



BMJ Open The Magnetic Couples Study: protocol for a mixed methods prospective cohort study of HIV-serodifferent heterosexual couples' perspectives and use of pre-exposure prophylaxis (PrEP)

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ABSTRACT

Introduction HIV transmission within serodifferent heterosexual couples plays a key role in sustaining the global HIV pandemic. In the USA, transmission within established mixed-status couples accounts for up to half of all new HIV infections among heterosexuals. Oral HIV pre-exposure prophylaxis (PrEP) is a highly effective prevention method, although underutilised among serodifferent couples. Moreover, there is a dearth of research on US HIV-serodifferent couples' perspectives and use of PrEP, alone or in combination with other prevention methods. In this paper, we describe the study protocol for the Magnetic Couples Study, designed to fill critical knowledge gaps regarding HIV-serodifferent heterosexual couples' perspectives, experiences and utilisation of PrEP.

Methods and analysis The Magnetic Couples Study is a mixed methods prospective cohort study designed to describe temporal patterns and identify determinants at multiple levels (individual, couple, HCF) of PrEP outcomes along the care continuum (PrEP awareness, linkage, uptake, retention and medication adherence) among HIV-serodifferent heterosexual couples residing in New York City. The study will also examine clinical management of PrEP, side effects and changes in sexual-related and substance use-related behaviour. A prospective cohort of 230 mixed-status couples already on oral PrEP was recruited, with quarterly assessments over 18 months; in addition, a cross-sectional sample of 150 mixed-status couples not currently on PrEP was recruited. In-depth semistructured qualitative interviews were conducted with a subsample of 25 couples. Actor-partner interdependence modelling using multilevel analysis will be employed for the analysis of longitudinal dyadic data. Framework analysis will be used to analyse qualitative data. A parallel convergent design will be used for mixed methods integration.

Ethics and dissemination The study was approved by the University of Rochester Institutional Review Board (RSRB00052766). Study findings will be disseminated to community members and providers and to researchers and policy makers.

Strengths and limitations of this study

- Prospective cohort study of pre-exposure prophylaxis (PrEP) implementation involving HIV-serodifferent heterosexual couples in the USA, a high-risk but understudied population.
- Longitudinal collection of quantitative, qualitative, biological and medical record data, including objective measures of PrEP adherence.
- Examination of multilevel (individual, couple, health-care facility) determinants of PrEP outcomes on the continuum of care.
- Sampling of study participants receiving PrEP and antiretroviral therapy across multiple healthcare facilities allowing for examination of site-level determinants.
- Threats to internal and external validity include bias from self-reported measures, sampling bias and lack of generalisability to non-urban areas.

BACKGROUND

HIV transmission within heterosexual couples in which one partner is HIV-negative and the other is living with HIV—so-called HIV-serodifferent couples—plays a key role in the global HIV pandemic,^{1–5} with couple-linked seroconversions accounting for between 30% and 50% of new HIV infections.^{4 6 7} In the USA, about one-in-four heterosexuals living with HIV has an established primary sexual partner who is HIV-negative;^{8–19} and such 'mixed-status' or 'magnetic' couples account for up to half of all new HIV infections among heterosexuals nationally.²⁰ The risk of HIV transmission within serodifferent couples has been observed to vary widely, from 0% to 20% per annum, depending on the type

