into the TRUST study. After the PrEP introduction, the PrEP willingness questionnaires were administered during the routine

TRUST clinics to all attendees irrespective of their PrEP introduction approach (the details of the enrollment is illustrated in figure 2.1). The TRUST – PrEP study enrollment started in April 2018 and ended in May 2019, while the study follow-up ended in June 2020.

Study Site:

This study was conducted at trusted community center in Abuja, Nigeria. The staff of this center have been well trained and have experience and demonstrated skills engaging MSM in the Nigerian setting.

Study population and eligibility criteria:

The study population was MSM residing in Abuja and its environs in North-central Nigeria. To be eligible for enrollment in the TRUST-PrEP study, the participant had to meet the parent study's (TRUST) criteria. This included being born "male" at birth, presented a valid coupon, history of receptive or insertive anal intercourse with another male in the prior 12 months, ability to provide informed consent in English or Hausa (the dominant local language). Furthermore, participants were at least 16years of age, considered able to access sexual and reproductive health and HIV care and research participation without parental consent[83]. In addition to this, they were HIV-negative and willing to consent to the use of daily oral PrEP and biological specimen collection at each visit for the study period. They met at least one of the screening criteria for "substantial risk for HIV infection".

1. Sexually active with a report of any of the following in the past three months
    a. Condomless vaginal or anal intercourse with more than one partner
    b. Sex partner with ≥ 1 HIV risk. HIV risks include:

Injection of drugs, has sex with men, Transgender person, sex worker, condomless sex with

multiple partners, unknown HIV status or living with HIV.

   c. Had a history of STI within the past 3 months based on self-report, lab diagnosis or syndromic STI treatment

2. History of sharing injection or injection materials in the last three months
3. History of sexual partner who is HIV positive and who had not been on effective HIV treatment in the last three months. A person was defined as not being on effective HIV treatment if they were less than 6 months on ART or had inconsistencies or unknown adherence.

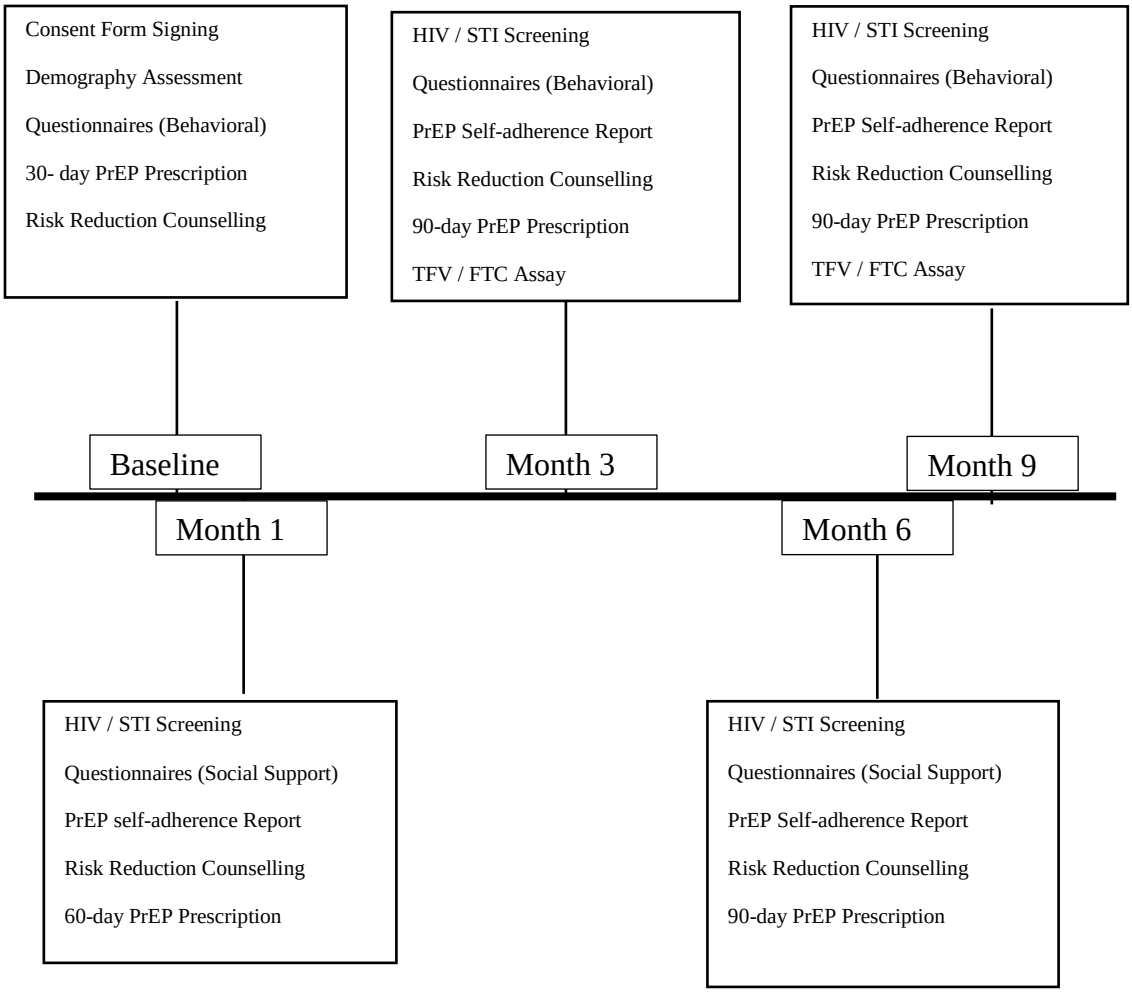
Data collection:

Participants included in this study were HIV-negative at baseline, willing to take PrEP for one year, signed the study consent form and had been enrolled in the parent study. Per protocol, TRUST-PrEP visits were at baseline, month 1, month 3, month 6 and month 9. The quantification assays for PrEP were done at month 3 and month 9 of the study. Clinical data was collected at baseline and followed up every 3 months for 12 months. Participants provided blood and rectal swab samples for testing of sexually transmitted infections (HIV, urethral and rectal Neisseria gonorrhea and Chlamydia trachomatis) at baseline and every three months. Behavioral questionnaires were administered at baseline, month 3, and 9 visits, whereas social support questionnaires were administered at months 1 and 6.

Clinical and laboratory data were collected with approved data collecting tools and stored with Microsoft Access and Excel databases. Besides the routine internal data quality assessment, a four to six monthly external data quality assessment as well as updates of

study are performed. Because the parent study is an ongoing cohort with data quality checks six-monthly, often resulting in data format updates, these updates can potentially alter some of our study's data estimates. To avoid this interference, the database for this study was frozen in December 2020.

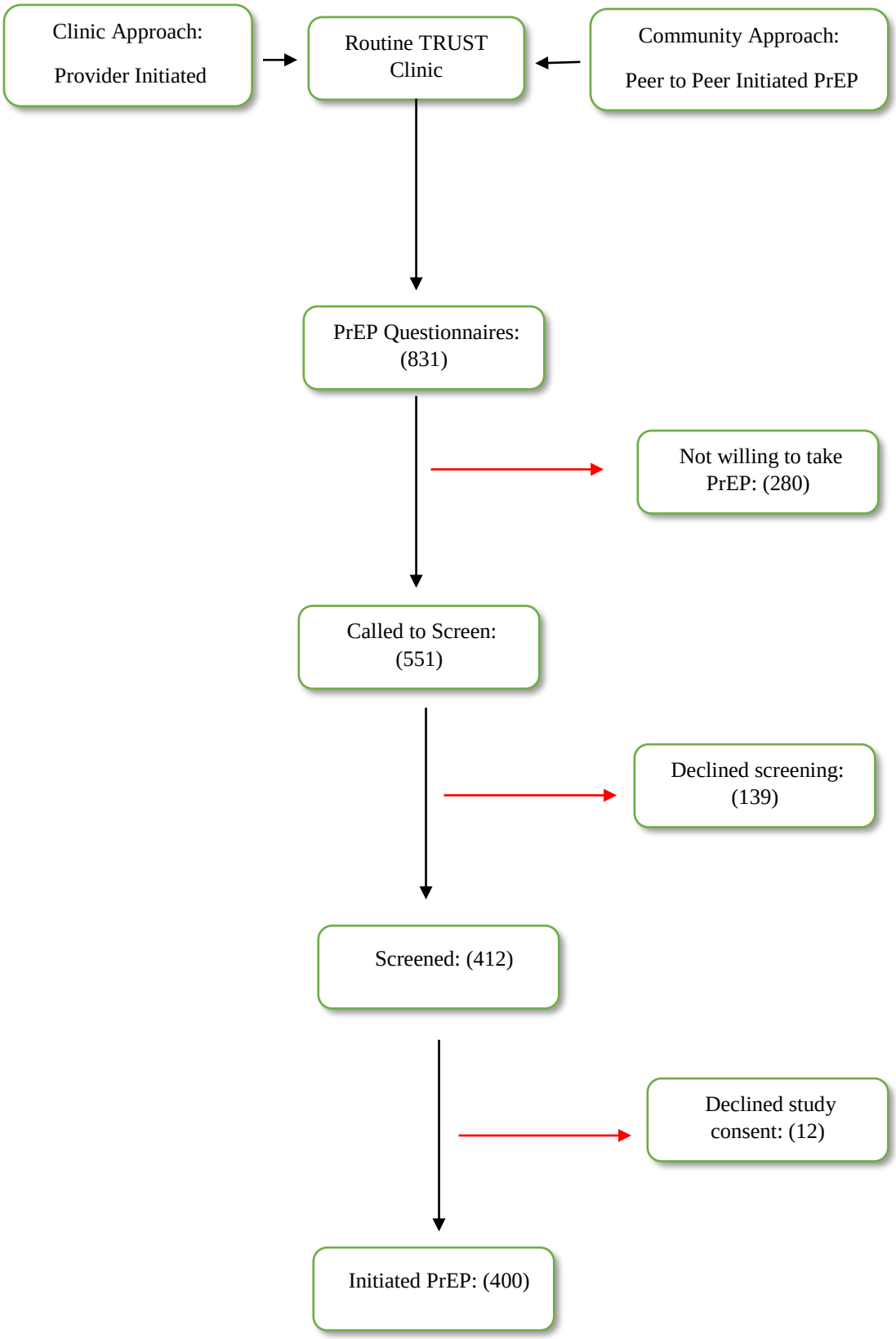
Figure 2. 1: Study procedures and Timeline



Study flow

Of the participants introduced to PrEP from either of the clinic or community approaches, 831 persons were HIV negative and answered the PrEP willingness questionnaires. Of this, 551 (66.3%) indicated a willingness and were called for screening. Only 412 of those called (74.7%) showed up for screening, and 400 of them initiated PrEP between April 2018 and May 2019.

Figure 2. 2: Study Sample Flow Chart



Laboratory methods:

The blood samples for biomarker assays were collected at month 3 and 9 follow-up visits. The study allowed a window of two weeks before and four weeks after the expected day of visit for participants that reported early or late respectively. The specimens were initially processed at the IHVN's bio-repository laboratory. They were centrifuged, separated and stored as serum at a temperature of -80 degrees Celsius centigrade. The samples were pooled until a minimum threshold of a hundred samples was met for shipping to the United States. The final liquid chromatography mass spectrometry (LCMS) analysis was at the John Hopkins University pharmacological laboratory.

The LCMS method for serum quantification:

TFV was isolated via protein precipitation and quantified via LCMS. The calibration curves were generated via linear regression with $1/x^2$ weighting. The range of calibration for serum TFV is 0.31- 1000ng/ml. Serum TFV or FTC below 0.31ng/ml were classified as below level of quantification (BLQ). The threshold values for defining not more than once a week, at least 4 times a week and daily use are $\leq$ 0.5ng/ml, 5.9ng/ml (4.6- 6.4) and $\geq$ 52.0 ng/ml(49-55.6) respectively based on the median TFV serum concentration at a steady state when taken under direct observation as done in clinical trials setting[28,84].

Sexually Transmitted Infection Screening

During study visits, the Aptima Combo 2 Assay (Hologic, Bedford, MA) was used to screen participants for rectal and urethral Neisseria gonorrhea (NG) and Chlamydia trachomatis (CT) irrespective of symptoms. Urine and rectal swab samples were transported weekly at 2–8 degrees Celsius to the Defense Reference Laboratory in Abuja.

Once the STI results were available (usually within 2-4 weeks), participants who tested positive were contacted for an immediate follow up treatment before their next "official" clinic visit appointment. After prescription and the course of antibiotics, they were re-tested during the follow up visits. In addition, participants were tested for HIV using Abbott Determine HIV-1/2 test kits. The parallel testing algorithm was followed by each participant at every visit[85]

Study Variables

Outcome variables:

Serum TFV measured as a continuous variable in nanogram per milliliter (ng/ml) was the outcome for Aim 1. The lower limit of quantification TFV was 0.31 ng/ml, and the range was from 0.31-1,000 ng/ml. The surrogate biomarkers (measured in ng/ml and dichotomized at < 5.9 ng/ml and ≥ 5.9 ng/ ml for non-protective PrEP adherence and protective PrEP adherence respectively) were the outcome variables for sub- Aim 1 and Aim 2 respectively. For the purpose of analysis, serum TFV was used as a proxy for TDF-FTC, since this was administered in a fixed-dose combination to study participants. Serum FTC was used for sensitivity analysis.

For Aim 3, the outcome variables were behavioral outcomes (condomless anal intercourse with last male partner and concurrent partnership with 2 or more male partners) and laboratory diagnosed sexually transmitted infections (anal and urethral *Chlamydia trachomatis* and *Neisseria gonorrhoeae*).

Predictor/Exposure variables

The primary predictor for Aim 1 was the self-report of daily oral PrEP adherence. This was reported on a 4 scale Likert data collecting tool as *"Poor", "Good", Very good" or "Perfect"* in response to the question *" How would you describe your adherence over the last one month?"* asked at every study visit. This was analyzed as a rank variable and categorical variable for aim 1 and sub-aim 1 respectively.

The primary predictor for Aim 2 was social support, measured in three domains (informational, instrumental, and emotional social support) by an 8 item question categorized using a previously validated social support instrument[86,87].

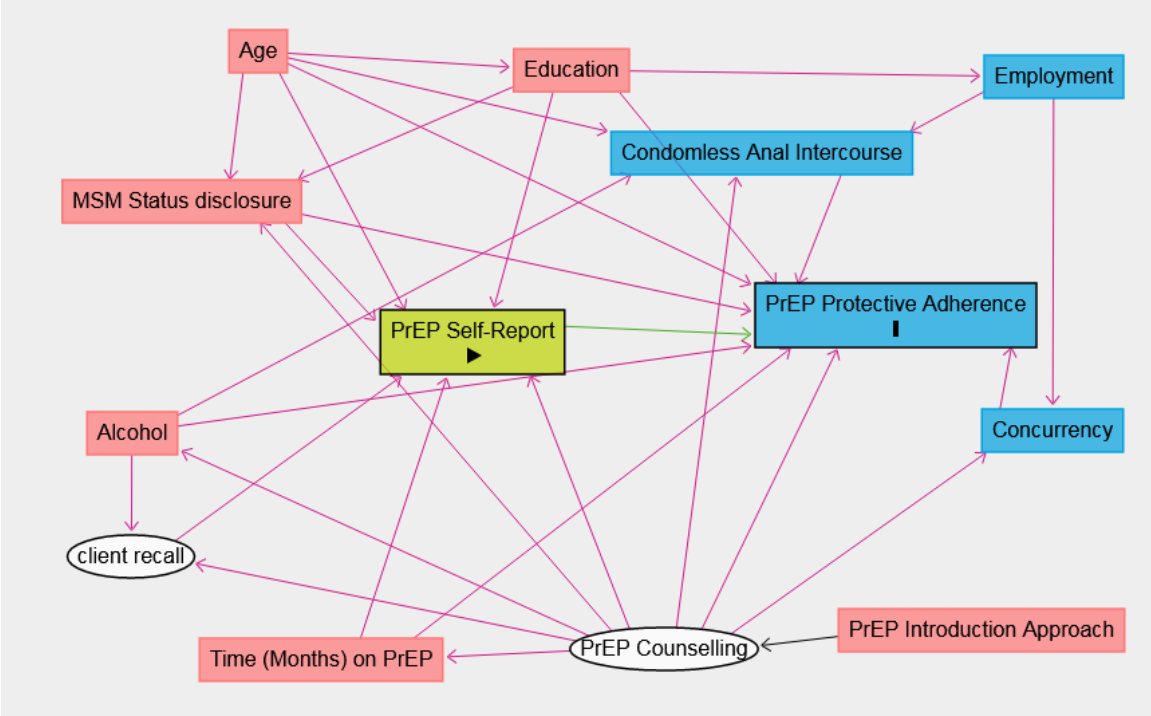
The primary exposure variable for Aim 3 was the study time categorized as pre-PrEP or post-PrEP periods.

Covariates (Potential confounders)

The covariates for the multivariable analysis were selected based on one or more of the following criteria. An association with the exposure/predictor ($p \leq 0.05$), association with the outcome ($p \leq 0.20$), based on literature, meets the minimum sufficient adjustment set in directed acyclic graphs[88] (DAG) and changes the regression coefficient estimates of the association between the outcome and predictor variable by at least 10%. Some variables were included based on clinical plausibility.

Directed Acyclic Graphs for Aims 1 and 3 are shown in Figures 2.3 and 2.4

Figure 2. 3: Directed Acyclic Graph[88] of the association between daily oral PrEP self –report and the biomarkers PrEP adherence.



