CCTG 595

A Multicenter, Randomized Study of *T*ext messaging to improve *A*dherence to *P*rEP *In R*isky MSM (TAPIR)

A Multicenter Trial of the California Collaborative Treatment Group (CCTG)

Sponsored by:

The California HIV/AIDS Research Program (CHRP)

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALERT	Active Linkage, Engagement, and Retention to Treatment
ARV	Antiretroviral Therapy
CCTG	California Collaborative Treatment Group
CD4	CD4 Lymphocytes
CRF	Case Report Form
CT	Chlamydia
DSMB	Data Safety and Monitoring Board
GC	Gonorrhea
HAART	Highly Active Antiretroviral Therapy
HIV-1	Human Immunodeficiency Virus – 1
iTAB	Individualized Texting for Adherence Building
mITT	Modified Intention to Treat
MSM	Men who have Sex with Men
NAAT	Nucleic Acid Amplification Test
PLWH	Persons Living With HIV/AIDS
PrEP	Pre-Exposure Prophylaxis
RPR	Rapid Plasmin Reagin
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SoC	Standard of Care
STI	Sexually Transmitted Infection
TPPA	Treponema Pallidum Particle Agglutination Assay
VAS	Visual Analog Scale
VDRL	Venereal Disease Research Laboratory

SCHEMA

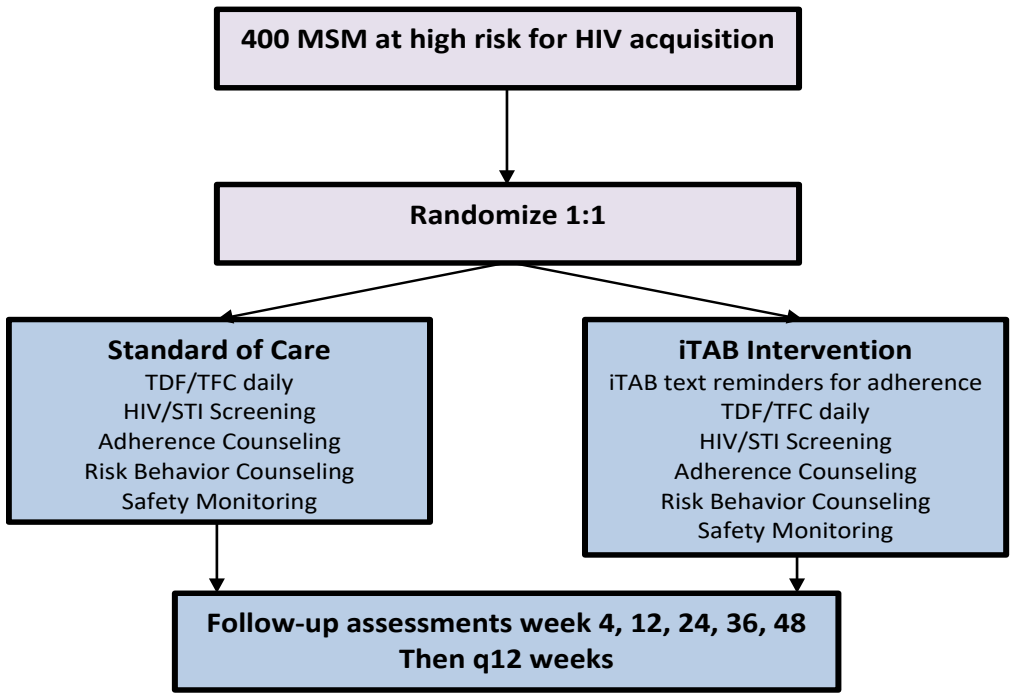
Design: CCTG 595 is a controlled, open-label, two-arm, randomized (1:1) clinical demonstration project to determine if the use of a text-message based adherence intervention (iTAB) improves retention and adherence to PrEP compared to standard of care (SoC) PrEP delivery.

Duration: Each subject will be followed for up to 48 weeks after enrollment of the last subject to a maximum of 96 weeks. The primary endpoint will be measured at 48 weeks.

Sample Size: A total of 400 subjects will be randomized, 200 per arm.

Study Population: Eligible subjects will include HIV-uninfected men who have sex with men (MSM) and male to female (M to F) transgender individuals who have sex with men at least 18 years of age and who have a recent history of high-risk transmission behavior.

CCTG 595 Study Schema



Stratification: The randomization will be stratified based on clinic site.

Intervention:	All subjects will start PrEP with TDF + FTC fixed dose combination given once daily. Subjects will be randomized (1:1) to either the iTAB text messaging adherence reminder intervention with SoC or the SoC alone arm. Subjects placed into the iTAB intervention arm will receive a personalized, automated texting system to maintain adherence and retention. Both groups will receive access to PrEP in accordance with standardized comprehensive methods of prescribing, risk reduction counseling, adherence counseling, and clinical assessments that include safety monitoring, as well as HIV and STD screening.
Regimen:	TDF 300 mg + FTC 200 mg fixed dose combination will be given orally once daily starting at the baseline visit (month 0) and continued throughout the study.
Outcomes:	The CCTG 595 primary outcome is defined as a composite endpoint of remaining on PrEP and having adherence > 90% over 48 weeks of follow-up. The adherence endpoint will be derived from the 4 day ACTG adherence assessment from each of the visits from week 4, 12, 24, 36, and 48. 'Adherent' will be defined as self-reported TDF/ FTC adherence of 90% or greater (at least 18 of 20 days). If a subject misses an adherence assessment within the window of a scheduled visit or discontinues study prior to week 48, then the missed visits will be counted no adherence for the time of that visit. All randomized subjects that were dispensed PrEP at baseline will be included in the modified intent-to-treat analysis.

1.0 STUDY OBJECTIVES AND HYPOTHESES

1.1 Study Primary Objective:

CCTG 595 will compare adherence to fixed dose TDF/FTC, between subjects randomized to receive SoC plus text message reminders versus SoC, when used for pre-exposure prophylaxis among MSM at high risk for HIV acquisition.

1.1.1 Hypothesis I
MSM and transgender M to F having sex with men with high risk of HIV acquisition randomized to the iTAB intervention will have higher self-reported adherence to TDF/FTC for PrEP over 48 weeks ('adherent' defined with a composite endpoint of continued retention on PrEP and ≥ 90% adherence to TDF/FTC at 48 weeks) compared to MSM that have comprehensive SoC alone.

1.1.2 Hypothesis II
MSM and transgender M to F having sex with men with high risk of HIV acquisition randomized to the iTAB intervention will have higher adherence to TDF/FTC for PrEP over 48 weeks, as measured by having five of five detectable qualitative FTC plasma concentrations at scheduled visits compared to MSM that have comprehensive standard of care alone.

1.2 Study Secondary Objectives:

1.2.1 To compare adherence to TDF/FTC in the iTAB versus SoC in the subjects that remain on PrEP (at 48 weeks and up to 96 weeks of follow up) by the continuous measure of percent days adherent by the cumulative 4 day ACTG and the visual analog scale (VAS) recall in an 'as treated' analysis.

1.2.2 To compare adherence to TDF/FTC in the iTab versus SoC groups for the duration of the study (up to 96 weeks). Adherence will be compared using the same outcomes as hypothesis I (self-reported to be on drug and 90% adherent) and II (100% detectable FTC at each scheduled visit) as modified intent to treat analysis.

1.2.3 To determine factors associated with poor adherence/lost to PrEP in study participants (outcomes of < 90% adherent on drug at 48 weeks by ACTG 4 day recall or discontinuation of drug). Factors associated with poor adherence to TDF/FTC will include demographics, ongoing

substance use, untreated mental illness, socioeconomic status, low health/HIV and system literacy, fear of disclosure and non-English language.

1.2.4 To determine the factors associated with discontinuation of TDF/FTC at any time point including change in perceived and actual risk of HIV acquisition, demographics, ongoing substance use, untreated mental illness, socioeconomic status, low health/HIV and system literacy, fear of disclosure and non-English language.

1.2.5 To determine the rate of HIV seroconversion in PrEP users and compare the iTAB to SOC arms for number of new infections as a proportion at 48 weeks and end of study.