and frequency of sexual behaviour and use of prevention methods.²¹

Until relatively recently, condoms were the only effective method of preventing HIV transmission within serodifferent couples. However, despite awareness of their mixed HIV status, consistent condom use among serodifferent couples ranges across studies from a low of 20% upwards to 75%.^{12 16 22–24} Moreover, male condoms are only 70%–80% effective at preventing HIV transmission.^{25–27} In contrast, robust evidence has shown that maintaining an undetectable viral load in the partner living with HIV provides complete protection from sexually transmitted HIV in serodifferent couples—affirming the dictum Undetectable=Untransmittable (U=U).^{28–30} Yet, there is limited evidence on the extent to which HIV-serodifferent couples are able to sustain viral suppression; a few studies indicate that only about half of partners living with HIV in mixed-status heterosexual couples are able to maintain long-term viral control (ie, sustained undetectable viral load).^{23 31} Barriers to sustained undetectable viral load include social determinants of health including racism, homelessness, poverty and access to medical care, which can inhibit one's ability to adhere to a daily medication regimen.^{32–35} Oral HIV pre-exposure prophylaxis (PrEP; 200 mg emtricitabine (FTC) in combination with 300 mg tenofovir disoproxil fumarate (TDF) or 25 mg tenofovir alafenamide (TAF)) has been added to the HIV prevention toolbox within the last decade. When taken daily as an oral medication, PrEP has demonstrated high levels of efficacy (>95%) in preventing HIV transmission among HIV-serodifferent heterosexual couples.^{36 37}

The US Centers for Disease Control and Prevention and the WHO have consequently recognised HIV-serodifferent couples as a high-priority group and have issued recommendations for PrEP and antiretroviral therapy (ART) to prevent dyadic transmission.^{38–40} However, there is a lack of data on PrEP awareness, acceptability, uptake and adherence among HIV-serodifferent heterosexual couples in the USA.^{20 41} There is also a dearth of research on couples' perspectives and use of PrEP in combination with ART and other prevention methods, and on the factors at multiple levels (individual, couple, healthcare facilities (HCFs)) that account for enacted prevention strategies in these couples.^{42–44} In addition, there is little evidence on how different HIV prevention strategies might affect sexual and substance use-related behaviours among US mixed-status couples.²⁰

The Magnetic Couples Study is an ongoing prospective cohort study funded by the National Institutes of Health, National Institute of Mental Health (R56MH103047; R01MH107371), designed to fill critical knowledge gaps regarding HIV-serodifferent heterosexual couples' perspectives on and experiences in the PrEP care continuum, with the goal of providing an evidence base to inform tailored HIV prevention interventions for this group. The specific aims of the Magnetic Couples Study are as follows: (1) examine trends and identify multilevel (individual, couple, HCF) determinants of awareness,

acceptability, uptake and retention of oral PrEP use among HIV-negative partners in US serodifferent heterosexual couples; (2) describe the temporal patterns and identify multilevel determinants of daily oral PrEP and ART adherence in both members of HIV-serodifferent couples, including the pharmacokinetic relationship between self-reported PrEP adherence and FTC/TDF/TAF drug concentrations in blood; (3) describe the temporal patterns and identify determinants of PrEP care utilisation compliance with recommended HIV testing and clinical management (PrEP visits, HIV testing and ancillary tests, counselling) as well as side effects and toxicity among PrEP users; and (4) identify predictors of changes in sexual and substance use-related behaviours among PrEP users and their partners living with HIV. In the current paper, we describe the study protocol of the Magnetic Couples Study.

METHODS AND ANALYSES

Design and samples

The Magnetic Couples Study employs a mixed methods observational design to characterise trends in PrEP use and identify deterrents and facilitators at multiple levels at each stage of the PrEP care continuum among heterosexual HIV-serodifferent couples. The study does not include provision of clinical care to participants, but examines PrEP utilisation and determinants of care as they occur in real-world settings. The study population consists of mutually disclosed HIV-serodifferent heterosexual couples in which members are age 18 years or older; in a primary heterosexual relationship for at least 3 months and have engaged in vaginal or anal sex in the last 30 days; are fluent in either English or Spanish; and reside in or around the New York City area. The construct of heterosexuality was based on dyadic identity as an opposite-gender/opposite-sex couple and could include both cisgender and transgender persons.