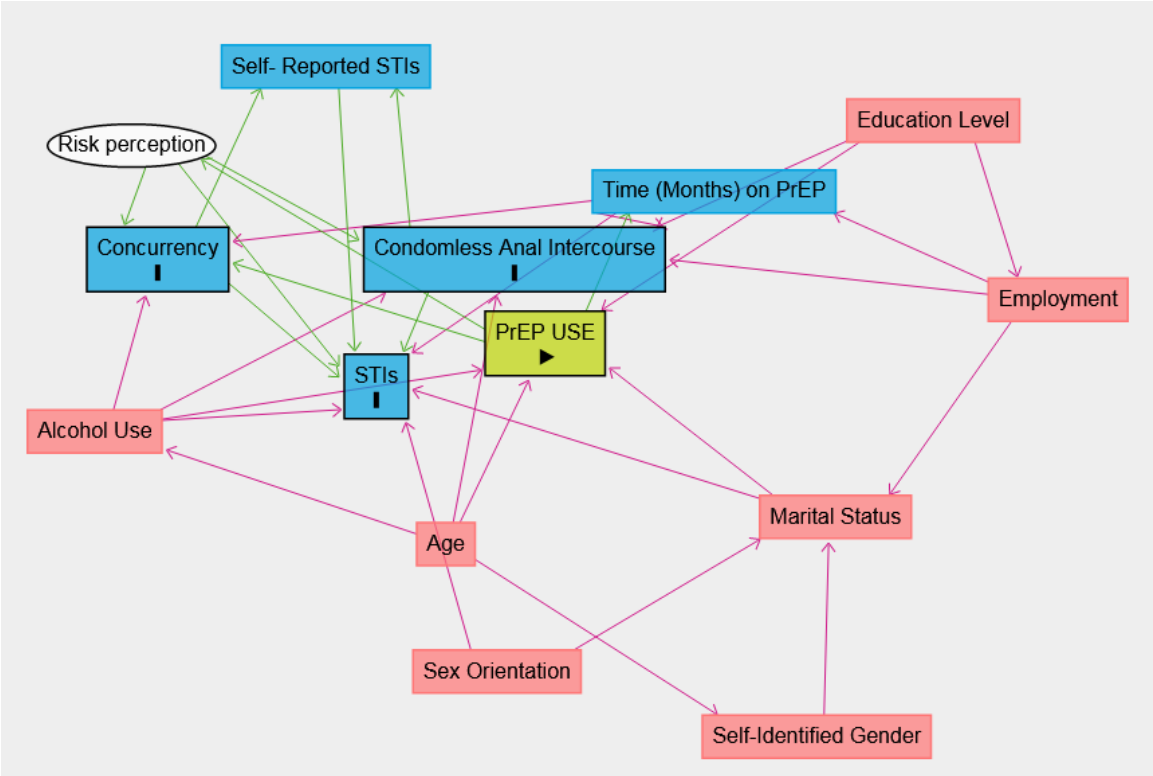
Legend

- exposure
- outcome
- ancestor of exposure
- ancestor of outcome
- ancestor of exposure *and* outcome
- adjusted variable
- unobserved (latent)
- other variable
- causal path
- biasing path

Summary

exposure(s)	**PrEP Self-Report**
outcome(s)	**PrEP Protective Adherence**
covariates	**11**
causal paths	**1**

Figure 2. 4: Directed Acyclic Graph[88] of the association between daily oral PrEP and prevalence of STIs, Concurrency and Condomless Anal Intercourse



Legend

- exposure
- outcome
- ancestor of exposure
- ancestor of outcome
- ancestor of exposure *and* outcome
- adjusted variable
- unobserved (latent)
- other variable
- causal path
- biasing path

Adjustment (total effect)

Minimal sufficient adjustment sets for estimating the total effect of PrEP USE on STIs,Condomless Anal Intercourse,Concurrency :

- Age, Alcohol Use, Education Level , Marital Status

Summary

exposure(s)	**PrEP USE**
outcome(s)	**STIs,Condomless Anal Intercourse,Concurrency**
covariates	**10**
causal paths	**17**

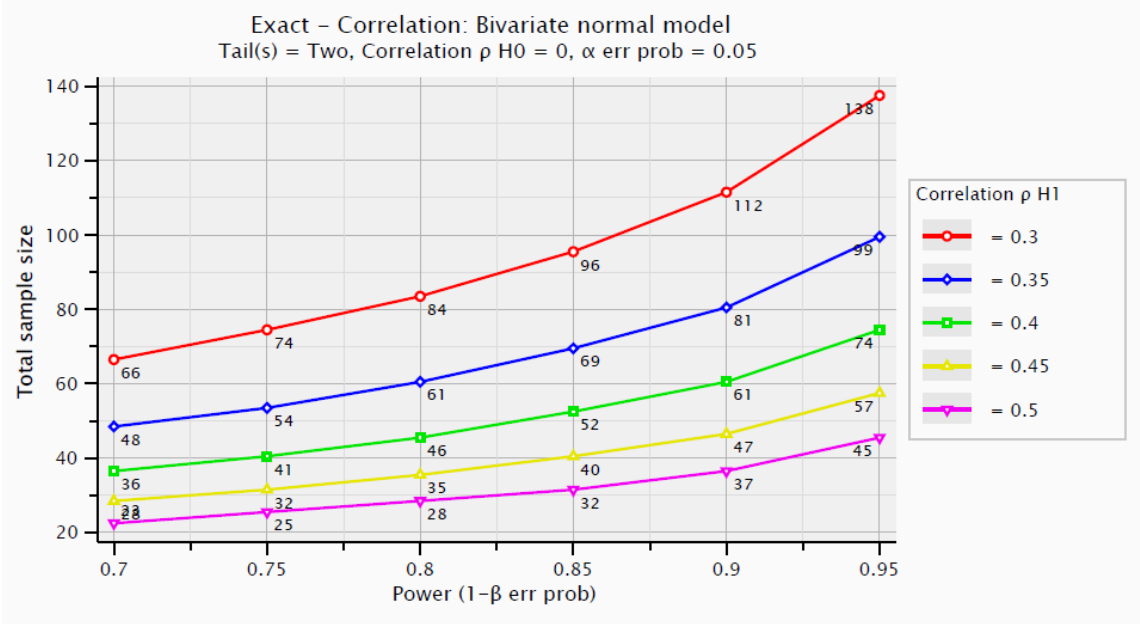
Sample Size and Power

Aim 1: To estimate the correlation between daily oral PrEP adherence by self- report and by serum Tenofovir and Emtricitabine levels.

All sample sizes and power analysis were calculated using G power 3.1.9.7 statistical software[89].

The sample size for Aim 1 was calculated using the assumption of correlation between dependent samples. Based on previous studies the correlation between self-report and biomarker surrogate report varies between 0.3 and 0.5[24,25]. For this hypothesis, there was an 80% chance of correctly rejecting the hypothesis that there is no discordance between self-reported PrEP adherence and serum level quantification of Tenofovir and Emtricitabine with a sample size of between 46 and 61 and a correlation of between 0.35 and 0.40 and alpha error of 0.05. (See figure 2.5)

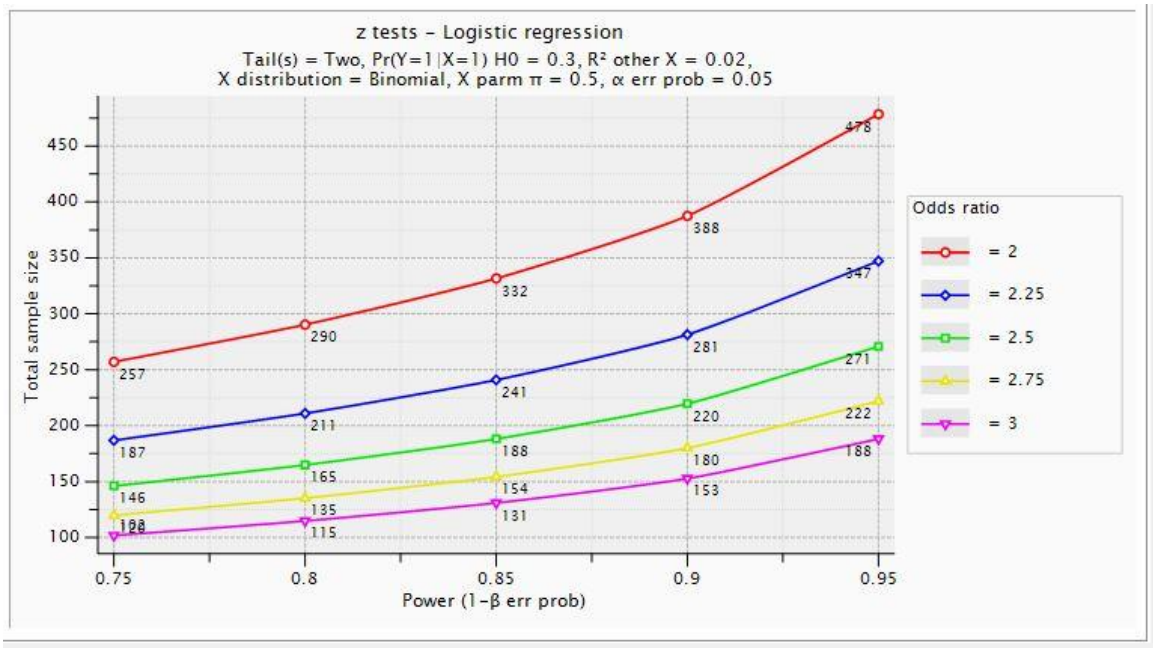
Figure 2. 5: Sample Size and Power Analysis for Aim 1



Aim 2: To assess the association between perceived or received social support and protective pre-exposure prophylaxis (PrEP) adherence

The sample size for this aim was calculated using the assumption of binomial distribution. Based on previous studies' reported odds of adherence, comparing those with and without perception of social support varies between 1.83 (95% CI: 1.27, 2.60) to 3.60 (95% CI: 2.55, 5.99)[55]. For this hypothesis, there was an 80% chance of correctly rejecting the null hypothesis that perception of social support is not associated with daily oral PrEP adherence with a sample size of between 165 to 211 participants, an alpha error probability of 0.05, and at least an OR of 2.25- 2.50. (See figure 2.6)

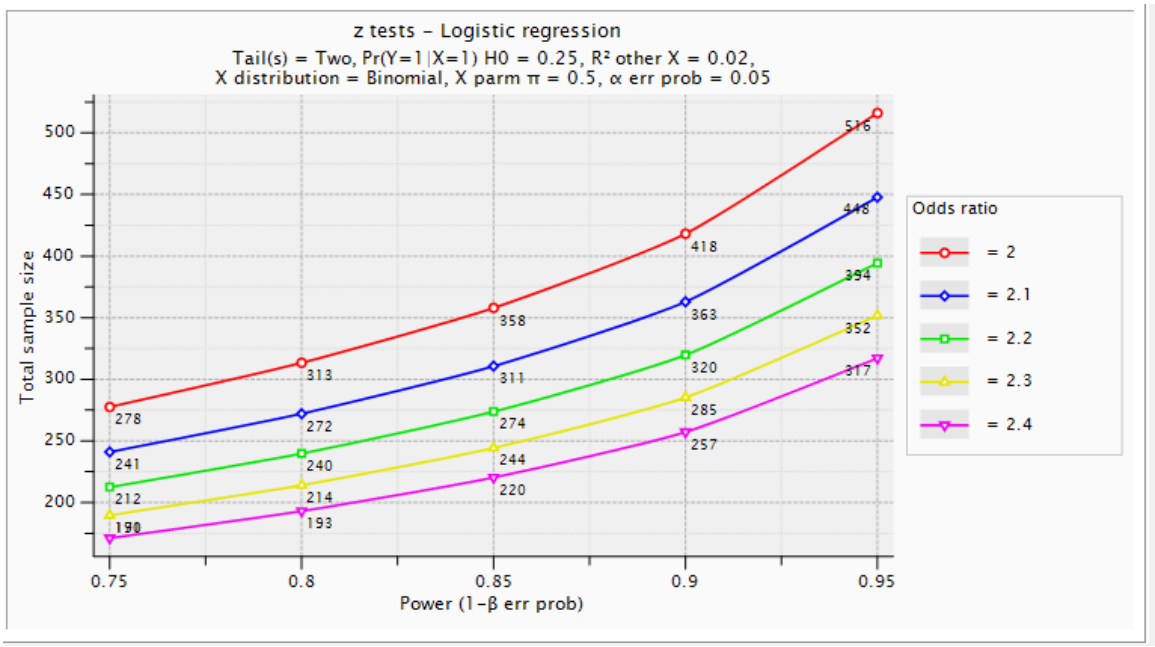
Figure 2. 6: Sample Size and Power Analysis for Aim 2



Aim 3: To estimate the effect of daily oral PrEP use on risky behavioral outcomes, that is, condomless anal intercourse among MSM in Nigeria.

The sample size was calculated based on the assumption of a binomial regression model. Previous studies have reported condom use during last sex with partners to range from between 40 -50% among MSM in Nigeria[90,91], as well as odds ratio (OR) between those with and without the use of daily oral PrEP ranges from 1.2 to 2.2[92]. For this hypothesis, there was an 80% chance of correctly rejecting the null hypothesis that daily oral PrEP is not associated with a change in condom use during last sex with a male partner, with a sample size of between 162 to 224 participants, an alpha error probability of 0.05 (See figure 2.7)

Figure 2. 7 : Sample Size and Power Analysis for Aim 3



Statistical Analysis:

Aim 1: Estimate the correlation between self-reported PrEP adherence and serum Tenofovir and Emtricitabine among MSM in Nigeria.

Exploratory Analysis:

After assessing for outliers and missingness, I utilized quantile- quantile (QQ) plots and box plots to assess the assumption of normality for variables. Numeric variables were expressed as a median and inter-quartile range and categorical variables were expressed as frequencies (percentages). Skewed variables were transformed using the QQ plots, box plots and coefficient of variation as a guide. For data variables to be re-coded, appropriate plots and distribution curves were plotted to determine the most clinically relevant and pragmatic boundaries.

Assessing Interactions:

Potential interaction variables were selected *a priori*, and an interaction term variable was created between the potential effect modifier and the primary predictor variable. A p value of less or equal to 0.05 was the criteria for significance of a potential interacting variable (effect modifier).

Assessing Confounding:

Categorical variables were assessed by frequencies and percentages, and continuous variables with medians and interquartile ranges. Baseline characteristics of participants were compared by the exposure (self-reported PrEP adherence) and the outcome (biomarkers assay) with Pearson's chi-squared and Fisher's exact tests as appropriate.

The covariates for the multivariable analysis were selected based on satisfying at least three of the following five criteria. An association with the exposure/predictor ($p \leq 0.05$), association with the outcome ($p \leq 0.20$), based on literature, meets the minimum sufficient adjustment set in directed acyclic graphs (DAG) and changes the regression coefficient estimates of the association between the outcome and predictor variable by at least 10%. Some variables were included based on clinical plausibility.

Analysis for statistical inference:

Aim 1: **Estimate the correlation between the self–reported adherence and Tenofovir / Emtricitabine (TFV-FTC) serum level measured in ng/ml between month 3 and month 9 study visits.**

A time-specific variable for each of the self-report and biomarker assay PrEP adherence variable to match study visit time points at month 3 and 9 were created. For the correlation between the self-report and biomarker surrogate PrEP adherence at each study visit, a Spearman's rank correlation method was used.

For paired assays (those with TFV-FTC quantification assay at different visit months), we made comparisons of the absolute changes between month 3 and 9 results using proportions and 95% confidence intervals. For each pair, we reported if there were no changes, negative changes, or a positive change between months 3 and 9. A positive change meant that the absolute value of an assay at month 9 was higher than month 3, while a negative change meant the absolute value of the assay was higher in month 3 than month 9. We used TFV quantification for this comparison.

Sub- Aim 1: **Explore the association between self-reported PrEP adherence and protective PrEP adherence**

The exposure variable for this sub- aim was the PrEP self-report and the outcome variable was the dichotomized biomarker assay (Protective adherence vs Non- protective adherence) using the 5.9ng/ml TFV threshold. A GEE model with an independent correlation structure was used to account for within-subject correlation of repeated measurements. This leveraged on the robustness of the sandwich variance estimates of the GEE method for potential misspecification of the most ideal covariance of the model[93].

Aim 2: **Determine the association between social support and pre-exposure prophylaxis (PrEP) protective adherence**

Exploratory Analysis:

The exposure variable was perceived functional social support categorized into informational, instrumental and emotional using a previously validated instrument[86,87]. A bi-variate analysis of factors associated with each social support domain was done with logistic regression.

The outcome for this aim was PrEP protective adherence. This was categorized (protective vs non – protective adherence) based on the TFV 5.9ng/ml threshold by Hendrix et al[28].

Assessing Interactions:

Potential interaction variables were selected *a priori,* and an interaction term variable was created between the potential effect modifier and the primary predictor variable. A p-value

of less or equal to 0.05 was the criteria for significance and therefore reporting of the stratified analysis by the interacting variable (effect modifier).

Assessing Confounding:

Categorical variables were assessed by frequencies and percentages, and continuous variables with medians and interquartile ranges. Distributions of variables were compared by their social support domains.

To be a confounder, a variable had to be associated with one or more of social support ($p \leq 0.05$), PrEP adherence ($p \leq 0.20$) in the bivariate analysis or based on literature review.

Criteria for entry in the multivariable model included any three of the following; association of the variable with the predictor, association with the outcome variable, significance in literature, and a change in the regression coefficient estimate of the primary predictor variable by at least 10%.

Analysis for statistical inference:

Logistic regression was used to explore the association between each of the social support domains and daily oral PrEP adherence. The models were created by adding one variable at a time to the crude model while assessing the change in significance and regression coefficient estimates. Variables that did not significantly improve the model fits were excluded except they had a known clinical significance.

Odds ratio and 95% confidence intervals were reported for each of the social support domains and their association with daily oral PrEP adherence.

Aim 3: **Determine the association between PrEP use and behavioral risk outcomes among MSM in Nigeria**

Exploratory Analysis:

Numeric variables were expressed as a median and inter-quartile range and categorical variables are expressed as frequencies (percentages). For data variables to be re-coded, appropriate plots and distribution curves were constructed to determine the most clinically relevant and pragmatic boundaries. In this aim, participants who had been in the parent study before PrEP initiation were compared with themselves post-PrEP initiation.

Analysis for statistical inference:

The outcome variable for this aim were risky behavioral outcomes (condomless anal intercourse with last male partners, concurrent partnerships with two or more male partners, and laboratory diagnosed STIs), while the exposure variable was the study time (pre-PrEP and post-PrEP periods). We compared participants' outcomes during pre- PrEP with themselves post-PrEP using a conditional logistic regression.

CHAPTER III: CORRELATES OF ADHERENCE MEASURES OF DAILY ORAL HIV PRE-EXPOSURE PROPHYLAXIS AMONG MSM IN NIGERIA IN AN OPEN LABEL STUDY.

Abstract

Introduction:

The WHO recommends pre-exposure prophylaxis (PrEP), a biomedical intervention that effectively prevents HIV acquisition among high-risk persons, given optimum adherence for any population with at least 3 per 100 – person-years HIV incidence rate. Among men who have sex with men (MSM) in Nigeria, the HIV incidence rate was 5.8 - 23.1 per 100-person-years in 2020. Findings are conflicting on self-reported PrEP adherence estimation of quantitative PrEP biomarkers. This study estimated the correlation as well as explored the sociodemographic and behavioral factors(age [16-24 years – younger vs ≥ 25 years-older]), condom use during last sex, concurrent partnerships, PrEP introduction methods, and time since PrEP initiation) associated with self-reported PrEP adherence and objective PrEP adherence in a low-income, high HIV burden, setting.

Methods

TRUST-PrEP was an open-label, single site-centered, prospective, five visits (baseline, month 1, 3, 6 and 9), one-year follow-up study that recruited 400 MSM in Abuja between April 2018 and May 2019 using provider-initiated and peer to peer PrEP introduction methods from the clinic and community respectively. The study exposure was self-reported PrEP adherence measured in ranks (poor, good, and very good), while the study outcome was serum Tenofovir (TFV) measured in nanogram per milliliter (ng/ml).

Protective PrEP adherence was defined as serum TFV concentration ≥ 5.9ng/ml. Clinical data, as well as biological samples for HIV, *Neisseria gonorrhea, Chlamydia trachomatis,* were collected at each visit except month 1 visit. Behavioral data were collected at baseline, month 3, and 9 visits. Serum samples for Tenofovir (TFV) and Emtricitabine (FTC) quantification assays were collected at month 3 and 9 study visits and analyzed using the liquid chromatography spectrometry methods (LCSM). A spearman's rank correlation was used to estimate correlations and Fisher's 95% confidence intervals. Generalized estimating equations with logistic regression was used to estimate the adjusted odds ratio for associations of self-reported PrEP adherence and other factors with protective PrEP adherence.

Results:

Of the 400 MSM (median age 23 [IQR 20-27] years) that initiated PrEP between April 2018 and May 2019, 314 quantification TFV and FTC serum assays for 219 persons were collected. Eighty-five (170/314, 54.1%) had paired assay between month 3 and 9 study visits. Of all persons with an assay, only 66/219, (30%, 95% CI: [24%, 36%]) had at least one record of protective PrEP adherence. Most participants, 68% (95% CI: 61%, 75%) over-reported their PrEP adherence.

Self-reported PrEP adherence and PrEP biomarkers were not significantly correlated. In bivariate analysis, clinic-based PrEP introduction, condomless anal intercourse during last sex, and disclosure of sexual orientation to the family had 5.40 (aOR: 95% CI: [2.67, 10.92]), 1.83 (aOR: 95% CI: [1.20, 2.79]) and 2.72 (aOR: 95%CI: 1.29, 5.72) increased odds of protective adherence respectively. In a longitudinal multivariable regression, self-reported PrEP adherence was not significantly associated with protective adherence. All

variables significant in the bivariate analysis except condomless anal intercourse were significant in the adjusted model.

Conclusion:

Self-reported PrEP adherence over-estimated protective PrEP adherence in this study, therefore we recommend a more objective method of assessing PrEP's adherence among the MSM in this population and similar settings. The clinic-based introduction method provided a one-stop haven for participants in this study, and hence may be an important facilitator of protective adherence in a highly homophobic setting like Nigeria.