1.2.6 To measure acquisition of other sexually transmitted infections (STIs); the proportion of subjects with any new STI at any site will be compared between the iTAB to SOC arms at 48 weeks and through the end of the study.

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1.2.7 To evaluate changes in risk behavior after initiation of PrEP (risk compensation) comparing baseline to subsequent visits for number of HIV positive/unknown status partners and any unprotected anal intercourse with an HIV positive/ unknown status partner.

1.2.8 To evaluate the safety and tolerability of daily TDF/FTC given for PrEP including discontinuation for any adverse event, serious adverse events and adverse events (grade 2 or higher).

1.3 Exploratory Objectives:

1.3.1 To describe changes over time of self-reported adherence in real time by texting.

2.0 INTRODUCTION

2.1 Study Background

Widespread deployment of PrEP will require operational research to study how best to integrate services into clinical care settings and to target them to various at-risk populations [1-3]. Randomized controlled trials of PrEP have shown a statistically significant reduction in acquisition of HIV among at-risk individuals in a research setting but provide little insight into how it could be practically applied. Implementing PrEP strategies will necessitate: 1) creation of an organizational framework to deliver services; 2) delineation of patient populations where PrEP should be targeted and would be most effective; 3) identification and removal of structural barriers to PrEP delivery (such as co-ordination of services between organizations, and establishing infrastructure to deliver services) and 4) establishing related services such as patient education, drug adherence counseling and reminder systems for medication adherence.

Sustainable programs for PrEP delivery may utilize either new clinical care systems or existing care providers such as treatment clinics, community care clinics, public health facilities or HIV testing sites. Adding PrEP to clinical HIV care may be the most efficient method considering the requirements for PrEP: 1) prescription of antiretroviral agents; 2) monitoring for adverse events and HIV acquisition; 3) interventions for risk reduction and drug adherence and 4) provision of comprehensive care for sexually transmitted infections, mental health and substance use [4].

This study will evaluate the integration of PrEP into clinical practice by identifying at-risk individuals at HIV testing sites, linking them to treatment clinics, and initiating and maintaining PrEP. This model for PrEP utilizes providers that are experienced with ARV drugs, adherence counseling, and care of high-risk patients. The CCTG clinical sites have successfully integrated other prevention interventions into their care delivery for previous studies and serve populations for which PrEP will be most needed [5].

HIV care clinics in California are familiar with the target population for PREP because the patient population is largely MSM who continue HIV transmission-associated behaviors. Epidemiological studies have found that MSM at the highest risk for acquiring HIV are those who have HIV positive partners, a sexually transmitted disease, multiple sexual partners, use methamphetamine, and attend specific venues such as bath houses and internet “hook-up” sites [6-8]. In the iPREX study, HIV acquisition among a diverse population of high-risk MSM was reduced by 44%, leading to current CDC guidance on PrEP which targets MSM who have “sustained” risk of HIV acquisition, normal renal function and negative HIV by EIA and no symptoms of acute HIV infection [9, 10].

Implementing PrEP for MSM will require education of the high risk groups since initial studies found only 47% had some knowledge of PrEP and only 4% were using PrEP [11]. Uptake

of PrEP is anticipated to be good in some high risk groups. Partners of HIV-infected individuals may be most motivated. In one study 80% of discordant heterosexual couples accepted PrEP during reproductive planning [12]. A similar study found that 74% of MSM, who received PrEP education, would consider taking it if available [13]. Therefore, increasing the community awareness and education of PrEP should increase interest, especially if barriers to referral for PrEP are minimized, and counseling and education are provided.

Once linked and engaged in PrEP, candidates will require a systematic approach to maintain follow-up and adherence to medication. The literature generally shows that adherence levels of 95–100% are needed to ensure optimal treatment effectiveness for the treatment of HIV [14]. Similarly, PrEP efficacy in iPREX was shown to be diminished with reductions in adherence [9]. In a nested case-control study, TDF and FTC drug levels were detectable in only 9% of individuals that seroconverted to HIV compared to 51% of the controls that did not acquire HIV [9]. Adherence is commonly defined as ≥ 90% of prescribed doses taken, but no single definition has achieved consensus across the literature and various definitions have be associated with worsened HIV disease outcome[15]. In iPREX, 90% adherence by self-report at 49% of visits was found to increase efficacy from 44% to 75% in HIV acquisition reduction. Barriers to adherence have been widely studied in HIV-infected individuals and summarized by Mills et al. [16]. From studies in developed countries the factors associated with adherence can be summarized as: 1) individual psycho-social factors (sense of stigma, feeling hopeless, having addiction diagnosis, mistrust of medical system and medications, problems with memory, poor understanding, low self-worth, finances, homelessness); 2) beliefs on medication (real or perceived adverse events, complicated regimens, uncertainly of effect); 3) daily schedules (irregular routines, coordinating adherence with social supports); and 4) issues of social cohesion (lack of trust in providers, social isolation, negative publicity in community, negative feedback from social network) [16]. Facilitators of adherence relevant to PrEP include 1) increasing self-worth and prioritizing health over addiction; 2) having 'faith' in the treatment and understanding adherence importance; 3) having daily routines and using reminder systems and 4) trusting providers, disclosing to social supports and feeling supported by social network. Maximizing adherence for PrEP will therefore require developing good relationships and providing ongoing heath education, counseling and reinforcement on HIV and PrEP. A promising method of reinforcing ART adherence is text messaging. In one study in a group of poorly adherent HIV-infected individuals, an increase in adherence from 42% to over 70% was observed in those receiving texting [17]. In this proposal, a comprehensive approach to routine clinical care will be expanded to provide the necessary elements for safely implementing PrEP. HIV prevention and PrEP education will figure prominently in the interactions with community and participants including reinforcement of the adherence message coupled with risk reduction counseling at each clinic visit. In the randomized component of the study, the ALERT worker will use text reminders as a strategy for enhancing PrEP adherence.

2.2 Study Rationale

TDF/FTC has been approved by the FDA as an agent for PrEP. As noted previously, there is no research on how PrEP will be delivered in the community setting. CCTG 595, will implement PrEP at three sites (UCSD, UCLA/Long Beach Health Department, USC) to explore the operationalization of PrEP by the community providers of HIV testing and HIV care. Critical to the implementation of PrEP will be to maintain adherence to drug. CCTG 595 will perform a randomized controlled study of the iTAB texting intervention for TDF/FTC adherence for PrEP. This intervention is meant to be a simple automated method to reinforce adherence.

3.0 STUDY DESIGN

3.1 Study Design

CCTG 595 is a comparative, interventional study that uses text messaging to improve adherence of PrEP in MSM and transgender that are at high risk of acquiring HIV. We will conduct an open-label, randomized, controlled clinical trial to evaluate an intervention strategy that uses a developed texting adherence method, the iTAB system, to improve adherence and retention compared to standard of care which will not have iTAB (see study schema). The RCT will occur in the context of implementation of PrEP at three large, diverse, urban HIV care clinics in the CCTG network at UCLA-Harbor, USC and UCSD and a fourth site at the Long Beach Public Health Department. These sites are collaborating with local testing sites to provide an integrated program that identifies individuals at highest risk for HIV acquisition and link them into preventive care that will provide the assessment, dispensing and monitoring of PrEP. A uniform system of HIV testing, risk assessment, health education and behavioral/adherence counseling will be developed for use at consortium sites.

Study enrollment criteria is based on the CDC guidance for PrEP use among MSM and transgender with ongoing risk for HIV infection. All subjects will be confirmed to be uninfected with no contraindication to TDF/FTC. Subjects will be randomized at baseline to iTAB versus SoC. Randomization will be stratified by CCTG site. Study visits will include screening, baseline, week 4 and 12 initial visits and then visits every 12 weeks. Visits for iTAB and SoC arms will both include routine HIV testing and counseling, STI testing, adherence counseling, and medical monitoring. Each visit will include a computer-assisted survey for self-reported adherence assessment and risk behaviors. Drug level monitoring will be performed for FTC qualitative levels in retrospect on banked samples and additional banked specimens will be available for future use and TDF measurement. Adherence by self-reported measures and FTC levels will be used for the main and secondary analyses of the study. Additional outcomes for the study will include changes in risk behavior and determinants of PrEP adherence. Outcomes will be assessed at 48 weeks and for the cumulative follow up of all participants. The study will continue for 48 weeks after randomization of the last participant (up to 96 weeks for any subject).