The HIV-serodifferent sample (n=580; 290 dyads) is composed of two arms: one consisting of a prospective cohort sample (n=460; 230 dyads), for which the HIV-negative partner had a current prescription for PrEP at the time of baseline enrolment; and the second consists of a cross-sectional sample (n=300; 150 dyads), for which the HIV-negative partner did not have a current PrEP prescription (figure 1). Couples in the non-PrEP arm were allowed to enrol into the PrEP cohort if they later received a PrEP prescription. Thus, the final sample of 290 unique couples include 230 couples enrolled in the prospective PrEP cohort (140 enrolled directly into the PrEP arm plus 90 couples referred from the non-PrEP arm) and 60 couples from the non-PrEP arm not referred to the PrEP cohort. A purposive subsample (n=25 dyads) drawn from the prospective cohort will be selected to participate in semistructured in-depth qualitative interviews to provide contextual data to aid in the interpretation of quantitative findings.

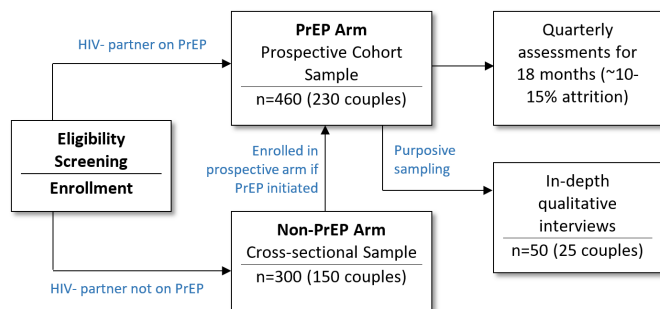


Figure 1 Couple enrolment into pre-exposure prophylaxis (PrEP) and non-PrEP study arms.

Timeline

Prospective cohort participants are enrolled in the study for an 18-month period, with data collection assessments at intake and at 3-month intervals (maximum seven observations per participant). Both members of each couple provide authorisation to access medical records spanning the period from 18 months prior to study enrolment to their terminal follow-up assessment (total 36 months). Intake enrolment for the study has been completed (June 2016–December 2019) and follow-up assessments are expected to be completed by late 2021.

Patient and public involvement

This 5-year PrEP implementation study, supported by the National Institute of Mental Health (NIMH; R01MH107371), was preceded by a National Institutes of Health (NIH) ‘High Priority, Short-Term Project Award’ (R56MH103047) designed to provide interim support for ‘highly meritorious’ ... ‘creative and innovative approaches’ prior to receiving full NIH funding. Conducted from September 2014 to February 2016, our team used this period of support to perform formative work in preparation for the full study, including conducting in-depth interviews with 27 HIV-serodifferent couples and 15 PrEP providers. We also interviewed administrators and formed partnerships with over 40 HCFs, service agencies and community-based organisations in New York City. This formative work helped inform all aspects of the study design and data collection. The full study protocol was pilot tested with 10 HIV-serodifferent couples prior to enrolling research participants. Public and stakeholder involvement continued during the main study in close consultation and involvement with the New York City PrEP Task Force composed of PrEP providers, patients, advocates, researchers and other stakeholders.

Recruitment and enrolment

Recruitment efforts focused on increasing awareness of the study among HIV-serodifferent heterosexual couples in the New York City area by employing five primary methods: (1) distribution of study posters and pamphlets (figure 2); (2) passive referrals from clinics, service agencies and community-based organisations; (3) social media campaign (Facebook, Twitter, Craigslist; project website); (4) traditional advertisements in newspapers, magazines,

WE'RE LOOKING FOR PARTICIPANTS!

We are seeking heterosexual (male/female) couples who are of “mixed” HIV status—one member of the couple is HIV-positive and the other is HIV-negative. If you are in a “Magnetic” relationship like this (mixed HIV status), we’d like to talk with you and your partner. We’d like to learn about your experiences as part of a Magnetic couple.

Each partner will receive \$75 (\$150 total), plus round trip metro fare, for each visit.

You and your partner may be eligible for follow-up study visits, in which case each of you may receive up to \$525 (\$1,050 per couple) for complete participation.