Introduction

A growing body of literature recognizes the critical role HIV infection prevention among men who have sex with men (MSM) play in controlling the end of the AIDS epidemic[1,94,95]. In many countries, MSM bear between 15 to 70% burden of all incident HIV infections[3] despite constituting less than 3%[96] of the population. Nigeria has the second-largest HIV epidemic[6], and it made up 8% of the annual HIV incidence globally in 2019[97]. Despite the intensified and consolidated efforts that have led to a demonstrable lower HIV prevalence among the general population over the past two decades[75], the continued increase in the HIV prevalence among MSM remains unabated[1,98]. The risk of HIV transmission per 100,000 sexual exposures is approximately 83 and 138 for condomless receptive penile-vaginal intercourse and condomless receptive anal intercourse, respectively[5]. As compared to the 3 per 100- person-years WHO's recommendation for initiating PrEP in any given population, the incidence rate of HIV among MSM in Nigeria was 5.8 - 23.1 per 100-person- years in 2020[99].

MSM living in Nigeria have peculiar challenges accessing health care services mostly because of the highly homophobic environment[78,100] as well as a high proportion of internalized homophobia[79]. In a previous Nigerian study[79], as high as a third of MSM reported internalized homophobia which in turn has been associated with worse health-seeking behaviors[80]. Therefore, making PrEP accessible to MSM in Nigeria, with an appropriate risk reduction messaging as well as adherence counselling, presents a discrete opportunity for an additional HIV prevention intervention.

Biomedical prevention chemoprophylaxis vis a vis daily oral HIV pre-exposure prophylaxis (PrEP) has been demonstrated to reduce HIV infection among high-risk groups including but not limited to MSM[9,26]. The most common reason PrEP implementation fails is poor adherence[9,101]. PrEP adherence has received considerable attention, and it continues to be a focus of discourse underscoring its importance in the global scheme of plans for ending new HIV infections. Addressing PrEP adherence is particularly challenging given that some PrEP users lack the inherent motivation typically associated with taking a therapeutic rather than a prophylactic medication[102]. Because of the strong association that has been demonstrated between adherence and the success of most PrEP implementation programs[9,10,103], several studies[17,19,49,50] have investigated various methods of PrEP adherence measurement over the past few years.

Since PrEP's approval by the FDA in the year 2012[42,43], dried blood spots[28,30,44], hair follicles[44–46], urine[29,47,48], and self-report[17,22,44,45,49,50] amongst others have been studied for PrEP adherence measures across various climes globally. Several investigators have combined at least two methods[22,49] typically including a less invasive, more cost-effective screening for PrEP adherence, or lack thereof routinely (e.g., self-reported adherence) and a more rigorous, typically more invasive objective method (e.g. Tenofovir[TDF] and Emtricitabine[FTC] serum quantification assay). Based on this model, some previous studies[17,51,52] have shown that self-reported PrEP adherence had sometimes over-estimated the subjective equivalence, for example, participants of the ATN-110 / ATN-113 over reported adherence by 40% (95%: 31%, 49%) In contrast, other studies[25,30,53] have shown that self-reported PrEP adherence is a good proxy for PrEP adherence. The debate about

the correlation between self-reported PrEP adherence and the PrEP biomarkers is still relevant.

While most of the studies[17,28,44] that have investigated the objective assessment of self-reported PrEP adherence among MSM have been done in high income, and relatively low HIV burden settings, there have been none in West Africa where most of the HIV epidemic burden lies. Therefore, the previous studies' generalizability to low-middle income and high HIV burden settings like West Africa may be limited.

This study measured the correlation between self-reported methods of daily oral PrEP adherence and the daily oral PrEP assay biomarkers (protective adherence) and factors (age, education, alcohol intake, and use of condom during last anal sex) associated with this in Nigeria, a low income, high HIV burden country. The main objective of this study was to estimate the correlation between self-reported PrEP adherence and the serum TDF and FTC assay that was further explored as a binary measure of protection. We hypothesized that there will be an increased discordance between the self-reported PrEP adherence and biomarkers estimate at month 9 compared with month 3, post-PrEP initiation.

Methods

Study design and sample population

The TRUST study group had previously reported that compared with MSM in earlier waves of recruitment, those in later waves are characterized by a low proportion of uptake of HIV voluntary counseling and testing, high rate of newly diagnosed HIV infection, low

uptake of clinical services, and a high viral load [82]. This informed the need for identification and engagement of key influential MSM among study participants recruited in the earlier waves, called popular opinion leaders (POLs) for didactic training on peer to peer PrEP introduction and recruitment of MSM from their networks[104]. A total of 32 POLs each had a four-week training in three batches between May 2018 and September 2018.

In the TRUST-PrEP study, we introduced the study participants to PrEP via two methods - the peer-to-peer introduction (also called community-based method) and the provider-initiated introduction (also called the clinic-based method). For the community-based method, the trained POLs engaged MSM within their community and networks, discussed PrEP with them, and recruited those interested via the use of coupons. Each POL was provided three coupons for each wave of recruitment of three MSM from their network. More coupons were rendered to POLs for a maximum of three waves of recruitment (that is, a POL had a minimum of 0 recruitment and a maximum of 9). On presenting to the clinic, the community recruited MSM were screened and assessed for eligibility for the TRUST study initially, and if eligible, they were required to complete the PrEP study willingness questionnaires before they were assessed for TRUST-PrEP study's eligibility. For the clinic-based method, providers discussed PrEP with all the MSM attending routine TRUST clinics and those interested were further required to complete the willingness questionnaires, screened and assessed for eligibility for the TRUST-PrEP study. The TRUST-PrEP study's enrollment started in April 2018 and ended in May 2019, and study follow-up continued until June 2020.

Study population and eligibility criteria:

The study population was MSM residing in Abuja, North-central Nigeria, and its environs.

To be eligible for enrollment in the TRUST-PrEP study, the participant had to meet the parent study's (TRUST) criteria. This includes "male" assignment at birth, history of receptive or insertive anal sex with another male in the last 12 months and the ability to provide informed consent in local language or English. At enrollment, they presented a valid study coupon, was at least 16 years of age (considered able to access sexual and reproductive health and HIV care and research without parental consent)[83], was HIV-negative and consented to use daily oral PrEP and biological specimen collection at each visit for the study period. They also met at least one of the screening criteria for "substantial risk for HIV infection".

1. Sexually active with a report of any of the following in the past three months
    a. Condomless vaginal or anal intercourse with more than one partner
    b. Sex partner with ≥1 HIV risk. HIV risks include:

Injection of drugs, sex with other males, Transgender person, sex worker, condomless sex with multiple partners, unknown HIV status, living with HIV

    c. Recent history of STI (within the past 3 months) based on self-report, lab diagnosis or syndromic STI treatment
2. History of sharing injections or injection materials in the last three months
3. History of sexual partner who is HIV positive and who has not been on effective HIV treatment in the last three months. A person is defined as not being on effective HIV treatment if they are less than 6 months on ART or have inconsistencies or unknown adherence.

Data collection:

This was a 5-visit study – baseline, Month 1, 3, 6 and 9. At baseline, demographic and behavioral information were collected, as well as biological samples (blood and rectal swabs) for sexually transmitted infections (HIV, urethral and rectal Neisseria gonorrhea and Chlamydia trachomatis). These biological samples were collected at every visit except Month 1. At month 1, an interviewer based, a 30-day PrEP self-reported questionnaire was administered and this was collected at every subsequent visit. At month 3, PrEP bio-markers assays were collected and this was repeated at month 9 as well. Post baseline follow up behavioral questions were asked at month 3 and 9. All participants included in study were HIV negative and consented to taking daily oral PrEP.

The study protocol allowed a window of two weeks before and four weeks after the expected day of visit for participants who reported early or late, respectively.

Laboratory methods:

The IHVN biorepository laboratory initially centrifuged, separated, and stored blood samples for PrEP quantification as serum at a temperature of -80° C. The samples were stored until a minimum threshold of a hundred samples was met for shipping to the United States. The final liquid chromatographic tandem mass spectrometry (LCMS) assay analysis[105] was conducted at John Hopkins University's pharmacology laboratory.

The serum TFV and FTC quantification:

Calibration standards and quality controls for TFV were prepared by spiking a set volume of working stock solutions into plasma. All standards and quality controls were aliquoted

and stored at ≤ -70 °C. TFV was isolated from plasma via protein precipitation and quantified via LCMS. The calibration curves were generated via linear regression with $1/x^2$ weighting. The range of calibration for serum TFV is 0.31- 1000ng/ml. A similar quantification method was done for FTC and the range of calibration was 0.31 – 5000ng/ml. Serum TFV and FTC below 0.31ng/ml were classified as below the limit of quantification (BLQ). The threshold values for defining not more than once a week, at least four times a week, and daily use are ≤ 0.5ng/ml (0.5-0.6), 5.9ng/ml (4.6- 6.4), and 52.0 ng/ml(49.0-55.6), respectively, based on the median TFV serum concentration at a steady state. Similarly, for FTC, the thresholds for defining not more than once a week, at least four times a week, and daily use are ≤ 0.8 ng/ml (0.4-0.9), 6.7ng/ml (5.4-7.6) and 70.9ng/ml (67.7 -81.9)[28,84] respectively based on the median FTC serum concentration at a steady state. Analyst 1.6 software (version 1.6.2 Build 8489) (SCIEX, Redwood city, CA) was used to acquire and analyze the chromatographic data[106].

Study Variables:

Outcome variable: Serum Tenofovir (TFV) and Emtricitabine (FTC) were measured as both continuous and dichotomized variables. The lower limit of quantification of TFV and FTC is 0.31 ng/ml, and the range is from 0.31-1,000 ng/ml and 0.31-5,000 ng/ml, respectively. For Aim 1 (main aim), we used a cube-rooted value of the absolute measure, that is *"cube-rooted ng/ml",* while for the sub-aim, TFV and FTC adherence were dichotomized at 5.9 ng/ml and 6.7 ng/ml, respectively, based on the median serum concentration of four tablets per week required for protective adherence[28]. In this study, we defined PrEP protective adherence as any serum TFV concentration equal to or higher than 5.9 ng/ml irrespective of assay time.

Exposure variable: The primary exposure for this study was the daily oral PrEP adherence self-report. This was reported on a 4 point Likert scale as *"Poor", "Good", Very good" or "Perfect"* in response to the question *" How would you describe your adherence over the last one month?"* asked at every study visit. For the main Aim 1, this was analyzed as a rank variable (poor, good, and very good). For the sub-aim 1, self-reported PreP adherence (SRPA= "Yes") was defined as those that reported "*very good"* or "*good*" and non-adherence (SRPA= "No") as those that reported "poor". Very few participants reported, "*perfect*", hence, that response was categorized with "very good".

Covariates: Demographic variables including age, an education level (≤ high school or > high school), marital status (never married or ever married), employment status (yes or no), gender identity (cisgender man, transgender women and others), and religion (Christianity, Islam or others). Age was dichotomized into (younger [16-24] or older [≥ 25 years]) a binary variable. Behavioral variables included sexual orientation (homosexual or bisexual), condom use during last sex with a male partner (yes or no), concurrent partnership with two or more male partners (yes or no), number of days drank alcohol in the past 30 days ("Alcohol use" 0-2 [No], ≥3 [Yes]). Others include the PrEP introduction approach (clinic-based or community-based), disclosure of sexual orientation to the family (yes or no), and study time – months since PrEP initiation (3 or 9).

Statistical Analysis:

A univariate analysis for each variable was conducted. To categorize self–reported PrEP adherence as a binary variable, an area under the curve (AUC) was estimated using a receiver operating characteristic (ROC) curve to evaluate how accurately each level of

self–reported adherence predicted protective adherence. The Youden's index was used to determine the self-report level with the optimal cut-off point for protective adherence[107]. Hence, "*perfect"*, "*very good*", and "*good*" were categorized as "PrEP adherent" and "*poor*" as PrEP non-adherent". We compared demographic, behavioral, and clinical characteristics between self-reported PrEP adherent and self-reported PrEP non-adherent respondents using Pearson's chi-square and fisher's exact test for categorical variables with a bivariate analysis. We sought to determine each baseline variable's association with the self-reported PrEP adherence using logistic regression to estimate crude odds ratio and 95% confidence interval. A partial spearman's rank correlation test, controlling for significant demographic variables, was utilized to examine the correlation between the biomarker PrEP assay and the self-reported PrEP adherence at month 3 and 9 visits respectively. In addition to Spearman's rank correlation, a smoothing plot using the loess procedure was fit to determine the non-parametric association between self-reported and protective PrEP adherence. The loess procedure[108] is ideal for data with outliers and a robust fitting. It also allows for good flexibility because of the less rigorous parametric assumptions required.

For paired assays (those with TFV-FTC quantification assays at different visit months), we made comparisons of the absolute changes between month 3 and 9 results using proportions and 95% confidence intervals. For each pair, we reported if there were no changes, negative changes, or a positive change between months 3 and 9. A positive change meant that the absolute value of an assay at month 9 was higher than month 3, while a negative change meant the absolute value of the assay was higher at month 3 than month 9. We used TFV quantification for this comparison.

To assess for potential effect modifier, potential interaction variable (age) was selected *a*

priori, and an interaction term was created with the self-reported PrEP adherence (primary exposure variable). A p-value of less or equal to 0.05 was significant. In addition, we used the Breslow-Day homogeneity test[109] to assess if age modified the association between the PrEP introduction method and protective adherence. This was done with the cumulative TFV quantification assay, irrespective of the time of collection. To be included in the multivariable analysis as a confounder, a variable needed to meet at least three of the five criteria. Be associated with the exposure variable ($p \leq 0.05$), the outcome ($p \leq 0.20$), a known confounder in the literature, be identified by directed acyclic graph (DAG) as a minimal set of priori confounders (age, educational status, PrEP introduction approach, Alcohol use and MSM disclosure of sex orientation). Variables were added to the model one at a time and retained if significant. The "Study time" variable was added for plausibility.

After testing the model fits of different within-subject correlation specifications, a generalized estimating equation (GEE) with an independent correlation structure was the most parsimonious correlation structure option. However, the GEE sandwich variance estimates are robust and can correct most correlation mis-specifications[93]. With regards to exposure and outcome variables, a complete case analysis was conducted for the Spearman's correlation. For other analyses, all variables missing the outcomes were treated with list-wise deletion and last observed carried forward for those missing exposure variables[110]. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC,USA).

Results

A total of 400 participants between the ages of 17 and 54 years initiated PrEP between April 2018 and May 2019. The participants' median age was 23 years with an interquartile range of between 20 and 27 years. The majority (51.3%) were introduced to PrEP from the community-based approach. A higher proportion (61.3%) had at least a secondary school education, 82% were employed, 84% self-identified as male gender, while 77% were bi-sexual. Almost all (98.9%) were never married.

A total of 314 PrEP biomarker assays from 219 respondents had at least one documented PrEP biomarker assay. Of those with PrEP biomarker assay, [66/219] 30% (95% CI: 24%, 36%) had protective PrEP adherence. Overall, there were 93 paired and 128 unpaired assays. An assay was paired if a respondent had at least two TFV and FTC quantification assays at different study visits. The vast majority ([85/93] 91.3%) of the paired assays were between the month 3 and 9 study visits. When comparing the absolute TFV serum assay level of paired samples at month 3 with those of month 9, [42/85] 49% (95% CI: 39%, 60%), had no changes, [35/85] 41% (95% CI: 31%, 52%) had negative changes, and [8/85] 9% (95% CI: 3%, 15%) had positive changes. Of the paired results with negative changes, [24/35] 68% (95% CI: 53%, 83%) had a detectable assay at month 3 but were undetectable at month 9 study visit. However, [9/11] 81% (95% CI: 59%, 100%) of those with detectable negative changes at month 9, not only had detectable assays at both study visits but had protective adherence as well. Comparing all paired assays with protective adherence at month 9, [15/85] 18% (95% CI: 10%, 26%) with those with protective adherence at month 3, [30/85] 35% (95% CI: 25%, 45%), there was a significant negative

change (Z= -2.60, p=0.01). All assays with no changes (N=42/85) had below the limit of assay quantification at both study visits.

Of all 219 respondents, 81 (37%) had a detectable assay (TFV ≥ 0.31ng/ml) and 66 (30%) achieved protective adherence (TFV ≥ 5.9ng/ml). Using the adherence benchmarks[28] of pharmacokinetics serum TDF, with >95% sensitivity and specificity for detection of the number of TDF taken in the past seven days, of those that did not achieve protective adherence, [138/153], it can be deduced that about 90% did not take any dose of TDF in the past week before their assay. In contrast, of those with protective adherence, [41/66], it can be deduced that 62% took their TDF every day of the last seven days before their assay. Of those with self-reported PrEP adherence records, [176/218] 81% (95% CI: 75%, 86%) reported at least "good" PrEP adherence over the past month of their interview date. Of all PrEP adherence self-reports paired with biomarkers assays, [120/176] 68% (95% CI: 61%, 75%) objectively over-reported their PrEP adherence. Table 3.1 shows the univariate analysis of baseline characteristics of study participants.

Table 3. 1: Baseline Characteristics of study participants (Univariate Analysis)

Characteristics	N=219 n (%)
Age (Years)	
Younger (16-24)	118 (53.9)
Older (≥25)	101 (46.1)
# Education	
≤ High school	80 (61.2)
> High School	53 (39.8)
Employment	
Unemployed	40 (18.3)
Employed	179 (81.7)
# Sex orientation	
Homosexual	27 (20.5)
Bisexual	105 (79.5)
# Gender identity	
Cisgender man	113 (85.6)
Transgender & Others	19 (14.4)
# Marital Status	
Never married	129 (98.5)
Ever married	2 (1.5)
# Condom use (last anal sex with male)	
Yes	125 (69.1)
No	56 (30.9)
# Concurrent partnership(with ≥2 males)	
Yes	61 (33.7)
No	120 (66.3)
# Alcohol in the last 30 days	
No	75 (56.4)
Yes	58 (43.6)
Same Sex Disclosure (Family)	
No	203 (92.7)
Yes	16 (7.3)
Same Sex Disclosure (Health Care Worker)	
No	143 (65.3)
Yes	76 (34.7)
PrEP introduction	
Community-based	100 (45.6)
Clinic-based	119 (54.3)
Protective Adherence	
No	153 (69.9)
Yes	66 (30.1)
# Self-Reported PrEP Adherence	
No	42 (19.3)
Yes	176 (80.7)
#: N does not add up to 219 because of missing variables.	

In the bivariate analysis (Table 3.2), stratified by self-reported PrEP adherence and non-adherence, the median and interquartile ranges of the age of those in each category were 23 (IQR: 20-27) and 25 (IQR: 22-28) years respectively; otherwise, there was no difference in baseline characteristics. However, some covariates were significantly associated with the protective PrEP adherence (biomarker assay) in this study (Table 3.3). Compared with participants introduced to PrEP from the community, those with PrEP introduction from the clinic had 5.4 increased odds (OR: 5.40, 95% CI [2.67, 10.92]) of protective PrEP adherence. Compared with older MSM, younger MSM had 42% decreased odds (OR: 0.58, 95% CI [0.33, 1.03]) of protective PrEP adherence. Compared with those who did not disclose their sexual orientation to family members, those that disclosed had 2.7 increased odds (OR: 2.72, 95% CI [1.29, 5.72]) of protective PrEP adherence. Compared with month 3 study visits, participants had 1.6 increased odds (OR: 1.61, 95% CI [0.80, 3.20]) of protective PrEP adherence at month 9 visits, however, this was not statistically significant. The Breslow-Day Test[109] for homogeneity of odds ratio was used to assess age as a potential modifier of the association between the PrEP introduction approach and protective PrEP adherence. After stratifying by age (older and younger), those with the clinic-based PrEP introduction approach, compared with the community-based approach had 2.9 (OR: 2.9, 95% CI: [1.18, 7.54]) and 6.4 (OR: 6.4, 95% CI: [2.30, 17.6]) increased odds of protective adherence in the older and younger strata, respectively. The common odds ratio was 4.2 (95% CI: 2.17, 8.40) and the p =0.26 for homogeneity of the odds ratio.