In order to have adequate representation of African Americans in the study population,

enrollment of non-African Americans will be capped at 85% of 400 subjects (340) to achieve at least 15% African Americans. If 340 non-African American subjects are enrolled, then enrollment for this subgroup will stop and the study will remain open only for African Americans.

3.2 iTAB Adherence Intervention

This proposal will perform a study of potential methods to improve adherence and retention by evaluating standard procedures versus the use of the iTAB platform. All subjects will receive SoC that will include health education, clinical assessments, laboratory safety monitoring, STI and HIV screening, HIV risk reduction counseling, assessment of psycho-social barriers, adherence counseling, and completion of a computer based survey.

Subjects will be randomized to 1) SoC clinic visits as outlined in section 6.0 and 2) SoC visits plus support using text messaging through the iTAB system. Subjects assigned to the iTAB intervention will have visits with the study coordinator to introduce the iTAB texting system, discuss contact information to assist in recovering the subject if they miss appointments and provide training on iTAB framework for texting supportive reminder messages and tracking adherence. The study will provide subject reimbursement to pay for unlimited text message use and in cases where a subject does not have a phone, the appropriate cell phone will be provided.

Daily dosing reminders will be sent for the first 6 weeks and then continue with reminders for the duration of the study. Both reminder timing and message content can be individualized. The study coordinator will work with the participant to select and refine 10 personal reminders from a list of pre-determined reminders that cover various themes shown to be effective in improving adherence (e.g., social support, loss frame, health gain, etc.) as developed through focus groups and targeted group feedback. These messages can be modified and the patient can choose to create their own reminders if they prefer. The coordinator will work with each participant individually to assure that adherence reminders are sent at times consistent with when the patient typically takes his medication. These reminder times can vary for different days of the week to accommodate for changes in schedule (e.g., 8 M-F, and 10 AM on Sat/Sun). Once the time is identified, the text reminder system is automated. Patients will confirm medication taking via text responses to the personalized reminders. If a participant does not respond on three consecutive occasions, a high alert message (chosen by the participant) will be sent. If the subject does not respond to this message, the study coordinator would initiate phone calls to contact the subject and explore barriers. The coordinator will continue to call the participant every 4 days until the participant re-engages with the iTAB system.

3.3 FTC Qualitative Plasma Concentration as an Adherence Marker

Adherence to prescribed treatment can be difficult to assess. One objective way to measure recent adherence is to measure plasma drug concentrations. FTC concentrations in plasma remain detectable throughout the dosing interval. Specifically, trough concentrations of FTC are approximately 60 – 70 ng/mL, and range from 10 – 300 ng/mL between subjects [23, 24]. Peak concentrations are approximately 1300 – 1800 ng/mL, and range from 600 to 2500 ng/mL. While many factors contribute to variability in plasma concentrations, such as drug-drug interactions and genetic differences in absorption and excretion, completely undetectable plasma concentrations of FTC are physiologically implausible for patients who are adherent with their regimen. Even with the sources of variability noted above, undetectable concentrations (< 1 ng/mL) would be 60 to over 1000 times less than the expected concentration depending on the time post-dose, and can be justifiably assumed to represent missed doses rather than pharmacokinetic variability. We plan for 400 subjects and in total will have 3467 levels (an average of 8.6 per person). Samples will be stored at each study visit (weeks 4, 12 and every 12 weeks thereafter).

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Main Study Inclusion Criteria

4.1.1 Man or transgender M to F who has sex with men.

4.1.2 Age 18 years or older.

4.1.3 Subjects must have substantial ongoing risk of acquisition of HIV as evident by one or more of the following:

- Has at least one HIV infected sexual partner for ≥4 weeks.
- No condom use during anal intercourse with ≥3 male sex partners who are HIV-positive or of unknown HIV status during the last 3 months
- No condom use during anal sex with ≥1 male partner and STI diagnosis during the last 3 months

4.1.4 Negative for HIV infection by rapid HIV test and confirmed negative by NAT or other sensitive method such as antibody- antigen test.

4.1.5 Acceptable laboratory values in the past 30 days:

- Calculated creatinine clearance of at least 60 mL/min by the Cockcroft-Gault formula (eCcr (male) in mL/min = [(140 – age in years) x (lean body weight in kg)] / (72 x serum creatinine in mg/dL)
- Alanine aminotransferase (ALT) and/ or aspartate aminotransferase (AST) < 3 x upper limit of normal (ULN)

- Hemoglobin > 9 g/dL
- Absolute neutrophil count > 750/ mm^3
- Platelets > 75,000/ mm^3

4.2 Main Study Exclusion Criteria

4.2.1 Unable to give informed consent.

4.2.2 Active hepatitis B (positive hepatitis B surface antigen (HBSAg) or HBSAg negative/ HB core antibody positive/ HBV PCR positive)

4.2.3 Has substantial medical condition, that in the opinion of the investigator would preclude participation, as defined by

- cardiovascular condition that may lead to an increased risk of complication if placed on study drugs.
- gastrointestinal condition that would impair absorption of study drugs.
- neurological or psychiatric condition that would significantly impair the ability to adhere to PrEP.
- calculated GFR < 60 mL/min
- alcohol or drug abuse or dependence that would significantly impair the ability to adhere to PrEP (only for those with severe impairment).
- Other medical condition that would unacceptably increase the risk of harm from study drug or significantly impair the ability to adhere to PrEP.

4.2.4 Suspected sensitivity or allergy to the study drug or any of its components.

4.2.5 Currently using an essential product or medication that interacts with the study drug such as the following:

- ART (including nucleoside analogs, non-nucleoside reverse transcriptase inhibitors, protease inhibitors or investigational antiretroviral agents)
- Agents with known nephrotoxic potential:
  - aminoglycoside antibiotics (including gentamicin)
  - IV amphotericin B
  - cidofovir
  - cisplatin
  - foscarnet
  - IV pentamidine
  - IV vancomycin

- oral or IV gancyclovir
- other agents with significant nephrotoxic potential

- Drugs that slow renal excretion
  - Probenecid
- Immune system modulators
  - Systemic chemotherapeutic agents (i.e. cancer treatment medications)
  - Ongoing systemic corticosteroids (with the exception of short courses of tapering steroid doses for asthma or other self-limited condition).
  - Interleukin-2 (IL-2)
  - Interferon (alpha, beta, or gamma)
- Other agent known to have a significant interaction with TDF or FTC

4.2.6 Proteinuria 2+ or greater by urine dipstick

4.2.7 Signs or symptoms suggestive of acute HIV infection

4.2.8 Any other reason or condition that in the opinion of the investigator would interfere with participation, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.3 Enrollment Procedures

4.3.1 Prior to implementation of this protocol, sites must have the protocol and consent form approved by their local institution review board (IRB). Sites must be registered with and approved by the CCTG Data Center. Site registration must occur before any subjects can be enrolled in this study.

4.3.2 Once a candidate for study entry has been identified, details will be carefully discussed with the subject. The subject will be asked to read and sign the consent form that was approved by both the local IRB and the CCTG Data Center.

4.3.3 A patient identification number (PID) will be assigned to each patient screened for the study. PIDs will include site code and be formatted to be compatible with the BIT data core. PIDs will not be reassigned even if the subject fails to enter the study. The PID must be included on every CRF and subject specimen during the study. Each site must maintain a master list of PIDs in a central location. The patient registration and inclusion/exclusion CRF must be completed on the online system.

5.0 STUDY TREATMENT

5.1 Regimens, Administration, and Duration

5.1.1 Regimens

Subjects will be randomized 1:1 to one of the two treatment arms:

ARM A: FTC/TDF 200/300 mg fixed dose combination once daily + iTAB
ARM B: FTC/TDF 200/300 mg fixed dose combination once daily

- Use of the FTC/TDF fixed dose combination is not allowed if the CrCl is <50 mL/min, which should be confirmed within 7 days. TDF/ FTC should be discontinued if confirmed.