Figure 2 English version poster for the Magnetic Couples Study (Image source: Getty Images #476852698).

subway signs and radio; and (5) peer-referral with a maximum of three referrals per enrolled couple. These methods directed those interested in the study to contact study staff directly by calling a toll-free phone number, text messaging, emailing or accessing the study website to obtain further information and undergo initial eligibility screening. Those who met the eligibility criteria were offered assistance for informing and recruiting their primary partner into the study using strategies developed by Witte and colleagues.⁴⁵

Once both members of the couple were deemed eligible, an appointment was scheduled for them to visit a centrally located research office in mid-town Manhattan and undergo eligibility verification, informed consent and intake assessment. Eligibility verification consisted of re-screening, HIV testing to confirm HIV-serodifferent status and administration of a couple verification screener to ensure that dyads were primary sexual couples.^{46 47} Eligible couples in which the HIV-negative partner had a current PrEP prescription (verified by the date on their PrEP medication bottle) were enrolled into the prospective cohort PrEP arm of the study; whereas couples not taking PrEP were enrolled into the cross-sectional non-PrEP arm of the study. If couples in the non-PrEP arm

Table 1 Description of study measures and data collection

Data type	Subjects/Source	Collection method (frequency)
Quantitative surveys	Prospective PrEP arm participants and cross-sectional non-PrEP participants (each member of the couple surveyed separately)	Audio computer-assisted self-interviews (ACASI) (PrEP arm participants: <i>intake, quarterly</i> ; non-PrEP arm participants: <i>intake</i>)
Medical records	Prospective PrEP arm participants (HIV-negative and HIV-positive partners)	Retrospective chart review and electronic extraction from participating clinics (past 3 years of records obtained at terminal follow-up)
HIV antibody test	Prospective PrEP arm and cross-sectional non-PrEP arm participants	OraQuick Rapid Antibody Test Advance HIV-1/2 test (<i>intake</i> : HIV-positive partner (both arms); HIV-negative non-PrEP arm (<i>intake and quarterly</i> : HIV-negative PrEP arm))
Serum creatinine level	Prospective PrEP arm, HIV-negative partner	Dried blood spot (DBS) assay for creatinine (<i>intake and quarterly</i>)
PrEP drug levels	Prospective PrEP arm, HIV-negative partner	DBS assay for quantification of TFV-DP (TDF, TAF) and FTC-TP (<i>intake and quarterly</i>)
Qualitative interviews	Purposively selected PrEP arm participants (each member of the couples interviewed separately)	Semistructured face-to-face interviews, audio recorded and transcribed (one-time during prospective period)
Healthcare facility characteristics	Extracted from quantitative surveys; medical records; public sources	Secondary data extraction

FTC-TP, emtricitabine triphosphate; PrEP, pre-exposure prophylaxis; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV-DP, tenofovir-diphosphate.

expressed an interest in PrEP, a referral was made to a PrEP provider at a preferred location. Couples enrolled in the prospective PrEP cohort who broke up during the study period were allowed to be retained in the study, but follow-up assessments for former partners were scheduled on different days. Survey data were collected on relationship status, break-ups and establishment of new relationships, which may have an impact on PrEP outcomes. Allowing both members of dissolved couples to remain in the study also reduced the risk of potential partner conflict. Contact information was collected and entered into a locator form for all enrolled couples. Each member of the couple is paid US\$75 for each completed office visit assessment, in addition to a travel reimbursement of US\$5.50 for subway fares to and from the research office. Enrolled couples are also paid US\$10 for each couple they refer into the study, with a limit of three referrals per couple.

Measures and data collection

The Magnetic Couples Study involves the collection of multiple types of data: quantitative surveys, medical record chart review and extraction, biological assays and qualitative interviews (table 1). Consistent with our specific aims, study outcome measures include PrEP acceptability, uptake, and retention (Aim 1), PrEP adherence (Aim 2), utilisation of PrEP clinical care and PrEP-related side effects (Aim 3), and sexual and substance use-related behaviour change (Aim 4).