Table 3.2: Baseline characteristics stratified by self-reported PrEP adherence among MSM in Nigeria

Characteristics	Total N=218 n (%)	SRPA (Yes) N=176 n (%)	SRPA (No) N=42 n (%)	p-value
Age (Years)				
Older (≥25)	100 (45.9)	77 (43.7)	23 (54.8)	0.20
Younger (16- 24)	118 (54.1)	99 (56.3)	19 (45.2)	
# Education				
≤ High school	80 (60.6)	68 (64.2)	12 (46.2)	0.09
> High School	52 (39.4)	38 (35.8)	14 (53.8)	
Employment				
Unemployed	39 (17.9)	30 (17.0)	9 (21.4)	0.50
Employed	179 (82.1)	146 (83.0)	33 (78.6)	
# Sex orientation				
Homosexual	27 (20.6)	20 (18.9)	7 (28.0)	0.30
Bisexual	104 (79.4)	86 (81.1)	18 (72.0)	
# Gender identity				
Cisgender man	112 (85.5)	92 (86.8)	20 (80.0)	0.36†
Transgender & others	19 (14.5)	14 (13.2)	5 (20.0)	
# Condom use(last sex)				
Yes	124 (68.9)	101 (69.2)	23 (67.6)	0.86
No	56 (31.1)	45 (30.8)	11 (32.4)	
# Concurrency (males only)				
Yes	66 (36.7)	56 (38.4)	10 (29.4)	0.32
No	114 (63.3)	90 (61.6)	24 (70.6)	
# Alcohol in the last 30 days				
0-2	74 (56.0)	60 (56.1)	14 (56.0)	0.99
≥3	58 (44.0)	47 (43.9)	11 (44.0)	
Same Sex Disclosure (family)				
Yes	16 (7.3)	14 (8.0)	2 (4.8)	0.47†
No	202 (92.7)	162 (92.0)	40 (95.2)	
Same Sex Disclosure (HCW)				
Yes	75 (34.4)	60 (34.1)	15 (35.7)	0.84
No	143 (65.6)	116 (65.9)	27 (64.3)	
Time				
Month 3	64 (29.4)	49 (27.8)	15 (35.7)	0.31
Month 9	154 (70.6)	127 (72.2)	27 (64.3)	
PrEP introduction				
Community-based	99 (45.4)	81 (46.0)	18 (42.9)	0.71
Clinic-based	119 (54.6)	95 (54.0)	24 (57.1)	

SRPA: Self-Reported PrEP Adherence. | HCW: Health Care Workers
Pearson chi-square and fisher's exact test [†] were used for categorical variables and categorical variables with expected cell count less than 5 respectively.
Missing variables [#] does not add up to N.

Table 3. 3: Independent association with Protective PrEP adherence among MSM in Nigeria

Characteristics	Total N=219 (%)	Protective Adherence (Yes) N=66 (%)	Protective Adherence (No) N=153 (%)	Crude OR (95% CI)	p- value
#Self-reported PrEP Adherence					
No	42 (19.3)	10 (23.8)	32 (76.2)	Ref	
Yes	176 (80.7)	56 (31.8)	120 (68.2)	1.96 (0.84, 4.53)	0.12
PrEP introduction					
Community-based	100 (45.7)	14 (14.0)	86 (86.0)	Ref	
Clinic-based	119 (54.3)	52 (43.7)	67 (56.3)	**5.40 (2.67, 10.92)**	**< 0.01**
Age (Years)					
Older (≥25)	101 (46.1)	39 (38.6)	62 (61.4)	Ref	
Younger (16-24)	118 (53.9)	27 (22.9)	91 (77.1)	0.58 (0.33, 1.03)	0.06
# Education					
≤ High school	80 (60.2)	14 (17.5)	66 (82.5)	Ref	
> High School	53 (39.8)	15 (28.3)	38 (71.7)	1.86 (0.81, 4.22)	0.14
Employment					
Unemployed	40 (18.3)	10 (25.0)	30 (75.0)	Ref	
Employed	179 (81.7)	56 (31.3)	123 (68.7)	0.96 (0.48, 1.91)	0.91
# Sex orientation					
Homosexual	27 (20.5)	9 (33.3)	18 (66.7)	Ref	
Bisexual	105 (79.5)	20 (19.1)	85 (80.9)	0.47 (0.18, 1.20)	0.11
# Gender identity					
Cisgender man	113 (85.6)	27 (23.9)	86 (76.1)	Ref	
Trans/ Others	19 (14.4)	2 (10.5)	17 (89.5)	0.37 (0.08, 1.73)	0.21†
#Condom use (last sex)					
Yes	125 (69.1)	32 (25.6)	93 (74.4)	**Ref**	
No	56 (30.9)	18 (32.1)	38 (67.9)	**1.83 (1.20, 2.79)**	**<0.01**
#Concurrency (Males)					
No	115 (63.5)	37 (32.2)	78 (67.8)	Ref	
Yes	66 (36.5)	13 (19.7)	53 (80.3)	0.78 (0.53, 1.14)	0.20
#Alcohol(last 30 days)					
0-2	75 (56.4)	19 (25.3)	56 (74.7)	Ref	
≥ 3	58 (43.6)	16 (27.6)	42 (72.4)	1.23 (0.72 , 2.13)	0.44
Same Sex Disclosure (family)					
No	203 (92.7)	56 (27.6)	147(72.4)	Ref	
Yes	16 (7.3)	10 (62.5)	6 (37.5)	**2.72 (1.29, 5.72)**	**0.01**
Same Sex Disclosure (HCW)					
No	143 (65.3)	36 (25.2)	107(74.8)	Ref	
Yes	76 (34.7)	30 (39.5)	46(60.5)	**1.50 (1.15, 1.98)**	**<0.01**
Time (Months)					
3	65 (29.7)	16 (24.6)	49 (75.4)	Ref	
9	154 (70.3)	50 (32.5)	104 (67.5)	1.61 (0.80, 3.20)	0.18

Generalized estimating equations (Logistic) regression was used to calculate OR and 95% CI.
Bolded confidence intervals indicate significance at $p < 0.05$.
Due to missingness [#] , all variables does not add up to N.

A crude spearman's rank correlation between ranked (poor, good and very good) self-reported PrEP adherence and TFV quantification assay (ng/ml, cube-rooted) PrEP biomarker assay at months 3 and 9 were 0.1 (95% CI: -0.12, 0.31) and 0.02 (95% CI: -0.20, 0.20), respectively. Table 3.4 shows more details of the FTC correlations as well as the correlation between other variables. After controlling for age, education, and employment, the partial Spearman's rank correlation between self-reported PrEP and biomarker assay at months 3 and 9 did not change.

Table 3.4: Spearman correlation coefficient between PrEP adherence methods

Spearman correlation coefficients of quantification of TFV-FTC [ng/ml, cube-rooted] and self-reported adherence measures [ranked poor, good and very good].				
	Serum TFV (Month 3) ṗ (95% CI) N	Serum FTC (Month 3) ṗ (95% CI) N	Serum TFV (Month 9) ṗ (95% CI) N	Serum FTC (Month 9) ṗ (95% CI) N
Self- Reported Adherence (Month 3) N	0.1 (-0.12,0.31) 81	0.2 (-0.04, 0.38) 81	0.1 (-0.08, 0.34) 81	0.2 (-0.01,0.40) 81
Self- Reported Adherence (Month 9) N	0.04 (-0.17, 0.24) 81	0.08 (-0.13, 0.29) 85	0.02(-0.20,0.2) 85	0.08(-0.14, 0.28) 85
All p values are less than 0.05. N: Number of observations. 95% CIs were calculated using Fisher's transformation method.				

To further explore the relationship between the two PrEP adherence methods, smoothing plots were fit using the residual plots as a guide for the best smoothing parameter value. The smoothing plots are shown in figures 3.1 and 3.2 below.

Figure 3.1: Fit Plots between self-reported PrEP adherence and biomarker assay at Month 3

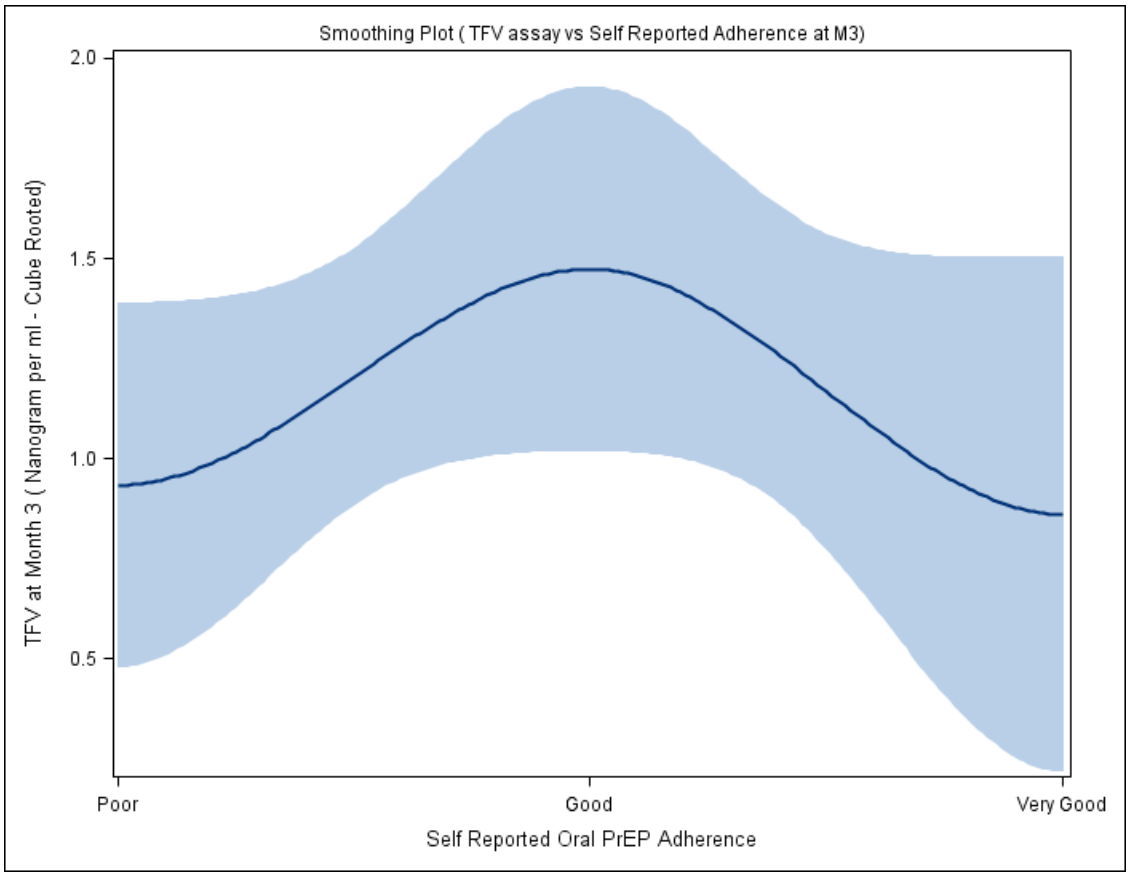
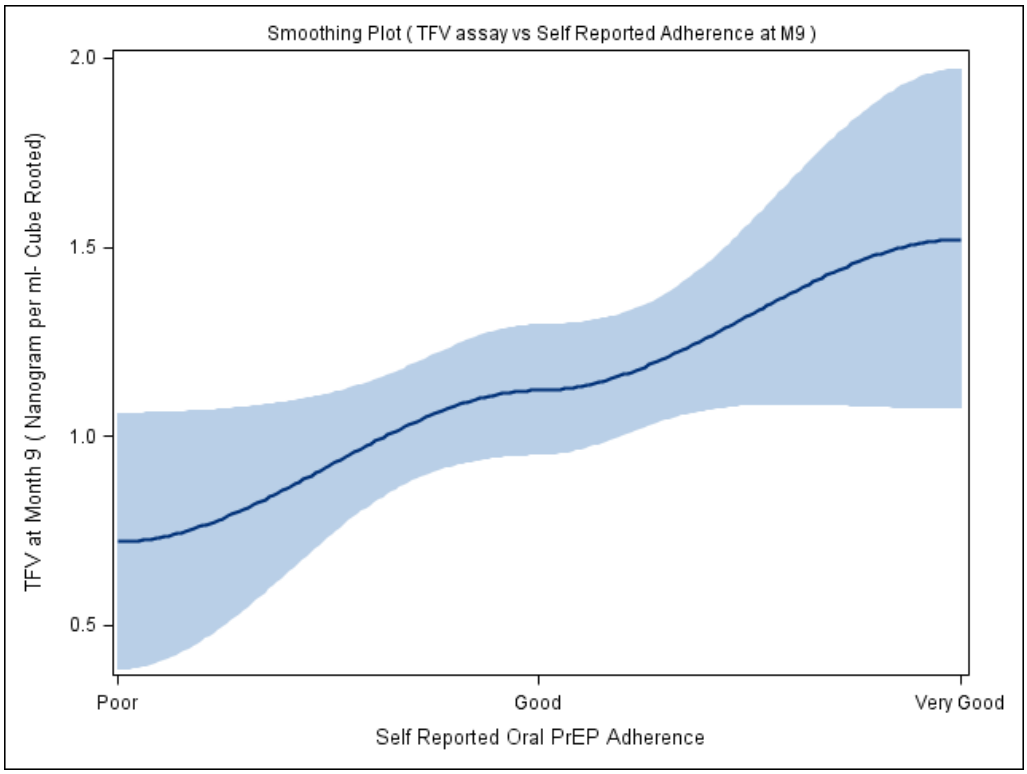


Figure 3.2: Fit Plots between self-reported PrEP adherence and biomarker assay at Month 9



At month 3 study visits, the association between self-reported PrEP adherence and biomarker assay was initially linear positive until it peaked at *"good,"* after which a negative linear association was observed with those that self-reported *"very good*." However, at month 9, there was a gradual linear association of self-reported PrEP assay and biomarkers and a further increased association between those who reported *"very good"* and their biomarker assay, unlike month 3.

In the multivariable GEE (logistic) regression analysis, only the PrEP introduction approach and disclosure of sexual orientation to family members remained significantly associated with protective PrEP adherence. Adjusting intra-subject correlations, those who self-reported PrEP adherence had 2.13 increased odds (OR: 2.13, 95%CI: [0.85, 5.18]) of protective PrEP adherence compared with those that self-reported poor adherence. Table 3.5 shows the multivariable regression analysis.

Table 3.5: Multivariable analysis of factors associated with PrEP protective adherence

Multivariable analysis of Self-reported PrEP adherence and protective PrEP adherence among Nigerian MSM				
Characteristics	Crude OR (95% CI)	p- value	Adjusted OR (95% CI)	p- value
Self-reported PrEP adherence				
No	Ref		Ref	
Yes	1.96 (0.84, 4.53)	0.12	2.10 (0.85, 5.18)	0.11
PrEP introduction				
Community-based	Ref		**Ref**	
Clinic-based	**5.40 (2.67, 10.92)**	**<0.01**	**8.35 (3.24, 21.52)**	**<0.01**
Age (Years)				
Older(≥25)	Ref		Ref	
Younger (16-24)	0.58 (0.33, 1.03)	0.06	1.02 (0.51, 2.05)	0.95
Condom Use (last anal sex)				
Yes	**Ref**		Ref	
No	**1.83 (1.20, 2.79)**	< 0.01	1.65 (0.99, 2.74)	0.05
Same Sex Disclosure (family)				
No	Ref		**Ref**	
Yes	**2.72 (1.29, 5.72)**	**0.01**	**3.60 (1.73, 7.51)**	**<0.01**
Time(month post-PrEP initiation)				
3	Ref		Ref	
9	1.61 (0.80, 3.20)	0.18	2.30 (0.98, 5.38)	0.06

Generalized Estimating Equations with an independent correlation structure was used for multivariable analysis. The model was adjusted for the PrEP introduction approach, participants' age, disclosure of sexual orientation to family members, condom use during last sex with a male partner, and time of the study.
Bolded confidence intervals indicate significance at $p < 0.05$.

The sensitivity, specificity, positive predictive value and negative predictive value of self-reported PrEP adherence using the biomarker assay as the gold standard test is 85% (95%

CI: 76%, 93%), 21% (95% CI: 14%, 27%), 32% (95% CI: 25%, 39%) and 76% (95% CI: 63%, 89%) respectively.

Regarding missingness, participants with a missing "alcohol use variable" were more likely to have had protective PrEP adherence than those not missing those variables in this study. The mean *"between study"* visits attrition rate in this trial was 23% (95% CI: 11%, 35%), starting with the 400 participants at the initial visit and 161 that completed all study visits.

Discussion.

This study suggests that among MSM in Nigeria, self-reported PrEP adherence is neither statistically significantly correlated nor associated with TFV-FTC quantification assay or protective PrEP adherence respectively. However, other findings provided more insight into PrEP adherence measures within the context of resource-limited settings. Of note, in this study, self-reported PrEP adherence overestimated protective PrEP adherence. Specifically, more than two-thirds of study participants over-reported their PrEP adherence. These findings are consistent with observations from Baker et al.[17] and Koss et al.[24] where a median of 40% and 75% MSM respectively over-reported their PrEP adherence in the Adolescent Medicine Trial Network (ATN110 and 113) daily oral PrEP safety and efficacy trials in 16 urban sites in the United States. In this study, if considered an adherence screening tool, self-reported adherence had a sensitivity of 85% (95% CI: 76%, 93%) and a specificity of 21% (95% CI: 14%, 27%). Although this may presently not meet the criteria for an ideal PrEP adherence screening test, given the context, it can be potentially enhanced to address immediate gaps and or implementation needs. To have

more insight into the potential enhancement of self-reported PrEP adherence, we needed to investigate it as well as other factors associated with protective PrEP adherence.

In this study, we sought to examine factors associated with protective PrEP adherence. We found that the PrEP's introduction approach and disclosure of sexual orientation to family members were both statistically significantly associated with the crude and adjusted odds of protective PrEP adherence. Participants introduced to PrEP from the clinic, and who had no interaction with the study-organized community peer-to-peer counseling sessions by opinion leaders, were significantly more objectively PrEP adherent than those recruited through the community-based approach. A possible explanation for this may be that the TRUST clinic might have provided a safer, more discreet space and more conducive environment for PrEP introduction counselling as compared to the counselling done within the community. Another plausible explanation may be related to the time that clinic-recruited participants had spent in the parent study (average of 32 days versus 10 days for clinic and community based respectively) before being enrolled in the TRUST-PreP study. This time might have conferred some stability, health-messaging reinforcement, experience, and understanding of their expectations from their health care providers on them, compared to those recruited from the community. These observed differences may also have resulted from the provider-initiated PrEP introduction having better experience with qualitative counselling about the commitment necessary for PrEP use as compared to the peer to peer counselling from the POLs. Furthermore, it was observed that participants introduced to PrEP at the clinic had 2.2 fold odds of being older than those introduced from the community, and in this study, older age had a trend with protective PrEP adherence. The trend suggested that the older the participants, the more likely they would achieve

protective PrEP adherence. Hence, we tested age as a potential modifier of protective adherence with the PrEP introduction approach, but the association persisted within the stratified models. This accords with findings from the US PrEP demonstration project [111], the HIV Prevention Trials Network (HPTN) 067 studies[44], and the ATN 100 and ATN 113 trials[17] where older age had been associated with PrEP protective adherence among MSM. Another factor associated with adherence in this study was participants' disclosure of sexual orientation to their family members. Our study had a significant correlation between those that disclosed their sexual orientation to their family members and those that disclosed to the health care workers. To avoid bias in the multivariate analysis, we included sexual orientation disclosure to family members has been associated with lower risk behavior[112] among bi-sexual men. In addition, past literature[113] has corroborated these results where disclosure of risk behaviors correlated with better antiretroviral therapy adherence among MSM.

In contrast to our hypothesis, we found no significant discordance between self-reported PrEP adherence at month 3 and month 9 study visits. This is unlike the findings from Koss et al.[24] where discordance between self-reported PrEP adherence and PrEP biomarkers levels increased as the studies progressed. In addition, unlike previous studies[24,25], where the average correlation between these two adherence methods was between 0.25 and 0.4, the correlation between self-reported PrEP adherence and protective adherence was much lower (from 0.02 to 0.2) in our study. Our study's lower correlation may be explained by a relatively higher proportion of non-adherence (63% participants with a below limit quantification of TFV) but a similar proportion of self over reported PrEP adherence as compared to previous studies.