5.1.2 Administering and Dispensing

Emtricitabine/tenofovir disoproxil fumarate fixed-dose combination containing 200 mg of emtricitabine and 300 mg tenofovir disoproxil fumarate will be administered orally as one tablet once daily with or without food.

Enough study product should be dispensed to last until the subject's next scheduled visit.

5.1.3 Duration

Subjects will participate in this study until 48 weeks beyond the enrollment of the last subject with a maximum duration of 96 weeks for any subject. Subjects may receive study treatment until their last study visit.

Subjects will receive study treatment for the duration of the study unless they meet criteria for discontinuation.

5.2 Study Product Formulation

Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF, Truvada®): 200 mg/300 mg coformulated tablet. Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Supply/Distribution

Emtricitabine/tenofovir disoproxil fumarate will be supplied by Gilead Sciences through the UCSD/AVRC Research Pharmacy and distributed to all sites.

The site pharmacist can obtain study product for this protocol by following the instructions in the CCTG-595 Pharmacy Manual.

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study product received from the UCSD /AVRC Research Pharmacy. All unused study product must be returned to the sponsor (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the CCTG-595 Pharmacy Manual.

5.4 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, site investigators must review the concomitant medications and study agent's most recent package inserts, Investigator's Brochures to obtain the most current information on drug interactions, contraindications, and precautions.

5.4.1 Prohibited Medications (Refer to Section 4.2 for addition information on prohibited medications).

5.4.1.1 All investigational drugs

5.4.1.2 All HIV vaccines

5.4.1.3 Any immunomodulators

5.4.1.4 Systemic cytotoxic chemotherapy

5.4.1.5 All other antiretroviral medications (excluding FTC/TDF given as PEP or PrEP)

5.4.1.6 Drugs with known nephrotoxicity

Subjects must have discontinued prohibited medications at least 30 days prior to entry.

5.5 Adherence Assessment

Throughout the study, the documentation of adherence to study drug is essential. The adherence questionnaire will be completed during each study visit. This will include the ACTG 4-day adherence questionnaire as well as the VAS over the previous 4 week period, except for the week 4 visit where adherence will be assessed since starting medication.

6.0 CLINICAL AND LABORATORY EVALUATION

6.1 Schedule of Evaluation

Schedule of Evaluations	**Screen**	**Study Weeks of Follow-up**									
	Within 30 days	0	4	12	24 or 72	36 or 60 or 84	48 or 96	End of Study or premature D/C	Post-study, 3-month	Suspected HIV/STI infection[4]	Interim for Missed Visit[5]
Visit Window			± 14 days								
Informed Consent	X										
Medical/Medication History	X										
Documentation of HIV status by rapid HIV test plus NAT or Ag/Ab combo assay	X										
Randomization		X									
Pre/Post Assessments[1]		X						X			
iPAD self–administered survey[2]		X	X	X	X	X	X	X		X	X
Risk reduction Counseling		X	X	X	X	X	X	X		X	X
Review PrEP adherence (ACTG 4 day and VAS)			X	X	X	X	X	X		X	X
Clinical Hx of STI and PREP use		X	X	X	X	X	X	X		X	X
Assessment of adverse events		X	X	X	X	X	X	X		X	X
Targeted exam (as clinically indicated)	X	X	X	X	X	X	X	X		X	X
Concomitant medications		X	X	X	X	X	X	X		X	X
Dispense TDF/FTC (if HIV rapid test negative)		X	X	X	X	X	X				X
Calcium and vitamin D intake						X[6]					
Phone call follow-up									X		

Schedule of Evaluations	Screen	Study Weeks of Follow-up									
	Within 30 days	0	4	12	24 or 72	36 or 60 or 84	48 or 96	End of Study or premature D/C	Post-study, 3-month	Suspected HIV/STI infection[4]	Interim for Missed Visit[5]
Laboratory											
CBC/Chemistry	X										
Calculated GFR (serum Cr)	X		X	X	X	X	X	X			X
Urine Dipstick	X		X	X	X	X	X	X			X
Rapid HIV Test		X	X	X	X	X	X	X		X	X
STI testing- throat, rectum, urine; blood RPR		X			X		X	X		X	X
Rectal swab (x2)		X			X[7]		X[7]				
HBsAg,/HBsAB/HBcAB	X										
If HBsAg-/HBsAB-/HBcAb+, Hepatitis B DNA PCR	X										
HIV RNA, CD4, HIV genotype, banked PBMC		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]		X[3]	X[3]
Plasma banked specimen		X	X	X	X	X	X	X		X[3]	X
Banked clotted blood		X									
Dried blood spot				X	X	X	X	X		X[3]	X
Urine for storage		X	X	X	X	X	X	X		X	X

[1] Pre: attitudes toward safe sex, disclosure, access to care, social support, texting ability, Kalichman sexual compulsivity; Post: satisfaction with iTAB; Pre/Post: HIV literacy, stigma and disclosure, AUDIT, DAST-10
[2]includes: risk behavior, adherence assessments, intention to adhere, PHQ9, SCID substance use screen
[3] Perform if HIV+
[4] Any time history or symptoms suggest potential HIV or STI, check with study MD for appropriate test
[5] Subjects may have an interim visit if past window of scheduled visit, next visit should be back to regular schedule
[6] To be performed at week 36 only
[7] Performed only once on or after Week 48 coinciding with STI screening (Week 48, 72, or 96)

6.2 Definitions for Schedule of Events and Timing of Evaluations

6.2.1 Screening Assessments

Occur prior to the subject taking any study medications, treatments, or interventions

Patient Registration: A patient identification number (PID) will be assigned to each patient screened for the study. PIDs should not be reassigned even if the patient fails to enter the study. The PID must be included on every CRF and patient blood sample. Each site must maintain a master list of PIDs in a central location. The patient registration and inclusion/exclusion CRF must be completed on the online system.

All subjects interested in screening for the PrEP project will sign an informed consent document that had been approved by local IRB at the site. Screening procedures (see schedule of evaluations) will include: determination of inclusion and exclusion criteria; confirmation of HIV status and screen for acute HIV symptoms. HIV serology will be performed as part of screening, including rapid HIV test and NAT or equivalent (antigen antibody test). Laboratory screening will include CBC, chemistry values, GFR (Cockroft-Galt) LFT and HBsAg. If a subject qualifies and signs consent the window to complete the baseline assessment and start PrEP will be two weeks.

6.2.2 Entry Evaluations (day 0)

Randomization: subjects that meet all the inclusion and exclusion criteria will be randomized at their day 0 entry visit. Subjects will be randomized to receive standard of care or the iTAB adherence intervention, stratified by site. Subjects randomized to the iTAB intervention will set up the customized text message stems and enter the timing of the text message reminders; the information will be entered in the online iTAB system by the study coordinator.

At baseline all subjects will receive HIV transmission risk reduction counseling by a health educator and detailed information about the use of PrEP, including the risks, potential adverse events and the critical importance of drug adherence.

6.2.3 On-Study Evaluations

After counseling, laboratory testing and randomization, participants will receive sufficient TDF/FTC study medication to last until the next scheduled visit (either 4 or 12 weeks) through the investigational pharmacy. Medication renewals will not be available if a subject misses a scheduled appointment. An informational pamphlet on TDF/FTC will be provided that will summarize the label package insert information for patients (in English or Spanish) with changes made to tailor the information for someone that is not HIV infected. Participants will be directed to take one pill once a day at a convenient routine time. If there are missed doses, participants will be told to take the next scheduled dose on time and not to take any additional pills to catch up. Bottles with any remaining missed doses will be returned to the pharmacy at the time of medication renewal and the number of untaken doses will be recorded. At each clinic visit, TDF/FTC medication adherence will be

reviewed by the clinician, adverse events will be queried and adherence and barriers to adherence will be discussed. All subjects will receive episodic adherence counseling within the confines of routine clinic visit. Each clinic visit will also include blood draw for calculated GFR (serum creatinine) and plasma FTC drug levels, and HIV testing. STI testing including NAT screening for GC and chlamydia from throat and rectal swabs and from urine and RPR from blood will be done at week 0 and every 24 weeks thereafter.