Quantitative surveys

Structured quantitative surveys are administered to all enrolled participants in either English or Spanish by

trained bilingual interviewers using a combination of computer-assisted personal interview (CAPI) and audio computer-assisted self-interview (ACASI) methods (online supplemental file 1). Couples are interviewed concurrently but separately in private offices. Members of HIV-serodifferent couples in the prospective PrEP arm complete the survey at baseline and quarterly for 18 months, whereas couples in the non-PrEP cross-sectional arm complete only a single intake survey. Surveys last between 1 and 1.5 hours and are designed with skip patterns such that each survey is tailored to the characteristics of the participant.

Quantitative survey items encompass ten major domains: (1) *Demographics* (eg, age, race, ethnicity, economic indicators, family composition); (2) *General Health* (eg, physical and mental health and treatment, history of sexually transmitted infections, reproductive health); (3) *Health Systems* (eg, provider satisfaction, access and barriers to care, healthcare utilisation); (4) *Healthcare Costs* (eg, insurance coverage, assistance programmes, out-of-pocket expenses); (5) *Structural Factors* (eg, stigma, discrimination, incarceration); (6) *Psychosocial Factors* (eg, social support, resilience); (7) *Relationship Function* (eg, gender roles, conflict resolution, communication, balance of power, closeness, commitment, trust, intimate partner violence); (8) *HIV* (eg, ART adherence, disclosure); (9) *PrEP* (eg, awareness, knowledge, acceptability, utilisation, adherence, formulation preference); (10) *HIV Exposure and Prevention* (eg, perceived HIV vulnerability, condom attitudes and use, viral suppression, sexual behaviour, substance use behaviour).

Medical records

Participants enrolled in the prospective PrEP arm are asked to voluntarily provide Health Insurance Portability and Accountability Act (HIPAA) authorisation to release their medical records obtained from their HCFs delivering ART (for participants living with HIV) or PrEP care (for HIV-negative participants); authorisation forms are completed at intake and updated at terminal follow-up assessment and requests to release medical records are submitted to appropriate HCFs to obtain participant records covering the preceding 36 months. Data obtained from medical records consist of 60 items per office visit and are extracted under the supervision of a nurse study coordinator trained and experienced in medical chart review and extraction. Medical record data cover the following domains: office visit date and purpose; health insurance; vital signs; major diagnoses (physical, mental and sexual health); tests and procedures performed; HIV test results; HIV biometrics (eg, CD4; viral load); ART adherence (provider notes from patient reports or pharmacy refill); ART regimens; PrEP history and care; other prescription medications; kidney and liver function; bone mineral density; vitamin/supplement use; ancillary services; and sexual history.

HIV antibody test

The HIV-serodifferent status of all couples (PrEP and non-PrEP arms) was confirmed at intake by HIV testing. In addition, all HIV-negative partners are administered an HIV test at each follow-up assessment. HIV testing is performed using the OraQuick Rapid Antibody Test Advance HIV-1/2 kit, with test kit controls performed on new batches (OraSure Technologies). Standard CDC HIV counselling is performed as part of the HIV testing protocol.

Serum creatinine level

As an indicator of renal function, serum creatinine levels are measured at intake and at all follow-up visits for HIV-negative participants in the PrEP arm. Dried blood spot (DBS) specimens are collected from participants using the PTS Pod System (PTS Diagnostics) and shipped to a commercial laboratory (CoreMedica, Lee's Summit, Missouri, USA) where assays are run and results are reported back via a secure portal. Creatinine levels are then converted to creatinine clearance values applying standard algorithms.

PrEP drug levels

PrEP (Truvada and Descovy) drug blood levels in HIV-negative participants are quantified as an objective measure of PrEP adherence. Descovy was approved by the US Food and Drug Administration (FDA) for PrEP part-way through data collection and some participants had their prescriptions switched to Descovy by their providers. DBS specimens are collected from HIV-negative partners enrolled in the PrEP arm at intake and quarterly follow-up assessments using the PTS Pod System.