A striking result from the multivariable GEE analysis was the trend of association between the study visit time (months post-PrEP initiation) and the protective PrEP adherence. The month 9 study visits had a two-fold increased odds of protective adherence compared with the month 3 study visits. This was in contrast to our observation from crude paired assay analysis, where there was a significant negative change (Z= -2.60, p=0.01) between those that achieved protective adherence at month 9 compared with month 3. That was however an un-adjusted analysis and with 54% of all the assays used for multivariable analysis. The multivariable analyses results may be suggestive of the need for a few months for those initiating PrEP to get used to the routine of a new daily medication. Although the smoothing plots examined self-reported PrEP as a correlate of PrEP biomarker quantification, a strongly linear positive month 9 correlation between self-reported "very good" and the biomarker assay suggests a similar trend about the better adherence outcome during month 9 visits compared with month 3 visits.

Previous studies[30,45,114,115] have demonstrated that TFV and FTC biomarker assays are particularly targeted for investigating recent (within the past 7 days) PrEP adherence. We, therefore, sought to leverage this to investigate our study participants' immediate past week adherence. It could be inferred from the TFV serum assay level that the majority of the participants (63%) did not take any TDF pill within the immediate past week, while ~7% took a sub-optimal (1-3 pills) dose. Interestingly, among the 30% with at least protective adherence, almost two-third took their pills daily within the last week of the assay quantification. Although this might be a consequence of white coat adherence [19,28,84] it is commendable in this setting.

This study has several limitations. Due to a high attrition and non-response rate, we had sizeable missingness on study variables. We, however, performed a sensitivity analysis to determine the best way to handle and interprete our study findings. We found that all variables except alcohol use were missing completely at random, relative with observed (outcome) variables. Therefore, our study variables missingness is not expected to impact the interpretation of our analysis. Another limitation was the high proportion of below-limit of quantifications (BLQs) of the biomarker assays. To address this, in addition to transforming the data, we also dichotomized it for ease of analysis. Because of the lower event-to-trial outcome than anticipated, our study may therefore have been underpowered to detect some outcomes. Finally, this study's biomarker assays do not provide evidence of protective evidence beyond a week, hence subjected to white coat adherence.

Notwithstanding these limitations, this study engaged the use of LCMS, the global gold standard[29] for quantification of PrEP biomarkers assay, hence the validity of our outcome measures. This study has added to our understanding of implementing PrEP among a population residing in a homophobic environment. In addition, the longitudinal nature of the study design likely conferred a temporal association in our study findings. Finally, the robustness of the multivariable variance sandwich estimator will likely make our study findings have less biased estimates.

Conclusion

In conclusion, we found that the correlates of self-reported and protective PrEP adherence measures have potentially pragmatic underpinning for HIV infection prevention in this population. Firstly, the methods deployed by the peer-to-peer approach, community PrEP

introduction may be counterproductive for PrEP implementation, especially in a new PrEP program. While other public health initiatives might have successfully engaged the peer-to-peer counselling, care must be taken to carefully understudy and contextualize these into the uniqueness of a vulnerable, mobile, and hard to reach population living in a MSM hostile environment. In future studies, we recommend a qualitative study post-PrEP adherence study to compare shared experiences of the adherent participants and those that were not. This might be useful for future PrEP programs in this setting. Next, it may be important to consider that participants enrolled in the study be allowed to engage with the routine clinics before offering them PrEP. A lesson learned from this study was that those that had experiential encounters with the clinics before initiating PrEP tended to have better outcomes. Yet another key lesson to note is that most people struggle with a new change in their routine initially as shown in this study. We, therefore, seek programs that will assist and or reinforce adherence within the first three months of PrEP initiation. Finally, more focused attention needs to be paid to the younger MSM as they seem to be more vulnerable to worse PrEP outcomes.

CHAPTER IV: THE ROLE OF SOCIAL SUPPORT ON DAILY ORAL HIV PRE-EXPOSURE PROPHYLAXIS ADHERENCE AMONG MEN WHO HAVE SEX WITH MEN IN NIGERIA.

Abstract:

Introduction: The effectiveness of daily oral pre-exposure prophylaxis (PrEP) is heavily hinged on adherence. Social support (SS) has been demonstrated to facilitate patients' medication adherence outcomes, but this has not been well documented among men who have sex with men (MSM) taking PrEP. We set to examine the association of SS with PrEP's adherence among MSM in Nigeria.

Methods: An open-label longitudinal single-site study initiated MSM in Nigeria on PrEP in a one-year follow up, five scheduled study visit (Baseline, month 1, 3, 6, and 9) in Abuja. Tenofovir (TFV) and Emtricitabine (FTC) assay quantification serum samples were collected at month 3 and 9 study visits and analyzed using the Liquid Chromatography Tandem- mass Spectrometry method. Protective PrEP adherence was defined as serum TFV $\geq$ 5.9 ng/ml, irrespective of the study visit month assay was collected. An eight-item, four-point Likert scale SS questionnaires were answered at month-1 study visit, and they were categorized into three domains (informational, instrumental, and emotional) with a validated tool instrument as a template. The SS questionnaires asked respondents about perceived informational SS (advice or information), instrumental SS (tangible aids or services) and emotional SS (expression of trust or care) from their peers. The highest-ranked two Likert scales for each item were categorized as positive "social support" perception in their respective domains. Clinical information was collected at each study visit and behavioral information at baseline, third and ninth month visit. Logistic regression

was used to estimate adjusted odds ratios (aOR) between each of the social support domains and protective adherence.

Results: Of the 400 MSM that initiated PrEP between April 2018 and May 2019, 219 participants (median age 23 [interquartile range 20-27] years) had at least one TFV-FTC assay. Of those with at least an assay, 66/219 (30%) achieved protective adherence and 148/219 (68%) reported perceived informational, 163/219 (74%), instrumental, and 118 /219 (54%) emotional SS respectively. Compared with older MSM (≥ 25 years), younger MSM (16-24 years) had 1.6 (OR: 1.60, 95% CI: [1.16, 2.12]) and 1.52 (OR: 1.52, 95% CI: [1.08, 2.15]) increased odds of perception of informational and instrumental SS respectively. Compared with participants that had community-based PrEP introduction, those that had clinic-based PrEP introduction had 40% (OR: 0.60, 95% CI: [0.45, 0.81]) and 34% (OR: 0.66, 95% CI: [0.47, 0.91]) decreased odds of informational and instrumental SS respectively. In multivariable analysis, participants with reported perceived emotional SS had 42% increased odds (aOR: 1.42, 95% CI: [1.00, 2.00]) of protective adherence.

Conclusion: Younger MSM and participants with a community based PrEP introduction method were more likely to have reported perceived Informational and Instrumental SS, but less likely to have achieved protective PrEP adherence. Emotional SS was associated with protective PrEP adherence among MSM in Nigeria. Programs with focus on personalized health-related experience sharing for emotional SS are needed especially for the younger MSM.

Introduction

The daily oral HIV pre-exposure prophylaxis (PrEP) is highly effective in preventing HIV acquisition among high-risk groups when adherence is optimal[12,28,116–118]. The Food and Drug Administration (FDA), Centers for Diseases Control and Prevention (CDC) and World Health Organization (WHO) have all approved[8,42,119] PrEP for use among high-risk groups, which include but are not limited to men who have sex with men (MSM). The prevention of HIV acquisition and transmission among high-risk groups is critical to the plan of the UNAIDS to end HIV by 2030[120] and the global success of PrEP implementation may play a critical role in this.

Social support has played key roles in psychological and behavioral patients' outcomes from previous studies[55–58] and has been demonstrated to buffer stressful health events (for example recovery from major surgeries), influence the state of the mind, and modify health-related behaviors[60] such as medication adherence and clinic appointment fidelity. A few studies[54,61,62] have examined the role of actual or perceived social support on anti-retroviral therapy (ART) adherence among MSM and other persons living with HIV, and there are even fewer studies[63,64] that have evaluated the role of social support among MSM taking PrEP. Assistance and support from friends and peers have been observed to promote patients' adherence by encouraging optimism, self-esteem and giving practical assistance[57].

The quantitative analysis of social support involves the measurement of the specific type (domain) of support received by the end-users. These domains are typically instrumental, emotional, and informational[58,121–123]. The instrumental domain addresses support that provides tangible aids and services, while the informational support focuses on health-

related advice, suggestions, or information. Lastly, emotional support relates to the expression of empathy, love, trust, and care of the end receivers. Some authors[55,124] have classified social support as functional (instrumental, emotional, and informational domains) as well as structural (marital status, living conditions, network size, etc.) Irrespective of the classification used, most authors seem to agree that the functional component of social support is integral to how the end-user objectively perceives or receives the support rendered [58,121–123].

A few previous studies[55,63,65] have examined the roles of social support on PrEP adherence among MSM. A mixed study in Philadelphia, Pennsylvania [63] examined the social support networks among young MSM and transgender women (TGW) of color receiving PrEP. They aimed to characterize the perceived social support for fifty young MSM and TGW taking PrEP by exploring relationships between social support, network structure, and the use of Tenofovir – Emtricitabine (TDF-FTC) based PrEP adherence. Family and friends were reported by 75% and 67% of the participants respectively as their most common support figures. Of the support figures, 48% and 36% of friends and family provided at least one of emotional, instrumental, and social interaction support towards participants' PrEP use. Most participants identified their friends as having the most supportive characteristics, which include mutual understanding, trust, and similar sexual orientation. Another study by Phillips et al[65], engaged RADAR, a longitudinal Chicago MSM study, to investigate the factors associated with PrEP support and disclosure among 700 MSM and TGW between June 2017 and April 2018. About 90% of the participants reported that those they disclosed their PrEP use to were supportive of them. More than half of all participants disclosed their PrEP use to their biological parents. Bisexuals and MSM

without gender identity were less likely to disclose their PrEP use. In addition, older MSM were more likely to know other PrEP users and this was associated with PrEP's disclosure to their medical provider. A meta-analysis[55] examined the association between social support and medication adherence among all literature from all medical and surgical specialties published between 1948 and 2001, although, this literature did not refer to the population by their sexual orientation. A hundred and twenty-two studies correlated social support with medication adherence. The standardized odds ratio demonstrated that the odds of adherence, compared with non-adherence, were 3.6 times (OR: 3.60, 95% CI: [2.55, 5.19]) higher among those that received practical (instrumental) social support. In addition, the risk of non-adherence was 1.35 times higher for patients who did not receive emotional social support, and this finding was robust, requiring at least 93 un-retrieved studies with null findings to invalidate the results.

Our literature review shows a heavier focus of past studies on the structural aspect of social support for MSM. The *"PrEP Together study"* is the only existing study[63], as far as we know, that has investigated some functional aspects of social support on MSM and PrEP adherence. They used a mixed-methods (qualitative and quantitative) approach and was conducted among 50 MSM from the youth empowerment project in Philadelphia. Hence, there is yet to be a purely quantitative analysis of functional social support roles in MSM's PrEP adherence. In this study, we will attempt to bridge this gap by investigating the functional component of social support with a more robust sample-sized study. This paper aimed to investigate the association between perceived functional social support by its domains and the PrEP's protective adherence outcome among MSM in Nigeria. We

hypothesized that MSM in Nigeria with demonstrably higher social support in each of the three domains would have different odds of PrEP adherence.

Methods

Study design and sample population

TRUST-PrEP was an open-label study nested in an ongoing prospective HIV prevention and treatment study the TRUST/RV368 (TRUST study) in Abuja. The TRUST study has been enrolling MSM since March 2013 using respondent driven-sampling method (RDS). RDS is an incentive-based, peer-driven sampling method[125].

Based on previously reported poor ART cascade navigation by MSM recruited in later waves [82], 32 key influential MSM called popular opinion leaders (POLs) were identified from the TRUST study and engaged for a 4-week didactic PrEP counselling training in three batches between May 2018 and September 2018.

Two methods of PrEP introduction were engaged in the TRUST-PrEP study- the peer-to-peer introduction (also called community-based method), via the POLs using the coupons and the provider-initiated introduction (also called the clinic-based method). For the community-based method, the trained POLs engaged MSM within their community, discussed PrEP with them, and recruited those interested via the use of coupons. Each POL was provided three coupons for each wave of recruitment of three MSM from their networks and communities. A maximum of 3 batches of coupons was given to each POL after each successive wave of recruitment. Each POL, therefore, had between a minimum of none to a maximum of 9 recruitment in the study. On presenting to the clinic, the community recruited MSM were screened and assessed for eligibility for the TRUST study

initially, and if eligible, they were required to complete the PrEP study willingness questionnaires before they were assessed for TRUST-PrEP study's eligibility. For the clinic-based method, providers discussed PrEP with all MSM attending routine TRUST clinics, and those interested were further required to complete the willingness questionnaires, screened, and assessed for eligibility for the TRUST-PrEP study. The TRUST-PrEP study's enrollment started in April 2018 and ended in May 2019, and study follow-up continued until June 2020.

Study population and eligibility criteria:

The study population was MSM residing in Abuja, North-central Nigeria, and its environs. To be eligible for enrollment in the TRUST-PrEP study, the participant had to meet the parent study's (TRUST) criteria. This includes "male" assignment at birth, history of receptive or insertive anal intercourse with another male in the preceding 12 months, and the ability to provide informed consent in English or the local language. At enrollment, they must present a valid study coupon, be at least 16 years of age, considered able to access sexual and reproductive health and HIV care and research without parental consent[83], HIV-negative, and be willing to consent to use daily oral PrEP and biological specimen collection at each visit for the study period. They must also meet at least one of the screening criteria for "substantial risk for HIV infection".

1. Sexually active with report of any of the following in the past three months
    a. Condomless vaginal or anal intercourse with more than one partner
    b. Sex partner with ≥1 HIV risk. HIV risks include:

Having sex with other males, injection of drugs, Transgender person, sex worker, unknown

HIV status, living with HIV and condomless sex with multiple partners.

   c. Has a history of STI within the past 3 months based on self-report, lab diagnosis or syndromic STI treatment

2. History of sharing injections in the last three months
3. History of sexual partner who is HIV positive and who has not been on effective HIV treatment in the last three months. A person is defined has not being on effective HIV treatment if they are less than 6 months on ART or has inconsistencies or unknown adherence.

In this study, we included those that met the above criteria and had at least one TFV-FTC quantification assay by the end of the study.

Data collection:

Excluding the baseline, there were four study visits at months 1, 3, 6, and 9 for the study. Social support information was collected at months 1 and 6 of the study but only data from month 1 was used. The blood samples for PrEP biomarker quantification were collected at months 3 and 9 of study visits. At each visit, participants completed questionnaires as part of an in-person interview and underwent a physical exam. HIV counseling and testing were repeated at each study visit (i.e., 3, 6, and 9 months).

Laboratory methods:

The details of this method have been described in an earlier paper, but briefly, the range of calibration for serum TFV and FTC are 0.31- 1000ng/ml and 0.31 – 5000ng/ml respectively. Serum TFV and FTC below 0.31ng/ml were classified as below the limit of quantification (BLQ). The threshold values for defining not more than once a week, at least four times a week, and daily use are ≤ 0.5ng/ml (0.5-0.6), 5.9ng/ml (4.6- 6.4), and 52.0

ng/ml(49-55.6), respectively, based on the median TFV serum concentration at a steady state[28]. Similarly, for FTC, the thresholds for defining not more than once a week, at least four times a week, and daily use are ≤ 0.8ng/ml (0.4-0.9), 6.7ng/ml (5.4-7.6) and 70.9ng/ml (67.7 -81.9)[28,84] respectively based on the median FTC serum concentration at a steady state. Analyst 1.6 software (version 1.6.2 Build 8489) (SCIEX, Redwood city, CA) was used to acquire and analyze the chromatographic data[106].

Study Variables

Outcome variables: Serum Tenofovir (TFV) and Emtricitabine (FTC) were measured as dichotomized variables. The lower limit of quantification of TFV and FTC is 0.31ng/ml, and the range is from 0.31-1,000ng/ml and 0.31-5,000 ng/ml, respectively. In this aim, all PrEP assay results were pooled. This was done for the purpose of a cross-sectional design with with the exposure variable. Participants without any record of TFV assay ≥ 5.9ng/ml was categorized non-adherent. Any participant with at least one TFV assay equal to or higher than 5.9 ng/ml, irrespective of assay time, was categorized as having a protective adherence. The dichotomization for TFV and FTC adherence was 5.9ng/ml and 6.7ng/ml, respectively, based on the median serum concentration of four tablets per week required for protective adherence[28]. In this study, we pooled all the quantification assay results during the study and defined PrEP assay adherence as any serum TFV concentration.

Exposure variables: The primary exposure for this study was the type of perceived social support received during the study period from peers (other MSM and friends). This was assessed at the month 1 visit of the study with an eight-item, 4-point Likert scale questionnaire. Utilizing a validated social support measurement scale[87,126] with an internal consistency of > 0.7 as a template, we classified the questions into three functional social

support domains –instrumental, emotional, and informational (This is shown below). The participants rated each item on the Likert scale. On the scale, "0" was "*strongly disagree*", "1" was "*disagree*", "2" was "*agree*" and 3 was "*strongly agree*". For this analysis, "0" and "1" were coded as "No" for social support, while "2" and "3" were coded as "Yes" for social support for the respective social support domains. Because a higher score indicated a higher level of social support, we re-ordered the Likert Scale for one question (emotional domain) to meet this criterion. The eight questions as categorized are shown below.

Instrumental domain questions:

1. *You can count on other MSM in your group of friends to borrow money*
2. *You can count on other MSM in your group of friends to accompany you to the doctor or the hospital*
3. *You can count on other MSM in your group of friends if you need somewhere to stay*

Emotional domain questions:

1. *You can count on other MSM in your group if you need to talk about your problem*
2. *You can trust the majority of the MSM you know*
3. *You can count on other MSM in your group of friends to help deal with a violent or difficult situation*
4. *In general, MSM in your group only worry about themselves* (Likert scale re-ordered)

Informational domain question:

1. *You can count on other MSM in your group of friends to help you find other MSM*

Since we made use of the month 1 assessment only for social support measurement, each participant had, at the most, eight questions answered. A participant was categorized as having some form of social support, that is, positive social support domain, if one or more of the questions answered in each social support domain category was in the affirmative (that is, strongly agreed or agreed). In other words for the emotional domain, if one or more of the four questions is answered in the affirmative, then they are classified as having "emotional support". If none of the questions were answered in the affirmative, then they are classified as having "No emotional support". This method of categorization was based on the literature[55] that has shown that any form of social support is beneficial to the respondents compared with none.

Covariates: Demographic variables including age (< 25 years [younger] or ≥ 25 years [older]), education level (≤ high school or > high school), marital status (never married or ever married), and employment status (Yes = 1 or no = 0). Behavioral variables included condom use during last sex with a male partner (Yes = 1 or no = 0), the number of days drank alcohol in the past 30 days (0-2=0 [No], ≥ 3=1[Yes]). We also collected variables on disclosure of sexual orientation to health care workers (Yes=1 or no=0).

Statistical Analysis:

Univariate analysis for each variable was conducted. In the bivariate analysis, stratified by each of the three study exposures, we tested all covariates for a significant association as well as reported crude association between each exposure variable and age, a known confounding variable in the literature[111], along with other variables with significance in

crude association with the exposure variables. In addition, we sought to determine the association of each social support domain (primary exposure) and the covariates with the protective adherence using Pearson's chi-squared association test.

For multivariable analysis, there were three final models one for each primary exposure. Logistic regression was used to determine the association between each of the three perceived or received social support domains at the month 1 visit and the pooled protective assay of all respondents, irrespective of visit time. Hence cross-sectional odds ratios and 95% confidence interval were reported.

To assess interaction, the age variable was selected *a priori*, and an interaction term variable was created between the potential effect modifier and the primary predictor variable. A p-value of less or equal to 0.05 was the criteria for significance and therefore reporting of the stratified analysis by the interacting variable (effect modifier). To be a confounder, a variable had to change the regression coefficient estimates of the primary exposure variable by at least 10% or be a known confounder in the literature.