Adherence and Behavioral Assessments

We will measure adherence using the ACTG medication adherence questionnaire [25]. At each follow-up visit, the ACTG four-day questionnaire will be administered using the web-based data capture system. The instrument tracks the number of doses skipped over the past four days and reasons why medications may have been skipped. In addition, we will ask their ability to adhere by Likert scale and use the Visual Analog Scale (VAS), which appears as an ordinal scale representing the percent of medication taken relative to that which has been prescribed over the past 4 weeks. Subjects are presented with a line anchored at 0% and 100% and are asked to mark a line on the scale indicating their own PrEP adherence [26].

In the standard study visit, the coordinator will perform HIV testing and blood work, review test results, provide TDF/FTC prescriptions, discuss medication use, adherence, risk reduction and troubleshoot any barriers. The standard behavioral survey will include assessment of TDF/FTC adherence, HIV transmission risk behaviors, substance use, depression scores and other risk behavior details (e.g. sexual partnerships, sexual acts, condom use).

Laboratory Safety Assessments

At follow-up clinic visits, all participants will have a blood drawn for creatinine clearance estimates. A rapid test for HIV will be performed. HIV test results will be provided during the clinic visit. If there are grade 3-4 adverse events (thought to be related to study medication- see toxicity section) or HIV seroconversion is detected, the participant will be called to discontinue TDF/FTC and to come to the clinic as soon as feasible. Any positive rapid test will be confirmed by Western Blot and HIV RNA; CD4 cell count and an HIV genotype for drug resistance will be done. Newly diagnosed HIV subjects will be counseled and be linked to HIV clinical care within the existing clinic or to another provider

designated by the participant. All PrEP-related clinic visits, laboratory testing and TDF/FTC medication will be provided by the study without charge to the subject.

FTC Qualitative Plasma Concentration as an Adherence Marker:

Plasma will be drawn at every visit starting at week 4 for FTC concentrations. Samples will not be run in real time and will not be available for clinical use.

Chlamydia, gonorrhea and syphilis testing

Subjects will have day 0 and every 24-week assessment to include urine and swabs from the rectum and throat for NAT testing for Chlamydia and gonorrhea. Blood will be drawn for RPR. In between visits, subjects will be told to come to the study nurse if they experience symptoms of an STI. They will also be asked if they were tested elsewhere between visits. All new STI cases will be referred to their provider or the Department of Health for treatment. They will be given a card to have filled out documenting treatment given, which they will be asked to bring back to their next study visit. All new STI cases will also be counseled on the need for partner therapy and will suggest that they receive assessment and treatment or partner delivered therapy. STI testing can also occur as an interim visit for high-risk exposure or symptoms suggestive of new STI.

Sexual Risk Counseling

Standard of care HIV risk reduction counseling will be providing to all participants consistent with pre- and post-test counseling for persons receiving community HIV testing. The study will provide streamlined in-person risk reduction counseling at each visit that will use the RESPECT paradigm of focusing on a single risk behavior as identified by the subject. The goal of brief and targeted counseling is to help the individual to identify his most significant risky behavior and to implement concrete actions to decrease the specific risk behavior until the next study visit. Participants will undergo this process at each visit.

6.3 Special Instructions and Definitions of Evaluations

6.3.1 Documentation of HIV infected status at screening

The lack of HIV-1 infection will be documented by any licensed screening antibody (rapid test plus NAT or Ab/Ag) test. A positive HIV test will be confirmed by a second EIA , Western Blot, or HIV RNA viral load.

6.3.2 Medical and Laboratory History

At screening, a medical history will be obtained and will be recorded in the source documents. The medical history should include any previous illnesses that might be consistent with acute HIV infection, history of STI and other routine medical conditions.

6.3.3 Medication History

At screening, a medication history (only of those taken within the last 30 days prior to entry) with actual or estimated start and stop dates will be obtained and recorded in the source documents and the concomitant medication CRF, including:

- All prescription medications.
- Non-prescription medications.
- Alternative therapies and/or dietary supplements.
- Allergies to any medications and their formulations must be documented.

6.3.4 Concomitant Medications

During study visits all antibiotics and other concomitant medications taken since the last visit will be recorded in the source documentation and entered into the concomitant medication log CRF.

6.3.5 Study Drug Modifications

No modifications of PrEP regimen will be allowed on this study. TDF/FTC may be temporarily held for adverse events as per section 7. TDF/FTC should be discontinued if any criteria for stopping are met (see discontinuation section). Discontinuation will be documented on the TDF/FTC discontinuation CRF.

6.3.6 Clinical Assessments

Targeted Physical Exam

A targeted physical examination will be based on any signs or symptoms previously identified that the subject has experienced within 30 days of entry or since the last visit. This examination will be performed at all visits when indicated. Documentation must include any symptoms consistent

with acute HIV infection.

Height and Weight

Height and weight will be measured at study entry.

Signs and Symptoms

All signs, symptoms, toxicities and deaths will be documented in the subject's record. At entry, all signs/symptoms experienced within 30 days of entry will be recorded on the CRFs. For all other visits including a suspected HIV infection visit, all Grade > 1 signs and symptoms will be recorded on the CRFs that have occurred since the last visit. Any signs or symptoms that lead to a change in treatment, regardless of Grade, will be recorded on the CRF. The source document will include date of onset and date of resolution, but the CRF will only record prevalence of a given adverse event since the previous study visit.

Refer to the ACTG Table for Grading Adult Adverse Experiences.

Diagnoses

The following should be recorded on the CRFs: HIV and STI diagnoses, malignancies, new medical conditions and death. The source document must include date of diagnosis and date of resolution.

6.3.7 Clinical Assessments for Detected STI

At all visits ask if the participants if they have had an STI in the interim, current symptoms.

6.3.8 Laboratory Evaluations

Record all designated laboratory values on the CRFs throughout the course of the study. All baseline values, regardless of toxicity, for specific laboratories will also be recorded on the laboratory CRF including: WBC, neutrophil count, hemoglobin, platelets, creatinine with estimated GFR (Cockcroft-Galt formula), glucose, AST/ALT, alkaline phosphotase and total bilirubin. All values of creatinine with estimated GFR (Cockcroft-Galt Formula) will be recorded in the CRF and performed as per the SOE.

Any laboratory toxicities that lead to a change in treatment, regardless of Grade, will be recorded on the adverse event CRF.

Refer to the Division of AIDS Table for Grading Adult Adverse Experiences.

6.3.9 Urinalysis

A dipstick urine test will be done at screening and every visit after day 0. Protein, glucose and leukocyte esterase will be recorded in the CRF.

6.3.10 T-cell counts and Virology tests

Plasma HIV-1 RNA

An HIV-1 RNA viral load will be performed at the site's local laboratory within 7 days of a new positive antibody test or NAT.

An HIV drug resistance test should be performed with detectable viral load of greater than 500 copies/mL.

CD4 T-cell enumeration will be performed to obtain absolute CD4+/CD8+ count and percentages within 7 days of new HIV diagnosis.

6.3.11 *Stored Plasma and other specimens*

Stored plasma will be collected at day 0, at all visits and with any new HIV diagnosis.

*Specimens will be stored at the site's local laboratory and batched shipped to the central laboratory (UCSD) after completion of the study.

6.3.12 *Pharmacokinetic Studies*

At each visit, record the time and date of the last 3 doses of TDF/FTC medication in the CRF. Dried blood spots will be stored at -80 at each visit beginning at Week 12 for possible future use for plasma and intracellular TFV and FTC pharmacology.

6.3.13 *Questionnaires*

At each visit, the subject should complete the self-reported questionnaires.

6.3.14 *Rectal swabs*

At day 0 and at one additional time point on or after Week 48, all subjects will have a rectal swab stored for possible future studies of the gut microbiome. These tests will be done in retrospect and not available for the subjects.

6.3.15 At day 0, all subjects will have blood stored for future use to examine host DNA. Subjects will sign a consent that informs them of the storage of material for possible host genomic testing.

6.3.16 Participants will be asked to recall food items eaten over the last 3 days at the week 36 visit. The calculator used in the ACTG 5280 study, which is adopted from the USDA database, will be used to quantify vitamin D and calcium intake (see Appendix VI).

6.4 Schedule of Evaluations for Subjects On-Study, Off-Medications

6.4.1 At any point, subjects may elect to stop study medications but remain on study. Subjects that stay on study but stop medications will not be allowed to resume again.