Specimens are shipped to an academic laboratory at the University of Colorado Anschutz Medical Campus for assay, which quantifies (1) tenofovir-diphosphate (TFV-DP) concentration (fmol/punch(es)), an estimate of the average amount of PrEP taken over the prior 2-month period; and (2) emtricitabine triphosphate (FTC-TP) concentration (pmol/punch(es)) for which a detectable sample indicates that the participant took at least 1 dose of PrEP in the last 48–72 hours for Truvada and up to the last week for Descovy.^{48 49}

Qualitative interviews

A subsample of HIV-serodifferent couples (n=50; 25 dyads) from the prospective PrEP arm participate in face-to-face in-depth semistructured qualitative interviews lasting about 1 hour (online supplemental file 2). Composition of the purposive sample will ensure variation on demographics, PrEP retention and adherence, condom use, and ART adherence and viral load. Once long-acting injectable (LAI) PrEP is approved and available, we will conduct an additional 10–15 interviews with HIV-negative partners who switch to LAI-PrEP. Interviews are conducted concurrently with each member of the couple individually in separate private offices; each partner receives US\$50 compensation. Interviews cover relationship dynamics, dyadic strategies for HIV prevention, sexual and substance use history, healthcare utilisation, including HIV or PrEP care, and experiences with providers and HCFs. The audio-recorded interviews are transcribed verbatim.

HCF characteristics

Characteristics of HCFs at which participants receive their PrEP or ART care will be extracted from multiple secondary data sources, including participant quantitative surveys, medical record data and public sources. Characteristics include type (eg, primary care; sexual health clinic), location (eg, access to public transportation), size (patient pool; number of providers), patient resources (eg, onsite pharmacy; social services); and PrEP and ART programmes (eg, support groups; patient navigation; financial assistance).

Data analysis

Quantitative analysis

Descriptive statistics will be used to characterise the sample on demographics and key variables. Generalised estimating equation (GEE) analysis will be performed on baseline data pooled from the PrEP and non-PrEP arms to identify predictors of PrEP acceptability and uptake. The actor-partner interdependence modelling (APIM) framework using multilevel modelling (MLM) will be employed for the analysis of longitudinal dyadic data in order to accommodate the nested data structure (repeated observations nested within individuals nested within dyads) and examine mutual partner influence over time in distinguishable dyads.^{50 51} This will permit estimation of PrEP user growth trajectories on outcomes

while directly assessing the impact of structural, dyadic and partner factors (time-variant and invariant) on outcomes.^{52 53} Multilevel models will also be specified to examine the interplay among PrEP adherence, ART adherence/viral suppression and condom use over time. MLM accounts for missing data (under assumptions of missing completely at random or missing at random) by full information maximum likelihood estimation.⁵⁴ Multilevel survival analysis will be used to model time to first event (eg, undetectable TFV-DP level), repeat events (eg, HIV testing) and termination of states (discontinuation of PrEP).^{55 56} SAS software (V.9.4; SAS Institute, Cary, North Carolina, USA) will be used to perform descriptive, GEE and APIM-MLM analyses; MPlus (V.8.4; Muthen & Muthen, Los Angeles, California, USA) will be used to perform survival analysis.

Power analysis

To determine appropriate sample sizes, power calculations were performed using NCSS-PASS software (V.21.0.2) with $\alpha=0.05$ and $\text{power}=0.80$ for two-sided hypotheses. Based on previous observations, adjustment for within-dyad correlation was set to $r=0.30$; and for longitudinal analysis, repeated measures correlation was set to $r=0.50$; we further assumed 15% attrition at terminal follow-up. For GEE analysis modelling PrEP uptake (binary outcome), a baseline sample of $n=290$ dyads (PrEP and non-PrEP arm observations) can detect an OR=1.35 or higher. For a three-level MLM of continuous outcomes (eg, PrEP medication adherence) and time to event (eg, time to PrEP discontinuation), a sample size of $n=460$ (230 dyads) can detect an effect size of $\text{Beta}=0.30$ ($R^2=0.09$).