All variables adjudged as confounders in each final model were included alongside each of the three primary exposure (social support domains). The models were created by adding all the variables that had met the criteria for inclusion at once.

Results:

Four hundred participants between the ages of 17 and 54 years initiated PrEP between April 2018 and May 2019. Of the 400 that initiated PrEP, only 219 had at least one record of serum TFV or FTC assay quantification (study outcome) by the end of the study period.

Of those with study outcomes, the median age was 23 years with an interquartile range between 20 and 27 years. A higher proportion (56.6%) had at least a secondary school (high school equivalent) education, 77.2% were employed, 83% self-identified as male gender, while 79.4% were bi-sexual. Almost all (96.7%) were never married.

Of all those with TFV serum quantification, [66/219] 30% (95% CI: 24%, 36%) achieved protective PrEP adherence at least once during study period. Similarly, from the same cohort, [163/219] 74% (95% CI: 68%, 80%), [118/219] 54% (95% CI: 47%, 60%) and [108/219] 49% (95% CI: 43%, 56%) had perceived instrumental, emotional and informational social support respectively at month 1 study visit. Table 4.1 shows the summary statistics of the participants' characteristics.

Table 4.1: Participants characteristics at baseline among MSM in Nigeria

Characteristics		n (%) N=219
Age (Years)	Median (IQR) 23 (20- 27)	
Younger (16-24)		123 (56.2)
Older (≥25)		96 (43.8)
Protective adherence		
No		153 (69.9)
Yes		66 (30.1)
Instrumental Social Support		
No		56 (25.6)
Yes		163 (74.4)
Emotional Social Support		
No		101 (46.1)
Yes		118 (53.9)
Informational Social Support		
No		111 (50.7)
Yes		108 (49.3)
PrEP Introduction		
Clinic-based		119 (54.3)
Community-based		100 (45.7)
Education		
≤ High school		124 (56.6)
> High School		95 (43.4)
#Employment		
Unemployed		45 (22.8)
Employed / Student		152 (77.2)
#Sex orientation		
Homosexual		45 (20.6)
Bisexual		173 (79.4)
#Gender identity		
Cisgender man		178 (83.0)
Transgender and Others		39 (18.0)
#Marital Status		
Never married		206 (96.7)
Ever married		7 (3.3)
Condom use during last sex		
No		71 (32.4)
Yes		148 (67.6)
# Alcohol use		
No		101 (56.4)
Yes		78 (43.6)
Same Sex Disclosure (HCW)		
No		175 (80.0)
Yes		44 (20.0)
#: N does not add up to 219 because of missing variables.		

In the bivariate analysis, compared with older MSM, the younger MSM were 60% [OR: 1.60, (95% CI: 1.16, 2.12)] likely to have perceived informational social support and 52% [OR: 1.52, (95% CI: 1.08, 2.15)] more likely to have perceived instrumental social support from their peers in the study. There was no association between age and emotional social support, [OR: 1.0 (95% CI: 0.75, 1.35)]. In addition, compared with those that had a community based PrEP introduction, participants who had a clinic-based PrEP introduction had 40% [OR: 0.60, (95% CI: 0.45, 0.81)] and 34% [OR: 0.66 (95% CI: 0.47, 0.91)] decreased odds of reporting perceived informational and instrumental social support respectively in the study.

In the bivariate analysis of factors associated with PrEP adherence, only the PrEP introduction variable was associated at a p-value of less or equal to 0.05. Table 4.2 provides the summary of this analysis.

We tested age as a potential effect modifier of the primary exposure variables in each of the models. The interaction term p-values with emotional, instrumental and informational social support exposures were 0.98, 0.58, and 0.28 respectively. Hence, age was not an effect modifier of any of the exposure variables in this study.

Table 4.2: Bivariate analysis of factors associated with PrEP protective adherence among MSM in Nigeria

Characteristics	Total	Protective adherence (Yes)	Protective adherence (No)	Crude OR (95% CI)	
	N=219 n (%)	N=66 n (%)	N=153 n (%)		p value
Informational SS					
No	111 (50.7)	33 (29.7)	78 (70.3)	Ref	
Yes	108 (49.3)	33 (30.6)	75 (69.4)	1.04 (0.58, 1.85)	0.89
Emotional SS					
No	101 (46.1)	31 (30.7)	70 (69.3)	Ref	
Yes	118 (53.9)	35 (29.7)	83 (70.3)	0.95 (0.53, 1.69)	0.86
Instrumental SS	56 (25.6)	18 (32.1)	38 (67.9)	Ref	
No	163 (74.4)	48 (29.5)	115 (70.5)	0.88 (0.46, 1.70)	0.70
Yes					
PrEP Introduction					
Community-based	100 (45.7)	14 (14.0)	86 (86.0)	**Ref**	
Clinic-based	119 (54.3)	52 (43.7)	67 (56.3)	**4.7 (2.43, 9.33)**	**<0.01**
Age (Years)					
Older (≥25)	96 (43.8)	35 (36.5)	61 (63.5)	Ref	
Younger (16-24)	123 (56.2)	31 (25.2)	92 (74.8)	0.59 (0.33, 1.05)	0.07
High school					
No	124 (56.6)	33 (26.6)	91 (73.4)	Ref	
Yes	95 (43.4)	33 (34.7)	62 (65.3)	1.47 (0.82, 2.62)	0.19
# Married					
Never	206 (96.7)	60 (29.1)	146 (70.9)	Ref	
Ever	7 (3.3)	3 (42.9)	4 (57.1)	1.83 (0.40, 8.40)	0.43
# Employment					
No	45 (22.8)	12 (26.7)	33 (73.3)	Ref	
Yes	152 (77.2)	39 (25.7)	113 (74.3)	0.95 (0.45, 2.02)	0.89
# Alcohol use					
No	101 (56.4)	31 (30.7)	70 (69.3)	Ref	
Yes	78 (43.6)	24 (30.8)	54 (69.2)	1.00 (0.53, 1.90)	0.99
Condom use during last sex					
Yes	148 (67.6)	39 (26.3)	109 (73.7)	Ref	
No	71 (32.4)	27 (38.0)	44 (62.0)	1.72 (0.94, 3.13)	<0.08
Same Sex Disclosure (HCW)					
No	175 (79.9)	49 (28.0)	126 (72.0)	Ref	
Yes	44 (20.1)	17 (38.6)	27 (61.4)	1.62 (0.81, 3.23)	0.17

SS: Social support
Crude odds ratio and 95% CI calculated using the logistic regression.
Bolded confidence interval indicate significance at $p < 0.05$. Due to missingness, variables marked '# 'may not add up to N

In multivariable analysis with logistic regression, age, employment status, and disclosure of MSM status to health care workers satisfied the criteria for inclusion in the final model for Model 1 (Primary Exposure: Informational support) and Model 3 (Primary exposure: Emotional Social Support). The age variable met the final model inclusion criteria for Model 2 (Primary exposure: Instrumental social support). The age variable met all these criteria based on its significance in literature[17,24], while the other variables had a more than a 10% change in regression coefficient estimates of the primary exposure in their respective models.

After adjusting for PrEP introduction, participants' age, employment status and disclosure of sexual orientation to health care workers. When compared with those without perceived emotional social support, those with perceived emotional social support were 42% more likely [OR: 1.42, 95% CI: (1.00, 2.00)] to have achieved protective adherence. The PrEP introduction method variable remained significantly associated with protective adherence irrespective of the social support domain. The clinic-based PrEP introduced participants compared with the community-based PrEP introduced had 4.8 [OR: 4.8, 95% CI: (3.15, 7.37)], 5.1 [OR: 5.10, 95% CI: (3.41, 7.61)] and 4.8 [OR: 4.85, 95% CI: (3.16, 7.42)] increased odds of protective adherence in models 1, 2 and 3 respectively, controlling for other variables in each model. Tables 4.3 – 4.5 show the final multivariable regression models for each of the three primary exposures.

Table 4.3: Multivariable analysis of social support (informational) factors associated with PrEP adherence among MSM in Nigeria

Characteristics	Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Informational SS				
No	Ref		Ref	
Yes	1.04 (0.58, 1.85)	0.89	0.90 (0.62, 1.29)	0.57
PrEP Introduction				
Community-based	**Ref**		**Ref**	
Clinic-based	**4.7 (2.43, 9.33)**	**<0.01**	**4.82 (3.15, 7.37)**	**<0.01**
Age(Years)				
Older MSM(≥25)	Ref		Ref	
Younger MSM (16-24)	0.59 (0.33, 1.05)	0.07	0.84 (0.59, 1.20)	0.34
Employment				
No	Ref		Ref	
Yes	0.95 (0.45, 2.02)	0.89	1.16 (0.60, 2.21)	0.65
Same Sex Disclosure (HCW)				
No	Ref		Ref	
Yes	1.62 (0.81, 3.23)	0.17	1.34 (0.95, 1.90)	0.10

Crude and adjusted odds ratios were calculated using Logistic Regression.
The model was adjusted for PrEP introduction methods, age of participants, employment status and same sex disclosure to family members. **Bolded** confidence interval indicate significance at $p < 0.05$

Table 4.4: Multivariable analysis of social support (Instrumental) factors associated with PrEP adherence among MSM in Nigeria

Characteristics	Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Instrumental SS				
No	Ref		Ref	
Yes	0.88 (0.46, 1.70)	0.70	1.22 (0.84, 1.78)	0.29
Prep Introduction				
Community-based	**Ref**		**Ref**	
Clinic-based	**4.7 (2.43, 9.33)**	**<0.01**	**5.10 (3.41, 7.61)**	**<0.01**
Age (Years)				
Older MSM(≥25)	Ref		Ref	
Younger MSM (16-24)	0.59 (0.33, 1.05)	0.07	0.76 (0.54, 1.06)	0.11

Crude and adjusted odds ratios were calculated using Logistic Regression.
The model was adjusted for PrEP introduction methods and age of participants.
Bolded confidence interval indicate significance at $p < 0.05$

Table 4.5: Multivariable analysis of social support (Emotional) factors associated with PrEP adherence among MSM in Nigeria

Characteristics	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Emotional SS				
No	Ref		**Ref**	
Yes	0.95 (0.53, 1.69)	0.86	**1.42 (1.00, 2.00)**	**0.04**
PrEP introduction				
Community-based	**Ref**		**Ref**	
Clinic-based	**4.7 (2.43, 9.33)**	**<0.01**	**4.85 (3.16, 7.42)**	**<0.01**
Age (Years)				
Older MSM(≥25)	**Ref**		Ref	
Younger MSM (16-24)	0.59 (0.33, 1.05)	0.07	0.83 (0.58, 1.18)	0.29
Employment				
No	Ref		Ref	
Yes	0.95 (0.45, 2.02)	0.89	1.09 (0.57, 2.09)	0.78
Same Sex Disclosure (HCW)				
No	Ref		Ref	
Yes	1.62 (0.81, 3.23)	0.17	1.28 (0.90, 1.81)	0.15

Crude and adjusted odds ratio calculated using the Logistic regression.
The model was adjusted for PrEP introduction methods age of participants, employment status, and same sex disclosure to family members. **Bolded** confidence interval indicate significance at $p < 0.05$

Regarding missingness, we used a complete case analysis with respect to the exposure and outcome variables.

Discussion

We found few studies in our review on the roles of social support in PrEP adherence among MSM. This is not surprising, given that the full operationalization of PrEP as the standard of care among MSM, even in the most resourced nations is still being navigated[127].

We found that those with perceived emotional social support were significantly more likely to have achieved protective PrEP adherence in this study. A clear benefit of perceived informational or instrumental social support with regards to PrEP adherence outcomes could not be identified.

The significance of emotional social support finding in our study is consistent with observations from the meta-analysis by Di Matteo et al.[128] that reviewed all literature between 1948 and 2001 on social support and found one hundred and twenty studies. This review was not specific to MSM. Of these studies reviewed, eleven investigated the association between emotional support and patients' adherence to their medications. A mean r effect size of 0.15, categorized as a strong significant association between emotional support and patients' adherence was reported. In addition, results from the meta-analysis showed that the risk of non-adherence was almost 1.5 folds higher in patients who did not receive emotional support, compared with those that did receive emotional support.

Another important finding in our study was the association between the participants' age and the perceived social support received. Compared with older MSM, the younger MSM had 1.6 and 1.5 times the odds of perceiving informational and instrumental social support respectively. It is intriguing to note that the social support domain most associated with PrEP adherence (emotional support) was not associated with the participants' age, and age was a moderately strong predictor of PrEP adherence in this study. In contrast to our study

findings, Neal Krause et al.,[129]reported that although there is a non-linear association between age and social support received, the older people reportedly had a higher perception of social support. However, their study, unlike ours, did not examine social support by its domains. Another study[130] from an urban mid-western American city among low social-economic status racial minority, lesbian gay, and bisexual adolescents examined the influence of age on sources of social support received and mental health outcomes. They reported that increasing age was associated with higher perceived social support from the participant's peers, compared to family members.

Age has been reported to be a significant predictor of PrEP adherence in past literature[17,30,111]. Our study findings accord with this observation between age and protective adherence among MSM in the literature. In our study, compared with older MSM, the younger ones had about 40% decreased odds of protective adherence independently. A similar finding was reported by Landovitz et al[30]., where they observed between 20 – 40% increased odds of below level of serum TFV quantification among the younger MSM (18-25years) taking PrEP. Another California study (California Collaborative Treatment Group) study team[19] examined the trajectories and predictors of PrEP adherence among MSM using a growth mixture modeling to identify subgroups of individuals with similar trajectories of text-reported adherence. They found that younger MSM (age was a continuous variable in this study) was associated with lower text-reported PrEP adherence. Although not significant, we observed from the trends of age tested as an interaction term with each of the social domains, that informational social support would likely have the highest implication on PrEP adherence outcome in older MSM.

There are other important findings in literature[62,128] not seen in our study. For example, in the meta-analysis by DiMatteo et al[128]., the standardized odds ratio demonstrated that the odds of adherence, compared with non-adherence are 3-fold higher among those that had received or perceived instrumental (practical) support in 29 studies. However, these studies were not conducted among MSM.

Our study is not without limitations. Perceived social support does not necessarily translate to received social support; hence, this might have potentially resulted in a non-differential misclassification of study exposure and hence might have caused an underestimation of our effect measures. Secondly, we did not perform a time-varying analysis between social support and PrEP adherence. PrEP adherence at a given study point may not necessarily reflect on the social support perceived at that same period by the participant. The direction of the effect of this on our effect measures is not predictable. Finally, we did not report an analysis of structural social support in this study. While we acknowledge its importance in social support assessment, it has been reported[55] that functional social support has a stronger effect on adherence than does structural social support, suggesting that the mere presence of people does not matter as much as the quality of relationships with them.

The study limitations notwithstanding, our study is among those fronting the quantitative assessment of the roles of functional social support in PrEP adherence among MSM. Given the impact social support has played in medication adherence across various health conditions[55], and its potential for galvanizing the implementation of PrEP in resource-limited settings, our findings are likely to provide insight for future studies on this. As far as we know, the only previous study[63] investigating the role of social support among MSM on PrEP was a mixed-methods study that assessed the type of social support received or

perceived with qualitative and quantitative methods. Our study is the first to use a purely quantitative method to assess the association between the type of social support perceived by MSM and their PrEP adherence outcome measures. Since our study exposure occurred and was collected (at month1) before the outcome (assay collection at months 3 and 9), there is the ascertainment of temporality between social support as exposure and PrEP adherence as the outcome in this study.

Conclusion

This study set out to assess the association between functional social support and PrEP adherence among MSM in Nigeria. There was a significant association between perceived emotional social support and protective PrEP adherence but not informational or instrumental social support. Younger MSM were more likely to have reported perceived informational and instrumental social support, conversely, those with clinic-based PrEP introduction were more likely to have reported decreased forms of this social support.

We recommend that future studies investigate the time-varying association of perceived social support domain with protective PrEP adherence. In addition, as there continue to be support programs for younger MSM, similar programs should be targeted to older MSM as well they seem to have reported less instrumental and informational support. Finally, enabling environment for the expression of emotional social support should be created in non-stigmatizing ways for MSM in this setting.

CHAPTER V: THE EFFECT OF DAILY ORAL HIV PRE-EXPOSURE PROPHYLAXIS ON BEHAVIORAL OUTCOMES AMONG MEN WHO HAVE SEX WITH MEN IN NIGERIA

Abstract:

Introduction: HIV Pre-exposure prophylaxis (PrEP) prevents HIV acquisition effectively among high-risk groups, including but not limited to men who have sex with men (MSM). However, there are concerns about potential behavioral modification following PrEP use among MSM. We aimed to estimate the effect of PrEP use on risky behavior modification among MSM in Nigeria.

Methods: TRUST-PrEP, an open-label, prospective cohort, initiated MSM on PrEP in Nigeria for five scheduled visits (baseline, months 1,3,6, and 9), one-year follow-up study in Abuja, nested in a parent study (TRUST). We identified TRUST-PrEP participants who had been in the TRUST study on or before Feb 15, 2016 and performed a pre-post-PrEP intervention analysis, engaging them as self-controls. With a conditional logistic regression, we estimated the odds ratio (OR) and 95% confidence intervals (CIs) of bacterial sexually transmitted infections (rectal *Chlamydia trachomatis*, rectal *Neisseria gonorrhea*, urethral *Chlamydia trachomatis*, and urethral *Neisseria gonorrhea*) and self-reported behavioral outcomes (Condomless Anal-Intercourse with last males [CAIs] and concurrent relationships with two or more male partners[Concurrency]), comparing post-PrEP with pre-PrEP study period.

Results: Of the 400 MSM that initiated PrEP between April 2018 and May 2019 in the TRUST-PrEP study, 206, with a median age of 24 years (interquartile range: [22-27]) were

eligible for pre-post-PrEP period analysis. In bivariate analysis, participants' age, employment status, and alcohol use in the last one month were identified as potential confounders of self-reported behavioral outcomes. Compared with the pre-PrEP period, participants in post-PrEP period had 3.5 increased odds (OR: 3.53, 95% CI: 1.10, 11.35) and 45% decreased odds (OR: 0.55, 95% CI: 0.37, 0.88) of being objectively diagnosed with rectal gonorrhea and reporting CAI respectively. There were no significant associations with other STIs and concurrency. In the adjusted analysis, participants had 51% decreased odds (adjusted OR: 0.49, 95% CI: 0.28, 0.84) of reporting CAI in the post-PrEP period.

Conclusion: There were trends of increased post-PrEP intervention STIs diagnosis but not sufficient evidence to determine if there was a PrEP associated risk compensation among MSM in our study, however, we recommend that attention be paid to these in future PrEP implementation studies. Culturally acceptable and personalized risk-reduction counseling sessions before and during PrEP implementation for MSM in Nigeria should be considered.

Introduction

On June 4, 1981, the Centers for Diseases Control and Prevention published an unusual finding of pneumocystis carinii pneumonia among five Los Angeles men who had sex with men (MSM) [131], and this later cascaded to the discovery of the human immunodeficiency virus (HIV). More than four decades later, MSM continue to bear the highest burden of the global HIV epidemic[94,95]. Since its approval by the Food and Drug Administration in 2012[42], HIV pre-exposure prophylaxis (PrEP) has altered the landscape of biomedical prevention of HIV acquisition among the high-risk groups, including but not limited to MSM by its proven efficacy and effectiveness[9,28,103,117,132]. PrEP has therefore emerged as a critical tool in the plan for ending new HIV infection globally by 2030 as proposed by the Joint United Nations Programme on HIV/AIDS (UNAIDS)[35].

There is an ongoing deliberation about whether the use of PrEP among MSM has resulted in increased risky behaviors, a concept generally referred to as behavioral risk compensation[67] (BRC) in low-income setting, as this has been demonstrated in high-resource countries. BRC theory suggests that people typically adjust their behaviors in response to their perceived risk level; in this context, PrEP uptake has been implicated in risk perception adjustment among MSM [68]. Previous studies[14,68–71] have examined BRC among MSM on PrEP, and there have been conflicting findings. Montano et al[72] examined sexual behaviors and sexually transmitted infection (STI) prevalence among 183 MSM in a Seattle STI clinic, who initiated PrEP between 2014 and 2017. At 12 months post-PrEP initiation, they found a 46% increased risk of MSM reporting *"never using condoms in the last 30 days"* compared with the initial PrEP visit (aRR:1.46, 95% CI: 1.13, 1.88).