Subjects will follow the same schedule as defined in Section 6.1 until the end of study. Study medications will not be dispensed at clinic visits, and evaluations related to counseling or monitoring of medications (including urine dipstick and serum creatinine) will not be performed. These include Adherence and Risk-reduction counseling and collection of dried blood spots. If the subject was randomized to the iTab arm, their account will be switched to "inactive."

STI and HIV rapid test screenings and questionnaires will still be administered as the schedule dictates.

6.5 End of Study Visit and Post-study 3-month Follow-up

6.5.1 At the End of Study (EOS) visit, subjects will be asked to complete additional questionnaires in addition to completing regular procedures. These surveys will assess subjects' experiences over the course of the study including changes in their medical insurance status, access to other health services, changes in their perceptions of PrEP and of their own health, and their opinions on the intervention.

Upon completion, subjects will not be dispensed PrEP and will be discontinued from the study.

Subjects that express the desire to continue PrEP after completing the study will be provided information regarding access and payment strategies.

6.5.2 Subjects that complete CCTG 595 will be approached EOS and asked to join a supplement-funded extension, consisting of a one-time phone call follow-up scheduled for 3 months post-study. The purpose of this extension is to examine sexual risk compensation and the impact of transition after cessation of study-provided PrEP.

Written consent will be obtained at EOS; subjects that have already completed their EOS visit will be contacted and verbal consent will be obtained over the phone.

At 3 months post-study, subjects will be contacted over the phone and asked questions regarding their current HIV status, their ability to access and maintain their PrEP regimen after EOS, and their ability to obtain health insurance coverage. If subject is off PrEP and/or has no health insurance, the subject will be asked for their reasons and possible barriers. Subjects will also be asked an abbreviated number of questions from surveys similar to those done during the main study, including measures assessing risk compensation, perceptions of PrEP efficacy, and adherence (if on PrEP).

7.0 TOXICITY MANAGEMENT

The management of medication related toxicities should be undertaken by the local investigators, with guidance available from the protocol team, protocol pharmacist and pharmaceutical sponsor, to ensure the optimal safety and efficacy for the individual subject.

7.1 General Management for Grade 1-4 Events

7.1.1 Grade 1 or 2

Subjects who develop a Grade 1 or 2 adverse event or toxicity may continue TDF/FTC without alteration of the dosage, except as noted below. Persistent grade 1 or 2 toxicity should be discussed with the protocol team. Those subjects experiencing Grades 1 or 2 adverse events which results in discontinuation of the TDF/FTC should continue to be followed on study, but off study medication.

7.1.2 Grade 3

Management of Grade 3 toxicities should be discussed with the protocol team via email. Please refer to the subsequent sections for management of specific events.

In the event that a subject develops a **symptomatic** Grade 3 reaction considered to be TDF/FTC-related, the study drug should be discontinued and the subject should be followed weekly until resolution of the adverse event. Once Grade 3 is resolved the subject should be followed on-study, but off study medication. For subjects with asymptomatic Grade 3 toxicity or laboratory abnormalities, the protocol team should be consulted for possible re-introduction of TDF/ FTC.

7.1.3 Grade 4

Subjects who develop a Grade 4 adverse event or toxicity judged to be TDF/ FTC-related will have the study drug permanently discontinued. For other Grade 4 events, if the toxicity or laboratory elevation is thought not to be due to TDF/FTC, TDF/FTC may be continued and laboratories repeated within 2 weeks (for example for asymptomatic elevation of CPK or triglycerides). If it is not possible for the investigator to discern another causative agent/ condition or if TDF/FTC could be the causative agent, then TDF/FTC must be discontinued. Subjects experiencing Grade 4 adverse events requiring permanent discontinuation of TDF/FTC therapy should be followed weekly until resolution of the adverse event. Once Grade 4 is resolved the subject should be followed on-study, but off study medication.

7.2 Management for Specific Adverse Events

7.2.1 Rash

Grade 1 or 2

TDF/FTC may be continued without interruption. Subjects with a Grade 1 or 2 rash may be treated symptomatically with permitted antipyretic, antihistamine and/or non-steroidal anti-inflammatory medications, but should be monitored closely by the local investigator.

Grade 3 or 4

Grade 3 or 4 rash necessitates that TDF/FTC be held unless the rash is determined to be unrelated to TDF/FTC. The rash should be followed closely for resolution and the subject followed on-study, off study medication.

7.2.2 Nausea and Vomiting

Grade 1 or 2

TDF/FTC may be continued without interruption. Subjects with Grade 1 and 2 nausea or vomiting may be treated symptomatically with permitted oral antiemetic therapies or antiemetic suppositories. Subjects will be instructed to take medications with food.

Grade 3 or 4

Subjects with Grade 3 TDF/FTC-related nausea and vomiting should interrupt TDF/FTC until the toxicity grade returns to Grade $\leq$ 2 or to baseline and be treated symptomatically. After discussion with the protocol team and if the subject is willing, the TDF/FTC may be resumed when symptoms have resolved. If Grade 3 nausea and vomiting recurs upon the resumption of TDF/FTC despite symptomatic treatment, TDF/FTC should be discontinued. Grade 4 nausea or vomiting will lead to permanent discontinuation of drug. Once resolved, the subject should be followed on-study, but off study drug.

7.2.3 Diarrhea

Grade 1 or 2

TDF/FTC may be continued without interruption. Subjects with diarrhea of any toxicity grade may be treated symptomatically with permitted antimotility agents.

Grade 3 or 4

For grade 3 diarrhea that is unresponsive to antimotility agents and for which an alternative etiology (e.g., infectious diarrhea) is not established, TDF/FTC should be interrupted until resolution of diarrhea to Grade ≤ 2 or baseline. If Grade ≥ 3 diarrhea recurs upon the resumption of study medications, TDF/FTC should be permanently discontinued. Grade 4 will lead to permanent discontinuation of study medication.

7.2.4 Hyperglycemia

Fasting hyperglycemia of > 110 to 125 mg/dL is considered evidence of impaired glucose tolerance. A fasting blood glucose level above 126 mg/dL is highly suggestive of diabetes mellitus. Subjects with fasting hyperglycemia may continue TDF/FTC at the discretion of the investigator but should be discussed with the protocol team via email. A confirmatory fasting glucose will be obtained within 4 weeks and prior to the institution of medical therapy. Hyperglycemia may be treated with oral hypoglycemic agents or insulin according to standard guidelines. Abnormal glucose levels will be monitored closely, and further laboratory repeats will be at the discretion of the site PI.

7.2.5 AST/ALT Elevations

Grade 1 or 2

TDF/FTC may be continued. Tests should be repeated and reassessed within 2 weeks if AST/ALT results are $\geq$ grade 2

Grade 3

All grade 3 or 4 elevations of AST/ALT should be discussed immediately with the protocol team via email. TDF/FTC may be continued for Grade 3 AST/ALT elevations at the discretion of the site investigator after discussion with the protocol team. Careful assessments should be done to rule out the use of alcohol, non-study medication-related drug toxicity, or viral hepatitis as the cause of the Grade 3 elevation.

Grade 4

TDF/FTC will be permanently discontinued for AST or ALT Grade 4 elevations, and the protocol team will be notified. The subject should have repeated AST or ALT evaluations until the levels have returned to < grade 2 or baseline. Once the AE is resolved, the subject should be

followed on-study, but off study medication.

7.2.6 Creatinine Elevations

TDF/FTC will be discontinued if the creatinine clearance is confirmed to be < 50 mL/min. Subjects should be followed as medically indicated until the creatinine returns to baseline. The protocol team will be notified within 48 hours of any permanent therapy discontinuations due to change in creatinine clearance.

If the serum creatinine increases more than 0.3 from baseline, the level should be repeated in 2 weeks. Elevations in creatinine will be monitored closely, and further laboratory repeats will be at the discretion of the site PI.

7.2.7 Anemia/Neutropenia

Subjects with Grade 3 anemia or neutropenia attributed to TDF/FTC should have all study treatment interrupted until the abnormality returns to Grade $\leq$ 2. Therapy may be resumed after the anemia or neutropenia has returned to Grade $\leq$ 2. If Grade 3 anemia or neutropenia recurs, TDF/FTC will be discontinued, and the protocol team will be notified.