Qualitative analysis

Transcribed audio-recorded interviews will be loaded into Dedoose (www.dedoose.com) software for analysis. Following Lewis *et al*,⁵⁷ a five-step framework analysis approach will be used to analyse and contextualise the qualitative data.⁵⁸ These steps include the following: (1) Familiarisation: transcripts will be read by the qualitative analysis team and descriptive summaries of each interview will be compiled, from which potential themes will be described; (2) Thematic framework: an initial set of deductive codes will be drawn from our conceptual framework and interview guides and combined with inductive categories drawn from emergent themes identified during familiarisation, producing a nascent code/subcode list; (3) Indexing: applying the code list, transcripts will be systematically coded with linked excerpts by multiple team members; redundant coding, comparison and iterative code modification with quality checks (eg, inter-rater reliability) will be used to produce a final consensus code list; (4) Charting: at the thematic level, a hierarchy of themes (and cross-linked codes) will be organised by primary outcomes, socioecological level,

and content; (5) Mapping and interpretation: charted themes will be summarised.

Mixed methods integration

For qualitative and quantitative data integration, we will follow the NIH 'Best Practices for Mixed Methods' guidelines established by Creswell and colleagues.⁵⁹ These guidelines provide a framework and taxonomy for the design, integrated analysis and interpretation of qualitative and quantitative data in mixed methods research. Within this framework, we will employ a parallel convergent design, in which qualitative and quantitative data are collected concurrently, with integration at the completion of data collection. Mixed methods data integration will involve connecting, embedding and merging. Qualitative data will be collected from a subsample of the quantitative cohort (connecting) and will be embedded within the larger quantitative study. Data merging will proceed through separate parallel analyses followed by matching on common themes using mixed data matrices structured by level and topic area to provide comparative depth and expansion of understanding.⁶⁰ Triangulation will employ a meta-inference framework, in which the coherence of data integration is interpreted as either confirmation, expansion or discordance. Confirmation occurs when both qualitative and quantitative analyses yield corroborating results; expansion is marked by the two sources of data illuminating different or complementary aspects of the phenomenon; and discordance occurs when qualitative and quantitative findings are inconsistent.⁶¹ Quantitative analysis will test hypotheses regarding the association of multilevel determinants on PrEP utilisation outcomes, with integrated qualitative data used to confirm, expand or contrast our understanding of how life history, contextual influences and participant perspectives shape these associations.

ETHICS AND DISSEMINATION

The protocol and procedures for the Magnetic Couples Study have been reviewed and approved by the institutional review board of the University of Rochester (RSRB00052766). The inadvertent loss of confidential and personal information is of primary concern for this study as it could pose potential risks to participants, such as legal consequences or social repercussions. To prevent this from occurring, study staff will maintain strict confidentiality and HIPAA requirements. ACASI methods in which participants directly enter responses to sensitive items into a computer programme help maintain confidentiality. In addition, all participant data are stored in deidentified form, with the exception of a locator form used to schedule follow-up visits, which is stored on a secure server with restricted access. A certificate of confidentiality was issued by the NIH to further protect sensitive information and subject confidentiality.

A second, related, ethical concern pertains to potential partner conflict or violence stemming from couples' joint

participation in the study. Methods developed by our team to successfully mitigate this concern include (1) being transparent regarding the content and format of the study protocols; (2) allowing each partner to self-select out of the study if they are concerned about their safety; (3) physically separating members of a couple for screening, enrolment and data collection, and instructing them not to discuss any aspects of the study with each other; and (4) providing research staff with training on partner notification programmes for newly HIV-diagnosed partners, and for dealing with and providing referrals for cases involving intimate partner violence.⁶²

Future dissemination of study findings will target four primary audiences: community members, providers, researchers and policy makers. Study findings will be shared with community members and providers through the dissemination of infographics through social media and a website as well as by holding forums and presentations in appropriate venues. Researchers and policy makers will be informed of study results primarily through scientific and policy conference presentations and journal articles. Emphasis will be placed on interpretation of findings towards implications for practice and actionable steps.