Similarly, the percentage of patients diagnosed with any STI with and without PrEP was 49.2 and 35.0%, respectively, culminating in a significant difference in mean STI cases diagnosed per person before PrEP compared with after PrEP use (0.5 vs 1.1 respectively; $p < 0.01$). A multi-site, open-label Australian PrEP study[51] recruited 114 MSM and presented 12- month interim analysis reports. There was a significant decline in condom use concomitant with a significant increase in STIs over this period. Compared to baseline, there was a 2.8 fold increase (aIRR: 2.77, 95% CI: 1.52, 5.56) for any STIs (syphilis, anal and pharyngeal gonorrhea, anal and urethral chlamydia).

In contrast, some studies[11,66,70,133] have not found an association between BRC and increased risky behaviors or STI prevalence. The EPIC study[133] was a randomized controlled trial evaluating the impact of a bi-directional text messaging intervention on PrEP study retention and adherence conducted in Chicago, Illinois. It reported that the overall risk of STIs and risky behaviors declined in both arms from baseline. Similarly, 400 HIV–negative MSM enrolled in US CDC safety trial[70] of Tenofovir Disoproxil Fumarate (TDF) at Atlanta, Boston and San Francisco reported that the overall indices of behavioral risk declined or remained stable during follow-up with the "mean number of partners and proportion of reporting condomless anal intercourse declining significantly[70]". At baseline, participants had a mean number of 7.25 sex partners and 57% reported condomless anal intercourse. At 12-24 month, they had a mean of 5.71 sex partners ($p <0.01$) and 52% reported condomless anal intercourse ($p=0.03$). Likewise, in the IPREX study[11] where 2,499 MSM from eleven sites in Peru, Ecuador, South Africa, Brazil, Thailand and US were enrolled. They reported that there was no evidence (Risk Ratio 0.9,

95% CI: [0.6-1.4]) of sexual risk compensation among participants who believed they received treatment compared to those who did not.

Currently, to the best of our knowledge, there are no studies on PrEP related risk compensation from Sub-Saharan Africa, the region with the highest burden of HIV globally[77]. Furthermore, much uncertainty still exists in the literature about the association between PrEP and behavioral risk compensation in MSM, especially in high HIV burden, low-income settings. The objective of this study was to estimate the effect of PrEP use on risky behavioral outcomes among MSM in Nigeria. We hypothesized that compared with the pre-PrEP period, MSM in post-PrEP period will have different odds of behavioral outcomes and sexually transmitted infections diagnosis.

Methods

Study design:

TRUST-PrEP was a single site, open-label, prospective cohort. It leveraged an ongoing prospective combination HIV prevention and treatment study, TRUST/RV368 (TRUST), in Abuja, Nigeria in the recruitment of HIV-negative MSM. In the TRUST-PrEP study, there were two methods of PrEP introduction: the peer-to-peer introduction from the community, via the popular opinion leader (POL) that used respondent driven sampling. RDS is an incentivized peer-driven referral method used to recruit other MSM[82,134]. The second was the provider-initiated introduction from the TRUST clinic. On presenting to the clinic, the community recruited MSM were screened and assessed for eligibility for the TRUST study initially, and if eligible, they were required to complete the PrEP study willingness questionnaires before they were assessed for TRUST-PrEP study's eligibility.

Providers discussed PrEP with all MSM attending the routine TRUST clinic and offered the willingness questionnaires to those that signify interest before further screening and assessment for the study. The study enrollment commenced in April 2018 and ended in May 2019, and study follow-up continued until June 2020.

Study population and eligibility criteria:

The study population was MSM residing in Abuja, North-central Nigeria, and its environs. To be eligible for enrollment in the TRUST-PrEP study, the participant had to meet the parent study's (TRUST) criteria. This includes being assigned "male" at birth, having a history of receptive or insertive anal intercourse with another male in the prior 12 months, and providing informed consent in the local language or English. At enrollment, they must present a valid study coupon, be at least 16 years of age (considered able to access sexual and reproductive health and HIV care and research without parental consent)[83], HIV-negative, and be willing to consent to use daily oral PrEP and biological specimen collection at each visit for the study period. They must also meet at least one of the screening criteria for "substantial risk for HIV infection".

1. Sexually active with a report of any of the following in the past three months
    a. Vaginal or anal intercourse without condoms with more than one partner
    b. Have a sex partner with one or more HIV risks. HIV risks include:

Injection of drugs, having sex with other males, Transgender person, sex worker, condomless sex with multiple partners, unknown HIV status, living with HIV.

    c. Has a history of STI within the past 3 months based on self-report, lab diagnosis or syndromic STI treatment
2. History of sharing injection or injection materials in the last three months

3. History of sexual partner who is HIV positive and who has not been on effective HIV treatment in the last three months. A person is defined as not being on effective HIV treatment if they are less than 6 months on ART or has inconsistencies or unknown adherence.

Data collection:

Excluding the baseline, there were four study visits at months 1, 3, 6, and 9. Behavioral information was collected at baseline, month 3 and month 9 visits through in person interviews. Participants provided laboratory samples for testing of sexually transmitted infections (HIV, urethral and rectal Neisseria gonorrhea and Chlamydia trachomatis). Laboratory tests were repeated quarterly.

Study Variables:

Outcome variables:

Behavioral Outcome:

These are responses to two behavioral questions asked during the in-person interviews at baseline, months 3, and 9. The questions asked were as follows: "*Now think about the last time you had anal sex with a male partner. Was a condom used at that time?"* (Variable name: condomless anal intercourse with last male partner). The second question was "*Do you currently have two or more regular male sexual partners at this time?"* (Variable name: concurrency). The possible responses for both questions were 1= *"Yes", 0= "No", "I do not know"* or refusal to respond. For this analysis, "*I do not know*" and refusal to respond were categorized as missing variables.

Sexually Transmitted Infection outcome:

The other outcomes were the prevalent laboratory-diagnosed STIs for each of rectal gonorrhea, rectal chlamydia, urethral gonorrhea, and urethral chlamydia assessed at every visit after baseline. Each of these was dichotomized into a 1 = "*positive"* or 0= "*negative*".

Exposure variables:

PrEP period (Time):

This was defined as pre-PrEP period and post-PrEP periods. The pre-PrEP period was between February 15, 2016, and the PrEP initiation date for each participant. The post-PrEP period was between the PrEP initiation date for each participant and June 15, 2020.

Covariates

Demographic variables including age (binary variable [16-24 and ≥25 years]), and employment status (yes or no) were assessed at baseline and three monthly. Other demographic variables including education level (≤ high school or > high school), marital status (never married or ever married), gender identity (cisgender man or transgender women and others), sexual orientation (homosexual or bisexual), and religion (Christianity or Islam and others) were assessed at baseline only.

Behavioral variables such as the variable "number of days taken alcohol in the past 30 days" (0-2= "No", ≥ 3= "Yes") were assessed at baseline and 9 months.

Statistical Analysis:

In this analysis, we identified TRUST-PrEP study participants who had been in the TRUST study on or before February 15, 2016, hence, a sub-set (N=206/400) of all participants that initiated PrEP was engaged. We conducted a univariate analysis for the baseline characteristics of the cohort. Furthermore, we performed a bivariate analysis with each of the self-reported behavioral outcomes (condomless anal intercourse and concurrency) to identify potential time-varying confounders for inclusion in the final multivariable analysis. Covariates that resulted in a greater than 10% change in the regression coefficient estimate of the primary exposure (study time) when added to the conditional logistic regression were considered confounders.

For multivariable analysis, we performed a pre and post-PrEP intervention analysis. The PrEP intervention was defined as the date each participant initiated PrEP. We therefore, compared participants who had been in the TRUST study on or before February 15, 2016, with themselves after initiating PrEP up until June 15, 2020, thereby serving as self-controls in this analysis. We performed a conditional logistic regression, using the unique study identification as the strata variable to estimate the odds ratio and 95% confidence interval between the study periods and STI prevalent cases and behavioral outcomes. In addition, we performed an adjusted conditional logistic regression for self-reported behavioral outcomes, based on the potential confounding variables identified from the bivariate analysis.

For all analyses, a complete case analysis method for all exposure and outcome variables was utilized. We used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and STATA version 15.0 (College Station, TX, USA) for all analyses.

Results:

Of the 400 MSM who initiated PrEP in this study between April 2018 and April 2019, only 206 were enrolled in the parent study on or before February 15 2016, and hence eligible for inclusion in this study for pre-post intervention analysis.

The median age at baseline of the cohort was 24 years with an interquartile range of 22 – 27 years. At the baseline of the pre-PrEP period, the majority (55.8%) of the participants were younger MSM (16- 24 years). A higher proportion (76.2%) reported their sexual orientation as bi-sexual and most (96.0%) were never married. More than a third (36.9%) reported condomless anal intercourse during their last anal sex with a male partner and 33.5% reported a current sexual relationship with at least two male partners. Table 5.1 shows the details of this analysis.

Table 5.1: Participants characteristics at baseline among MSM in Nigeria

Characteristics	n (%) N=206
Age (Years) **Median (IQR): 24 (22-27)**	
Older (≥ 25)	91 (44.2)
Younger (16-24)	115 (55.8)
# Education	
≤ High school	115 (56.1)
> High school	90 (43.9)
# Employment	
Unemployed	40 (22.1)
Employed	141 (77.9)
# Married	8 (4.0)
Never married	194 (96.0
Ever married	
# Religion	155 (77.1)
Christian	46 (22.9)
Muslim	
# Sex orientation	
Homosexual	49 (23.8)
Bisexual	157 (76.2)
#Gender	
Cisgender man	169 (82.4)
Transgender /Others	36 (17.6)
#Alcohol use	110 (63.6)
No	63 (36.4)
Yes	
Condomless Anal Intercourse	
No	130 (63.1)
Yes	76 (36.9)
Concurrent relationship with ≥ 2 males partners	
No	137 (66.5)
Yes	69 (33.5)

#: N does not add up to 206 due to missing variables.

Table 5.2: Bivariate Associations of Condomless Anal Intercourse with last male partners among MSM in Nigeria

Characteristics	Total	Condomless Anal Intercourse			
	N=206	(Yes) N=76	(No) N=130	Crude OR	
	n (%)	n (%)	n (%)	(95% CI)	p-value
Age (Years)					
Older (≥25)	91 (44.2)	31 (34.1)	60 (65.9)	Ref	
Younger (16-24)	115 (55.8)	45 (39.1)	70 (60.9)	1.24 (0.70, 2.20)	0.45
# Education					
≤ High school	115 (56.1)	41 (35.7)	74 (64.3)	Ref	
> High School	90 (43.9)	34 (37.8)	56 (62.2)	1.10 (0.62, 1.94)	0.75
# Employment					
Unemployed	40 (22.1)	14 (35.0)	26(65.0)	Ref	
Employed	141 (77.9)	52 (36.9)	89 (63.1)	1.08 (0.52, 2.26)	0.82
# Sex orientation					
Bisexual	157 (76.2)	59 (37.6)	98 (62.4)	Ref	
Homosexual	49 (23.8)	17 (34.7)	32 (65.3)	0.88 (0.45, 1.73)	0.71
# Gender identity					
Trans/ Others	36 (17.6)	14 (38.9)	22 (61.1)	Ref	
Cisgender man	169 (82.4)	62 (36.7)	107 (63.3)	0.91 (0.45, 1.90)	0.80
# Married					
Never married	194 (96.0)	72 (37.1)	122 (62.9)	Ref	
Ever married	8 (4.0)	3 (37.5)	5 (62.5)	1.02 (0.24, 4.38)	0.99†
Concurrency					
No	137 (66.5)	47 (34.3)	90 (65.7)	Ref	
Yes	69 (33.5)	29 (42.0)	40 (58.0)	1.39 (0.76, 2.51)	0.28
# Alcohol use					
No	110 (63.6)	45 (40.9)	65 (59.1)	Ref	
Yes	63 (36.4)	22 (34.9)	41 (65.1)	0.78 (0.41, 1.47)	0.43

Logistic regression was used to calculate OR and 95% CI. #: Due to missingness, not all variables may add up to N. †: Fisher's exact test was used to calculate the OR and 95% CI.

Table 5.3: Bivariate Associations of concurrency with male partners among MSM in Nigeria

Characteristics	Total	Concurrency			
	N=206	(Yes) N=76	(No) N=130		
	n (%)	n (%)	n (%)	Crude OR (95% CI)	p- value
Age (Years)					
Older (≥25)	91 (44.2)	31 (34.1)	60 (65.9)	Ref	
Younger (16-24)	115 (55.8)	38 (33.0)	77 (67.0)	0.96 (0.53, 1.71)	0.88
# Education					
≤ High school	115 (56.1)	40 (34.8)	75 (65.2)	Ref	
> High School	90 (43.9)	29 (32.2)	61 (67.8)	0.89 (0.50, 1.60)	0.70
# Employment					
Unemployed	40 (22.1)	13 (32.5)	27(67.5)	Ref	
Employed	141 (77.9)	47 (33.3)	94 (66.7)	1.04 (0.49, 2.20)	0.92
# Sex orientation					
Bisexual	157 (76.2)	56 (35.7)	101 (64.3)	Ref	
Homosexual	49 (23.8)	13 (26.5)	36 (73.5)	0.65 (0.32, 1.33)	0.24
# Gender identity					
Trans/ Others	36 (17.6)	9 (25.0)	27 (75.0)	Ref	
Cisgender man	169 (82.4)	60 (35.5)	109 (64.5)	1.65 (0.73, 3.74)	0.23
# Married					
Never married	194 (96.0)	62 (32.0)	132 (68.0)	Ref	
Ever married	8 (4.0)	4 (50.0)	4 (50.0)	2.13 (0.52, 8.79)	0.99†
Condomless Anal Intercourse (Last sex)	130 (63.1)	40 (30.8)	90 (69.2)	Ref	0.28
No	76 (36.9)	29 (38.2)	47 (61.8)	1.39 (0.76, 2.51)	
Yes					
# Alcohol use					
No	110 (63.6)	36 (32.7)	74 (67.3)	Ref	
Yes	63 (36.4)	25 (39.7)	38 (60.3)	1.35 (0.71, 2.57)	0.36

Logistic Regression was used to calculate OR and 95% CI. #: Due to missingness, not all variables may add up to N. †: Fisher's Exact test was used to calculate the OR and 95% CI.

In the bivariate analysis, we examined the independent association of each covariate with the self-reported behavioral outcomes. After assessing for confounding, the variable alcohol use satisfied the criteria for condomless anal intercourse while the variables age

and alcohol use did for concurrency. In addition, the variable age met the criteria for confounding with the "All STIs" outcome. We, therefore, included these variables as confounders in the multivariable analysis.

In the multivariable analysis (Table 5.4), we performed a pre-post-PrEP period analysis with conditional logistic regression. Compared with the pre-PrEP period, during the post-PrEP period participants had 3.5 increased odds (aOR: 3.53: 95% CI: 1.10, 11.35) of laboratory diagnosed rectal gonorrhea. In contrast, compared with the pre-PrEP period, during the post-PrEP period participants reported a 43% decreased odds (aOR: 0.57: 95% CI: 0.37, 0.87) of condomless anal intercourse with last male partner.

Table 5.4: Multivariable Analysis Conditional Logistic Regression for Pre-Post-PrEP intervention

Lab diagnosed STI and behavioral outcomes (S|E)	Post-PrEP vs Pre-PrEP period Crude OR(95% CI)	p-value
Rectal Chlamydia (163| 422)	0.98 (0.31, 3.09)	0.96
Rectal Gonorrhea (163| 422)	**3.53 (1.10, 11.35)**	**0.03**
Urethral Chlamydia (162 | 421)	0.86 (0.16, 4.59)	0.85
Urethral Gonorrhea (161 | 419)	1.41 (0.08, 23.57)	0.80
Condomless anal intercourse with last male partners (205| 775)	**0.57 (0.37, 0.87)**	**<0.01**
Concurrent partnership (205 |773)	1.12 (0.78, 1.61)	0.54
STI [All] (160| 418)	0.98 (0.35, 2.75)	0.96

S |E= Number of **Strata** and **Events** used in the analysis. Crude odds ratios were calculated using the Conditional Logistic Regression procedure. **Bolded** confidence intervals indicate significance at $p < 0.05$.

After adjusting for alcohol use, compared with the pre-PrEP period, the participants had 51% decreased odds (aOR: 0.49: 95% CI: 0.28, 0.84) of reporting condomless anal intercourse with last male partners in the post-PrEP period. For the concurrent relationship

with two or more male partners and all STIs outcome, there was no significant difference between pre and post-PrEP periods after adjustment for potential confounding variables (See Tables 5.5- 5.7)

Table 5.5: Multivariable Analysis of Factors Associated with Condomless Anal Intercourse with last male partners

Multivariable analysis of factors associated with risky behavioral outcomes (CAI) among MSM in Nigeria				
Characteristics	Crude OR (95% CI)	p- value	Adjusted OR (95% CI)	P value
Study time				
Pre- Period	Ref		Ref	
Post – Period	**0.57 (0.37, 0.87)**	**0.01**	**0.49 (0.28, 0.84)**	**0.01**
Alcohol use in last month				
0-1	Ref		Ref	
≥2	1.06 (0.46, 2.43)	0.89	1.16 (0.46, 2.95)	0.76
Crude and adjusted odds ratio were calculated using the conditional logistic regression. **Bolded** confidence interval indicate significance at $p < 0.05$. Model was adjusted for alcohol use in the last one month.				

Table 5.6: Multivariable Analysis of Factors Associated with Concurrency with male partners

Multivariable analysis of factors associated with risky behavioral outcomes (Concurrency) among MSM in Nigeria				
Characteristics	Crude OR (95% CI)	p- value	Adjusted OR (95% CI)	P value
Study time				
Pre- Period	Ref		Ref	
Post – Period	1.12 (0.78, 1.61)	0.54	1.39 (0.85, 2.29)	0.19
Alcohol use in last month				
0-1	Ref		Ref	
≥ 2	1.23 (0.60, 2.52)	0.57	0.83 (0.35, 1.96)	0.67
Age (Years)				
Older (≥ 25)	Ref		Ref	
Younger (16 -24)	1.47 (0.78, 2.78)	0.24	1.99 (0.76, 5.18)	0.16
Crude and adjusted odds ratio were calculated using the conditional logistic regression. Model was adjusted for alcohol use in the last one month and age of the participants				

Table 5.7: Multivariable Analysis of Factors Associated with ALL STIs

Multivariable analysis of factors associated with all STIs among MSM in Nigeria				
Characteristics	Crude OR (95% CI)	p- value	Adjusted OR (95% CI)	P value
Study time				
Pre- Period	Ref		Ref	
Post – Period	0.98 (0.35, 2.75)	0.96	0.79 (0.22, 2.89)	0.73
Age (Years)				
Older (≥ 25)	Ref		Ref	
Younger (16-24)	0.74 (0.22, 2.49)	0.63	1.97 (0.31, 12.41)	0.47
Crude and adjusted odds ratio were calculated using the conditional logistic regression. Model was adjusted for the age of participants.				

Discussion

This study aimed to explore the relationship between the use of daily oral PrEP and adjustment in sexual risk behaviors among MSM in Nigeria. The results from this study have demonstrated some level of inconsistencies between the self-reported behaviors of the participants and their clinical outcomes. While the study participants were more likely to have reported a significant decreased condomless anal intercourse with their last male partners in the post-PrEP period, compared with the pre-PrEP period, there was evidence of an increase in clinically diagnosed rectal gonorrhea. However, there were no significant differences between the pre and post periods diagnoses of rectal chlamydia, urethral gonorrhea, and urethral chlamydia. In addition, when all STIs prevalence were compared between both pre and post-PrEP periods, there were no significant differences.