Grade 4 anemia or neutropenia will result in permanent discontinuation of study medication if it is due to TDF/ FTC.

8.0 CRITERIA FOR TREATMENT DISCONTINUATION

8.1 Criteria for Discontinuation from Study

8.1.1 Diagnosis of HIV infection.

8.1.2 Request by the subject to withdraw.

8.1.3 Request of the primary care provider if s/he thinks the study is no longer in the best interest of the subject.

8.1.4 Clinical reasons believed life threatening by the study physician, even if not addressed in the toxicity management of the protocol, and can no longer continue in follow up.

8.1.5 Subject judged by the investigator to be at significant risk of failing to

comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.

8.1.6 At the discretion of the CCTG, FDA, CHRP or pharmaceutical sponsors.

8.1.7 Misses two consecutive scheduled visits prior to 48 weeks.

8.1.8 Misses one scheduled visit after 48 weeks.

9.0 STATISTICAL CONSIDERATIONS

A formal Statistical Analysis Plan (SAP) will be drafted and finalized prior to database lock. The SAP will contain a more detailed and/or comprehensive presentation of statistical methods, attention to any changes of substance to planned analysis procedures relative to those indicated in the protocol, and is the final authority for all statistical analyses. The following section briefly describes the planned statistical analyses. In case the language in this section differs from the language in the SAP, the SAP takes precedence.

9.1 Primary Endpoints

Adherent to PrEP through 48 weeks is defined as a composite endpoint of continuing on study (made all scheduled visits within window in the 48 week period) and on study medication and greater than or equal to 90% adherent to medication defined by self-report of $\geq$ 18 of 20 doses of medication on the 5 ACTG adherence questionnaires at weeks 4, 12, 24, 36 and 48. Missing adherence forms will be imputed as no doses taken.

9.2 Secondary Endpoints

9.2.1 Adherent to PrEP by FTC measurement at 48 weeks and at the end of study follow-up is defined by attending all scheduled visits and having detectable FTC.

9.2.2 Adherent to PrEP in continuous follow up is aggregate percentage of self-reported ACTG days of adherence where missed schedule visits are counted as 0/4 days.

9.2.3 Poor adherence is considered those with <90% self-reported adherence by ACTG 4 day survey or if discontinued drug. Subgroup analysis should explore the endpoint for discontinuation for reasons other than quit drug for lack of risk or confirmed adverse event.

9.2.4 Safety and tolerability defined as: i) discontinuation of TDF/ FTC for any

toxicity; ii) grade 2 or higher adverse event or laboratory toxicity; iii) serious adverse event; iv) death

9.3 Randomization and Stratification

We will conduct an open-label, randomized, controlled, two-arm, clinical strategy trial for PrEP adherence. Subjects will be randomized (1:1) to one of two arms: the **Standard of Care** (SoC) or the **iTAB** enhanced adherence arm. Randomization will be stratified by clinic site. A total of 400 subjects (200 per arm) will be randomized and followed in the study for 48 weeks after enrollment of the last subject.

Once eligibility and consent are confirmed, randomization will occur using the web-based CFAR BIT data management system.

9.4 Study Power and Sample Size Justification

The primary objective for this study is to compare the proportion of subjects that reach the composite endpoint, defined as: continued retention and adherence to PrEP. Sample size calculations were based on a two-sided, two- sample binomial test to compare the differences in composite endpoint proportions between the intervention arm and the standard of care arm. Since attrition is a component of the composite endpoint, attrition rates are not used as an adjustment in the power calculations. Assuming 200 subjects per group in each of the two groups (for a total of 400 subjects) and alpha set to 0.05, we have 94% power to detect a difference of 15%, assuming that 30% with a composite endpoint rate in standard of care and that 15% with endpoint in the intervention arm. We have 84% power to detect as small a difference of 13% between the two groups (i.e., 30% versus 17%).

9.5 Monitoring

The study team will review all adverse events during PrEP therapy by cumulative reports, both arms combined in aggregate, on a monthly basis. Adverse events will be graded using the ACTG toxicity grading scale and recorded using standard CCTG AE electronic data capture. The study investigators will monitor safety events in aggregate on monthly team calls. An independent Data Safety and Monitoring Board (DSMB) will not be used for this study.

9.6 Analyses

9.6.1 Statistical Analysis Plan

In general, analyses will incorporate the modified intent-to-treat (mITT) principle, namely, all randomized participants dispensed study medication will be included in the analysis. The primary analysis compares the iTAB enhanced proportion of adherence to the SOC arm.

For all secondary analyses of interest, no adjustments for multiple comparisons will be made and a p-value of 0.05 will be considered statistically significant. Demographic and baseline measurement variables will be summarized via standard descriptive statistics. There will be no interim analyses for futility or efficacy conducted.

9.6.2 Analysis of Primary Outcome

The primary analysis will use a two-sample binomial test for proportions to determine if the intervention arm will produce an improved composite endpoint rate compared to the standard of care arm. Fisher's exact test will be used along with a 95% confidence interval. As a sensitivity analysis, the two components of the composite primary endpoint will be analyzed separately (retained on PrEP and Adherence > 90%). A Fisher's exact test will be used to compare rates of study discontinuation between the active intervention arm versus standard of care arm.

9.6.3 Analysis of FTC Plasma Concentrations

With repeated qualitative FTC assays in each subject over time, adherence will be defined using a continuous and categorical metric. The percent adherence, calculated as number of detectable samples divided by total number of samples measured, will be compared between intervention and control using a two- sample t-test (or an appropriate non-parametric alternative if parametric assumptions fail). For strict mITT analyses, subjects that are missing a FTC concentration at any time point (whether due to missed visit or TDF/ FTC discontinuation) will be defined as having an undetectable FTC concentration while per protocol analyses will consider only available data (i.e., no imputation for missing values). A categorical metric of good adherence (> 90% of concentrations detectable) will be compared between intervention and control with the Fisher's exact test.

9.6.4 Analysis of additional Secondary outcomes

The incidence rate of STI will be compared between SOC and ALERT- iTAB intervention arms using Fisher's exact test as will the rate of HIV seroconversion between groups (the rate of new HIV is expected to be low). In order to evaluate hypothesis 3c (factors associated with the composite primary endpoint of on therapy and adherence > 90%), multivariable logistic regression models will also be used. A subgroup analysis by treatment arm will be conducted, looking at each arm separately. Descriptive analysis will be performed within each subgroup

to compare adherent versus non-adherent subjects. The models will include the following potential covariates: demographics, ongoing substance use, untreated mental illness, socioeconomic status, HIV risk transmission behaviors, low health/ HIV and system literacy, fear of disclosure and non-English. Further, any covariates (including stratification factors) that are simultaneously unbalanced at baseline (univariate $p < 0.10$) and associated with the outcome (univariate $p < 0.15$) will be included in the model as observed confounders. Sub-group analyses based on race/ ethnicity, gender, primary language, socioeconomic status by randomization arm will also be conducted. Secondary endpoints for adherence will be analyzed analogously to the primary endpoint.

9.6.5 Safety and tolerability of daily TDF/FTC given for PrEP including discontinuation for any adverse event, serious adverse events and adverse events (grade 2 or higher) will be compared between study arms. Descriptive statistics will be used to characterize safety events. Fisher's exact test will be used to compare discontinuation rates due to safety and incidence rates of adverse events and serious adverse events. The time to TDF/ FTC discontinuation for adverse events will be compared between groups using the log-rank test and plotted using Kaplan-Meier curves. Similar analysis will be done for the time to discontinuation for any reason (including drop-out or subject electing to stop PrEP due to lack of perceived risk for HIV).