DISCUSSION

Although the efficacy of daily oral PrEP for HIV prevention in heterosexual serodifferent couples is well established, implementation research examining determinants of PrEP uptake, retention, adherence and clinical management among US mixed-status heterosexual couples is lacking.²⁰ Despite the many ongoing and completed PrEP demonstration and implementation projects,⁶³ to our knowledge, the Magnetic Couples Study is the only prospective cohort study to examine PrEP implementation among HIV-serodifferent heterosexual couples in the USA.

In this paper, we describe the study protocol of the Magnetic Couples Study, which was developed through a collaboration of researchers at the University of Rochester, the New York City Department of Health and Mental Hygiene, New York University, Columbia University, Massachusetts General Hospital/Harvard University, and the University of Colorado in partnership with over 40 HCFs, service agencies and community-based organisations in New York City.

Strengths of the study include (1) implementation of a mixed methods multilevel approach involving the collection of quantitative and qualitative data; (2) collection of data on the characteristics of HCFs where participants receive their ART or PrEP care, allowing for analysis of associations with HCF characteristics; (3) extraction of study participants' medical record data from clinical sites to assess medical history, ART and PrEP care, and healthcare utilisation; (4) assays of DBS samples collected from HIV-negative partners at each assessment visit to objectively measure PrEP adherence; (5) HIV-testing of both

partners at intake to confirm HIV-serodifferent status, and continued HIV testing of the negative partner to document seroconversions; (6) collection of data from both members of HIV-serodifferent couples, which allows for more accurate modelling of measurement error, dyadic function and mutual influence; (7) 18-month follow-up assessments on quantitative surveys and biological data and 36-month medical record review allowing for analysis of longer-term trends in ART and PrEP utilisation and their determinants; (8) a comparative sample of HIV-serodifferent couples not on PrEP including a subsample of those who subsequently initiate PrEP and enrol in the prospective cohort, thus allowing for modelling of PrEP uptake as well as retention in care and adherence; and (9) a sampling plan designed to reach participants through multiple forms of media as well as via agency and peer referrals, thus not limited to a few clinical sites.

A number of methodological limitations are also inherent in the study. There is a potential for sampling bias favouring couples who are capable of visiting our research office in mid-town Manhattan during regular working hours; although we attempt to accommodate some couples by scheduling assessments after hours or on weekends, the majority of assessments are conducted during regular work hours. The study is also limited to couples residing in the New York City area and findings may not generalise to less urbanised areas or other regions of the USA. However, New York City contains the highest prevalence of persons living with HIV nationally, including heterosexuals in serodifferent relationships. Our study was open to transgender men and women, as long as they reported being in an opposite-gender serodifferent relationship, but the small subsample of transgender persons enrolled in the study might lack adequate power to perform subgroup analysis. In addition, study results may not fully generalise to same-sex couples as PrEP provision among such couples may be affected by a unique set of determinants and relationship dynamics.^{20 64–66} Much of the quantitative data is based on self-report, which can be subject to various forms of bias, including social desirability and recall bias.⁶⁷ We attempted to mitigate these sources of bias by employing ACASI methods for sensitive items in the survey, minimising the recall period, collecting identical data from both members of the couple to better model measurement error, and collecting key variables using biological assays and medical chart review.

Knowledge generated from the Magnetic Couples Study will help inform the development of couple-based models of care for dual HIV treatment and prevention involving HIV-serodifferent heterosexual couples. Such couple-based interventions, while not uncommon in African countries, remain relatively untapped in the USA.⁶⁸ Successful provision of PrEP in this group requires an understanding of factors operating concurrently at multiple levels (individual, couple, HCF) that facilitate or impede optimal implementation. The Magnetic Couples Study will identify multilevel time-variant and

time-invariant determinants of PrEP implementation outcomes among a cohort of HIV-serodifferent heterosexual couples over an 18-month assessment period. Findings will inform optimal methods for healthcare providers across different settings to provide effective models of PrEP and ART care delivery for HIV-serodifferent USA couples, including issues related to ethics and confidentiality surrounding couple-based care.

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