Our study findings of increased bacterial STI diagnosis post-PrEP intervention accords with the previous studies[51,135,136]. A retrospective longitudinal study[135] reported a higher percentage (49.2% vs. 35.0%) of any STIs diagnosis at 12 months post-PrEP initiation compared with initial PrEP visits among MSM between October 2014 and April 2017 in a Washington STD clinic. Similarly, a multisite open-label Australian study[51] reported a 5(aIRR: 5, 95% CI: 1.33, 45.41), 3 (aIRR: 2.81, 95% CI: 0.38, 124.4) and 2 (aIRR: 2.16, 95% CI: 0.90, 6.27) fold increased incidence per 100 person-years of rectal gonorrhea, urethral chlamydia and rectal chlamydia respectively among MSM 12 month post-PrEP initiation compared with baseline. A leading Canadian sexual health clinic, Montreal's Clinique Medicale l'Actuel, conducted a study [136] between 2010 and 2015, which reported an overall 72% (IRR: 1.72, 95%CI: 1.22, 2.40) increased risk of STIs incidence among MSM 12 months post-PrEP initiation. Compared to controls offered HIV post-exposure prophylaxis, 12-month risk of STI incidence was 76% higher (aIRR: 1.76, 95% CI: 1.14-2.71) among PrEP users.

On the contrary, while we found a decreased reported CAI with PrEP use with some trends of increased STI diagnosis, previous studies[51,135,137,138] with trends or increased STI diagnosis reported concomitant increased CAIs with PrEP use. Montano et al[135]. reported a 46% increased risk (aRR:1.46, 95% CI: 1.13,1.88) of MSM reporting never using condoms in the prior 30 days at 12 months post-PrEP initiation, compared with initial PrEP visits. A plausible reason for this might be that MSM in Nigeria have a higher social desirability behavior compared with MSM in other climes.

Similar to some of the previous studies[68,135,138], we examined these self-reported behaviors from the same participants pre and post-PrEP periods or intervention. For more objectivity,

laboratory-diagnosed STIs may be a more acceptable way of assessing behavioral risk adjustment in MSM. Non-significant changes in the number of sexual partners post-PrEP intervention corroborate with some of the previous studies[68,135,138], all of which reported no changes in the number of sexual partners post-PrEP intervention.

Rectal gonorrhea had 3.5-fold increase in diagnosis in the post-PrEP period, compared with the pre-PrEP period, although this was an unadjusted analysis. A possible explanation is that rectal gonorrhea may be asymptomatic in many men[140], and they were probably unaware of this until they got tested. This finding in our study corroborates a modeling study[66] in which "PrEP related STI screening resulted in a 17% and 16% absolute increase in the treatment of asymptomatic and rectal STIs, respectively[66]". Another possible explanation is that there might have been an increased frequency of STI screening (ascertainment bias) among HIV-negative MSM in our study, who were not previously motivated to attend clinic visits before their PrEP study enrollment. Urethral chlamydia, which is more likely to be symptomatic in men, had a lower, non-significant prevalence in our study. A similar finding was reported in the Seattle STD clinic[135], but their highest pre-post-PrEP differences were noted with rectal chlamydia, which was not as significant as rectal gonorrhea in our study.

Our study was not without limitations. First, we cannot rule out social desirability bias concerning self-reported behavioral outcomes in our study. In addition, it may be challenging for participants to accurately recall all activities they engaged in, in the past month, especially if they were without significant memory anchors. Next, although a three-monthly STI screening was the routine in both the parent and our study, we cannot rule out the possibility of ascertainment bias for the PrEP users. Finally, we did not identify any

significant confounder for rectal gonorrhea in our study, hence we reported the crude odd ratio. However, there might be residual confounding we missed out, although this is less likely with a pre-post intervention analysis.

Its limitations notwithstanding, we engaged self-paired match (pre-post-PrEP) analysis, which is a desirable way of controlling for residual confounding in longitudinal studies. This method of analysis is likely to decrease bias in our study findings. Finally, as far as we know, this is the first study examining the behavioral risk compensation among MSM taking PrEP in the sub-Saharan African region, which has the highest global at-risk and affected populations for HIV transmission, prevention, and treatment [140].

Conclusion:

We set out to determine the association between the use of daily oral PrEP among MSM living in Nigeria and behavioral risk compensation. We found evidence consistent with some increased odds, as well as, no association with clinically diagnosed bacterial STIs in the post-PrEP periods, compared with pre-PrEP periods. In addition, there was decreased self-reported condomless anal intercourse during the post-PrEP period. Although the evidence of PrEP associated behavioral risk compensation in our study was not distinct, there might be a need for a higher index of suspicion of PrEP associated STIs among MSM taking PrEP in Nigeria and those in similar settings.

The implication of our study findings should inform future studies to address the following. There is a need to clarify the apparent disconnect between self-reported behavior and the trends of the clinical STI diagnosis. Further studies are required for the more evidence-

based interventions on the use of PrEP and behavioral risk compensation in this population. While these studies are ongoing, there is a need for discussion of the guidelines on the use of antibiotics among MSM taking PrEP in the light of potential antibiotic resistance already reported among certain MSM networks[73,141]. Finally, we recommend future studies in resource-limited settings to investigate culturally acceptable strategies for engaging MSM to prevent potential risk adjustments following PrEP use.

CHAPTER VI. DISCUSSION OF DISSERTATION RESULTS

This study assessed a topical subject on the use of HIV pre-exposure prophylaxis (PrEP) among a population of men who have sex with men (MSM) living in Nigeria, a highly homophobic setting. The findings highlight a potential intersection in the transition of PrEP implementation, from tightly controlled clinical trial settings in a high-income setting to real-life implementation in a low resource, high HIV burden setting. The pragmatism of this study is expected to be relevant to MSM living in resource-limited settings, their support networks, health care workers, and other invested parties working towards ending new HIV infections by 2030[120].

Self-reported PrEP adherence and serum quantification of Tenofovir (TFV) / Emtricitabine (FTC).

Contrary to our hypothesis, we did not find an increasing discordance between self-reported PrEP adherence (SRPA) and Tenofovir (TFV)/ Emtricitabine (FTC) serum quantification levels at month 9 compared with month 3 study visits. This was partly explained by the low proportion of TFV and FTC detectability (37%) in our study. When compared with previous studies whose mean correlation between SRPA and PrEP biomarkers ranged from 0.25 to 0.40 [19,25], ours was much lower, between 0.02 to 0.18.

In our study, participants over-reported their subjective PrEP adherence. Social desirability bias is a known limitation of self-reported health behaviors, and this is consistent with other studies[142,143].

We had some intriguing findings comparing the trend of the proportions of protective adherence achieved during visits months (month 3 versus month 9). When paired assays

(N [number of participants] =85) were compared between the same study participants at month 3and month 9, a significant proportion (0.18, p=0.01) of persons who, at month 3, achieved protective adherence, failed to achieve protective adherence at month 9. However, when the pooled assay results (N=219) were analyzed in multivariable analysis, there was initially no significant difference in the un-adjusted protective adherence for study month visits, however, on adjustment, this changed. Compared with month 3 visits, month 9 visits had a trend of association with protective adherence with a p=0.06.

In the exploration analysis of the association between self-reported PrEP adherence and protective adherence, we found a consistently significant association of the PrEP introduction methods (clinic-based versus community-based) as well as the disclosure of sexual orientation ("Yes" versus "No") with protective adherence in both unadjusted and adjusted multivariable analysis. In addition, younger MSM (16-24 years) were less likely to achieve protective adherence as compared with the older (≥ 25 years) MSM.

Social support and PrEP protective adherence

We found a significant association between participants with perceived emotional social support and protective PrEP adherence. Our study findings are in accord with previous studies[55,63] that have identified emotional social support as a key component of patients' adherence to their prescribed medication.

However, in contrast to our hypothesis, participants with perceived informational or instrumental social support did not demonstrate different odds of PrEP protective adherence in our study. Interestingly, we found that participants with a higher perception of either informational or instrumental social support were likely to be younger than those with lower or no perceptions of such support. Similarly, participants who had peer-to-peer

(community-based) PrEP introduction method were more likely to be younger when compared with those with provider-initiated PrEP introduction (clinic-based). To further understand the role of age in our findings, we conducted a stratified analysis, but age did not significantly modify the association between social support domains and PrEP protective adherence. This may be due to limited power. However, the stratification by the PrEP introduction method had some intriguing findings.

First, the Breslow-Day test for homogeneity of odds ratio was significant (p=0.038) for the informational social support domain, implying that the perception (or lack thereof) of informational social support may alter the direction of the measure of association of PrEP's adherence between those with community versus clinic-based PrEP introduction methods. The community based PrEP introduction participants had a 58% decreased odds (OR: 0.42, 95% CI: [0.22, 0.80]) of protective PrEP adherence, while the clinic-based PrEP introduction participants had a 10% decreased odds (OR: 0.90, 95% CI: [0.64, 1.27]) of protective adherence. Secondly, it was surprising to find that despite a strong association of clinic-based PrEP introduction with protected PrEP adherence across all three social support domains, on stratification within MSM with a perception of instrumental social support, findings were different. Participants with community based PrEP introduction had 29% increased odds of protective adherence (OR: 1.29, 95% CI: [0.57, 2.92]) while those receiving clinic PrEP introduction had 5% (OR: 1.05, 95% CI: [0.73, 1.52]) increased odds of protective adherence. Although this difference was not statistically significant, it was still quite surprising that perceived instrumental social support had such a trend on PrEP adherence among MSM. It is also worthy of note that irrespective of the PrEP introduction

method, those with perceived instrumental support were more likely to have achieved PrEP adherence as compared with those with perceived informational social support.

PrEP use and Behavioral risk compensation in MSM

There were inconsistent findings between some of the reported self-behaviors and some of the objectively clinically diagnosed sexually transmitted infections during post-PrEP period, compared with pre-PrEP period in our study.

Our findings reinforce the need for an objectively measured clinical biomarker alongside self-reported behavioral outcomes, given the role social desirability bias appeared to have played in our study. From the analyses (pre-PrEP period vs post-PrEP periods), study participants reported significantly decreased occurrence of condomless anal intercourse with the last male partners. On the contrary, laboratory-diagnosed rectal Neisseria gonorrhea was significantly associated with post-PrEP period, although this was an unadjusted analysis. When all laboratory-diagnosed STIs were pooled, they were not significantly increased in the post-PrEP period compared with the pre-PrEP period contrary to our hypothesis of different odds between both periods.

Our findings of no change in any STIs and no change in concurrent number of male relationships are consistent with the previous studies[69,92,136]. However, unlike the previous studies[51,69,138] where participants reported increased CAI post-PrEP, with concomitant increased STI diagnosis, our study participants reported decreased CAI post-PrEP.

As far as we know, this study is the first to estimate the effect of PrEP use on the behavioral outcome and STIs in Nigeria and West Africa; hence, it lays a foundation for an innovative

and responsive HIV prevention discourse, especially in Sub-Saharan Africa where most of the burden of new HIV infection and transmission still thrives. In addition, findings from this study might begin to provide insight into the clinical implications of scaling up PrEP implementation in a low middle-income setting.

Our methods of analysis – paired analysis (with conditional logistic regression), are very likely to reduce unmeasured and or residual confounding in our estimates.

Study Limitations.

We had some limitations in this study; hence, our findings should be interpreted in this light. First, this was a one-centered, one-state study from a thirty-six-state country. This might cause some concerns about the generalizability of our study findings. However, the Federal Capital Territory, the geographical location of the study is a heterogeneous and cosmopolitan capital city. Hence, the geo-tribal population distribution that typifies other parts of the country is unusual here. We, therefore, think that this study's results are generalizable to MSM in Nigeria and similar settings.

Second, the parent study, and by extension, our study recruited MSM through a respondent-driven sampling method, which is an incentive-based, network analysis driven recruitment method. Ideally, our analysis ought to have been weighted based on the density of the network and or the wavenumber of the recruitments. In this study, we did not weigh our findings, and this may have caused some level of selection bias. This bias may present in form of exaggerated homophily[144] (tendency to form ties between two nodes that have common attributes e.g. age, sexual orientation, infection status, etc.) in our study population. As much as we know, we controlled for most of the potential measurable bias

(e.g. similar ages, sexual orientation, gender, etc.) that the un-weighted RDS might have introduced in our study population. However, the unmeasured ones may have persisted.

Third, Nigeria is quite a homophobic environment, especially given the same-sex prohibition bill that was passed into law on January 7, 2014[145]. This has been reported[81] to have a deleterious effect on the health-seeking behavior of MSM in Nigeria, a population that hitherto had been hard to reach. This law might have limited the participation of MSM who otherwise might have been more involved in the study.

Fourth, we had a high attrition rate in our study. The mean "between study" visit attrition rate was 23% (95% CI: 11%, 35%) and the overall rate was 59% (95% CI:55%, 65%), starting with 400 MSM initiating PrEP and ending with 161 who completed the last follow up visits. This may have been one of the fallouts of the previously discussed point on Nigeria being a highly homophobic and at times, challenging environment for same-sex studies. This might have led to under-powering some of our analyses and might have attenuated some of our expected effect measures.

Fifth, some of the outcomes (for example, TFV-FTC serum level quantification) for our study had a lower event-to-trial ratio than anticipated. Of the 219 persons with an assay, only [81/219], 37% had a detectable serum level of TFV quantification. Almost two-thirds of the samples of all the TFV-FCT assay results were below the limit of quantification. This may have led to underestimating the sample sizes and power we assumed when planning for our study. This might also lead to an attenuating of effect measures or a decrease in the ability to reject a null hypothesis when indeed it was false (Type II error).

Sixth, we had a moderate percentage (9.5%) of missing variables in our study. We however conducted sensitivity analyses to determine the characteristics of the missingness. In most cases, they were missing completely at random and as such we do not expect this to significantly impact inferences from our data analysis. For some variables, we used the "last observed carry forward" method. We could not conduct multiple imputations for the missing continuous variables (e.g., TFV-FTC quantification) because of the high proportion of missingness and the non-normal nature of the data distribution. In all cases, we analyzed our samples based on a complete case analysis for the exposure and the outcome variable.

Seventh, two of the three of the outcomes in our study were directly related to the measurement of serum quantification of TFV-FTC. A white coat adherence-in which a patient takes his medication during the week of clinic visit- cannot be ruled out with our liquid chromatography-mass spectrometry quantification method, which at best detects TFV-FTC use within the last seven days of the assay.

Eighth, we did not measure social support as a time-varying variable, and as such, our study may have not have provided optimal inferences for MSM who had a significant change in social support attribute after the month 1 visit in the 12-month study.

Implications and Future directions

Based on our study findings, the following are the potential implications.

On PrEP Implementation:

When feasible and available, PrEP implementation programs might consider a clinic-based (provider-initiated) PrEP introduction for prospective PrEP clients rather than a community-based (peer-to-peer-initiated) method. The consistent and strong association between clinic-introduced PrEP participants and protective adherence in our study (Aims 1 and 2) was unlikely to be exclusively due to differences in the counseling expertise of health care providers versus peer-to-peer counselors. We postulate that the TRUST clinic served as a one-stop-shop haven for MSM. As such, when counseled for PrEP in this environment, they were more likely to participate conscientiously; as compared to when counseled within the community where some of them live, especially since the vast majority (more than 90%) in our cohort did not disclose their sexual orientation to their family members.

We also observed that participants who had the clinic-based PrEP introduction had spent more time as TRUST study participants, and had attended the routine clinic for some time before PrEP introduction. This is not the typical case with participants introduced from the community, who initiated PrEP within a shorter time after enrollment. Therefore, it might be helpful to allow some time (for example, at least 30 days) for all newly enrolled patients to have a grasp of clinic flow and their expectations before PrEP enrollment. While there needs to be a balance between timely enrollment and missed opportunities for HIV prevention, we think the benefits of evidence-grounded, robust introduction for PrEP participants may outweigh a more “hurried” process, as our study suggests. In addition,

there might be a need to buttress activities that enhance instrumental social support among the clinic-based participants as they seemed to have reported less of this kind of support.

We also observed that apart from the sub-set analysis of the paired samples, most participants from the larger data set seem to have better PrEP adherence at month 9 as compared with month 3. This might be because irrespective of their health status, patients may struggle to fit a new daily oral medication into their lives. Therefore, an intensified, elaborate adherence enhancing strategies to assist new PrEP users, such as coded short messages on their phones may be helpful to navigate these initial challenging periods Another possible explanation is that individuals with poorer adherence were lost before the 9 month visit.

Finally, on implementation, social support programs, targeting the creation of safe spaces for personalized-experience sharing among PrEP users (for example a clinic-based web/ social media application) might foster the emotional social support that was associated with PrEP adherence in our study. Older MSM may also need to be targeted by such programs for tailored enhanced information sharing and tangible aid and service support, as this sub-group reported a lower perception of these forms of social support in our study.

On clinical implication:

Our findings show some shreds of evidence of post-PrEP increase diagnosis of laboratory-diagnosed STIs. This indicates a need for health care providers to have higher indices of suspicion for STIs among PrEP-taking MSM, beyond the routine three monthly screening. The WHO's current STI treatment guidelines support syndromic management of STIs, which proposes STI diagnosis based on specific clinical symptoms, such as genital

discharge and ulcers[146]. However, WHO also recognizes the high proportion of STI cases that are asymptomatic, and thus also supports the use of laboratory-based diagnosis where tests are available and affordable[146]. Even after diagnosis and provision of treatment, health care providers would need to conduct active case-finding for STI treatment failure, and refer such patients for appropriate specialized treatment to avoid the spread of antibiotic resistance[147]. Active surveillance may be needed, especially for *Neisseria gonorrhea*-induced antibiotic resistance[141]. In addition, partner notification for MSM diagnosed with STIs has been proposed[147]. The decision to prescribe prophylactic antibiotics for MSM taking PrEP might need to be appropriately weighed against the potential risk of abuse and consequent antibiotic resistance. Although the ANRS IPERGAY randomized controlled trial reported a significantly decreased STI incidence among MSM who had post-coital, on-demand HIV post-exposure prophylaxis and doxycycline [148], the decision to prescribe prophylactic antibiotics might still need to be tailored on an individual need basis for those taking PrEP, based on their history and risk profile.

On Epidemiological implication:

Our study recorded a low PrEP protective adherence of 30% (95% CI: 24%, 36%). In a high-HIV burden country like Nigeria[74], optimal PrEP adherence is imperative, to prevent the continuous transmission of HIV among MSM and their sexual networks, most of whom are women, and their potential offspring (approximately 72% of participants reported vaginal sex with a woman in the last one month at baseline). This has implications for reducing the number of new child HIV infections in Nigeria, in addition to reducing the high HIV incidence among MSM. These are public health issues that require close

multidisciplinary collaboration among relevant local and international stakeholders, including MSM living and not living with HIV, health care workers, technical working groups, the government of Nigeria, and the international agencies. Solutions will have to be built around pooled resources to address the challenges we have observed and reported in this study.

On Cost Implication:

We did not conduct an economic analysis for PrEP use among MSM in Nigeria, however, we envisage that the cost/cost estimates of PrEP and antibiotic scale-up among MSM will need sustainability factored if this will be implemented for population-level impact.

Future directions:

Our study further sheds light on the need for point-of-care PrEP adherence assessment tests [29,48]. This will enhance the prompt assessment of the current biomarker level assays and timely counseling for patients. Recall bias is common for many people, not only participants such as in our cohort, who may not recall all activities in the past three months when assay results were being discussed with them. In addition, PrEP assays that can detect markers from the past 14 days might be a better reflection of PrEP adherence. There are presently ongoing clinical trials for injectable for long-acting PrEP including among MSM[33]; when this becomes available, PrEP adherence might significantly improve and not remain a major drawback of PrEP.

Future implementation research should include investigating and tailoring evidence-based interventions (EBIs) for PrEP implementation among MSM in Nigeria. There is also a need for the follow-up and dissemination of the EBIs from the grassroots by engaging the local,

state, and federal government stakeholders, thereby informing and sensitizing the Nigerian government to take action on these findings.

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