10.0 PHARMACOLOGY PLAN

10.1 Sample Assay Methods

FTC concentrations will be measured in the Pediatric Clinical Pharmacology Laboratory of the University of California, San Diego by a validated, Liquid Chromatography-Mass Spectrometry (LC-MS) method. The laboratory is registered with the ACTG Quality Assurance/Quality Control proficiency testing program [27] and successfully completes proficiency testing for the accuracy and precision of the FTC assay every 6 months. Inter-assay variability is less than 6% for low, middle and high controls. The lower limit of detection of FTC is approximately 1 ng/mL (the lower limit of quantitation is 11.8 ng/mL). For qualitative assays, unknown samples will be measured in the presence of internal standard to determine if the FTC ion peak is present (≥ 1 ng/mL) or absent (< 1 ng/mL). Stored plasma samples will be bulk testing of qualitative presence of FTC at the end of follow-up. Additional pharmacology analyses will be done in retrospect and the specific analysis will be included in the SAP prior to data log and sample testing.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to be Kept

Case report forms (CRFs) will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by the PID provided by the CCTG Data Unit upon registration and the linkage to the PID will be kept in paper copy only in a locked cabinet in a secure office at the study sites available only to the site investigators.

Subject self-reported surveys that are performed electronically will be automatically stored in the electronic database secured by the CFAR BIT group for the CCTG.

11.2 Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the CCTG Data Unit.

11.2.2 It is the responsibility of the CCTG Data Unit to assure the quality of computerized data for this study.

11.3 Clinical Site Monitoring and Record Availability

11.3.1 Site monitors provided by the CCTG will visit participating clinical research sites to review the individual subject records including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (e.g., physician progress notes, nursing notes, individual hospital charts), to ensure protection of study subjects, compliance with the protocol and accuracy and completeness of records. The monitors also will inspect sites's regulatory files to ensure that regulatory requirements are being followed.

11.3.2 The investigator will make study documents (e.g., consent forms and CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB or the site monitors.

11.4 Serious Adverse Experience (SAE) Reporting

Serious adverse events are not expected in this study. All SAEs must be documented on the SAE Reporting Form within 5 working days of site awareness of the event and submitted to the CCTG Data Unit.

12.0 HUMAN SUBJECTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for the oversight of the study. A signed consent form will be obtained from the subject. The consent form will describe the purpose of the study, the procedures to be followed and the risks and benefits of participation. A copy of the consent form will be given to the subject.

12.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be stripped of any patient identifiers (name, birthdate, medical record number) and only identified by the coded PID in order to maintain subject confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only and analyzed centrally without any possibility of linking subject identity with subject data. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB and governmental agencies.

12.3 Study Discontinuation

The study may be discontinued at any time by the IRB or other government agencies as part of their duties to ensure that research subjects are protected.

13.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by CCTG policies. Any presentation, abstract or manuscript will be made available for review by pharmaceutical supporters prior to submission.

14.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood and blood products; appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All infectious specimens will be transported using packaging mandated in the Federal Code of Regulations, CDC 42 CFR Part 72. Please also refer to individual carrier guidelines, e.g., FedEx, Airborne, for specific instructions.

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16.0 APPENDICES

APPENDIX I: SAMPLE OF INFORMED CONSENT

UNIVERSITY OF CALIFORNIA - SAN DIEGO
CONSENT TO ACT AS A RESEARCH SUBJECT

TITLE: CCTG 595: A Multicenter, Randomized Study of Text messaging to improve Adherence to PrEP during In Risky MSM (TAPIR)

Drs. Sheldon Morris, Constance Benson, Maile Karris, Scott Letendre, Susan Little,,Jill Blumenthal, Richard Haubrich, David Moore, and their associates are conducting a research

study sponsored by the California Collaborative Treatment Group (CCTG) to determine if using text-message based adherence interventions can improve retention and adherence to Pre-exposure Prophylaxis (PrEP) in HIV-negative men who have sex with men (MSM) and male to female transgenders who are at high-risk for HIV acquisition.

Before you can decide whether or not to volunteer for this study, we would like to let you know about the study's purpose, how it may or may not help you, any risks to you, and what is expected of you. This process is called informed consent.

The FDA recently approved a fixed dose combination of tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) to reduce the risk of HIV infection in uninfected individuals who are at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners. From other studies, we know that the use of PrEP in HIV negative individuals has been shown to reduce acquisition of HIV among at-risk individuals. We also know that the more a person takes the PrEP medication (called adherence), the more effective it is.

The purpose of this study is to evaluate a promising method of reinforcing PrEP adherence using text message. In this study, we will hope to learn if text message reminders increase PrEP adherence.

You have been asked to participate in this study because you are HIV-negative and are sexually active with men and are at ongoing risk for acquiring HIV.

DURATION OF THE STUDY

The study will enroll about 400 people at all participating sites. We plan to enroll about 250 subjects at UCSD. If you participate in the study, you have up to 11 visits at the UCSD Antiviral Research Center (AVRC) for at least 1 year and up to a maximum of 2 years.

PROCEDURES

If you agree to participate in this study, the following will happen:

To see if it is okay for you to participate in this study, you will first come to the clinic for a study visit known as a "screening" visit. At your first visit, this consent form will be reviewed with you and you will be asked to sign it.

Once you sign this form and agree to participate, we will confirm your HIV status, screen for symptoms of recent HIV infection and perform a medical/medication history. You will also be asked to complete a survey on a computer. Because you will be asked questions about your sexual, and drug using history and practices, the computer you will use to complete this survey will be in a private location in the clinic.

Approximately 2-3 tablespoons of blood will be drawn for laboratory tests including blood count, chemistry values, liver function and kidney tests, HIV test and Hepatitis B will be obtained.

Your Screening visit will take about 1 to 2 hours.

Entry Visit:

The information gathered at your screening study visit will determine if you are able to take part in this study. If you qualify for the study, you will return to the clinic for your "entry visit". At your entry visit, you will have the following procedures done:

- A medical and medication history will be taken. This will include any recent or previous drug history and anti-HIV drugs you have taken.
- Sample will be obtained for the following tests:
  - Screening for sexually transmitted infections (STIs). In addition to the urine and blood sample, a throat and rectal swab will need to be done in order to screen for STIs. These collected samples and swabs will be tested to see if you have gonorrhea, Chlamydia, or syphilis. These samples will be taken at entry and every 24 weeks after your entry visit. .

    The test in your throat will be done by inserting a cotton swab (Q-Tip) into your mouth and gently turning it to collect the sample.

    The test in your rectum will be done by carefully inserting a cotton swab and gently turning it to collect the sample.

    If your tests show that you have an STI, our study staff will refer you to your medical provider for treatment. If you do not have a provider, you will be referred to the public health clinic where treatment will be provided at a small fee or free to those who cannot afford this fee. According to California state law, study staff are required to give the public health department the names, contact information and treatment records of people who have a positive test result for chlamydia, gonorrhea or syphilis.
  - Blood to be stored for future study-related tests including the amount of PrEP medicine in your blood.
  - An additional sample from your throat and rectum may be taken for future study related tests.
  - Approximately 2-3 tablespoons of blood will be drawn at the entry visit.

At this entry visit, you will be randomized (assigned by chance, like flipping a coin) into one of the following two groups. You have an equal chance of being assigned to either group.

Group 1: PrEP daily, HIV/STI screening, adherence and risk behavior counseling, and safety monitoring

Group 2: PrEP daily, HIV/STI screening, adherence and risk behavior counseling, and safety monitoring as well as iTAB text adherence reminders

The PrEP medicine is TDF/FTC combination pill. At this study, visit Groups 1 and 2 will complete a survey that is done on a computer in a location that is private so no one can see the answers to any questions you type into the computer. The survey will ask specific question about your sex life and recreational drug use. Groups 1 and 2 will receive detailed information about the use of PrEP, including the risks, potential adverse events and the importance of drug adherence. You will be provided with enough TDF/FTC to last until your next visit. You will be instructed to take one pill once a day at a convenient routine time.

Group 2 will be introduced to the iTAB (Individualized Texting for Adherence Building) system by a study worker who will help you select and refine 10 personal reminders from a list of pre-determined reminders. The study worker will help you to set adherence reminders that are sent at times consistent with when you typically take medications. You will be provided with information about how the iTAB texting system works. If you are in Group 2 and do not have a cell phone, you will be provided with one at this time.

This study visit will take about 1 - 2 hours.

Clinic Study Visits (Month 1, 3, 6, 9, 12 and every 3 months thereafter)

You will come to the clinic at 1 month and then every 3 months (3, 6, 9, 12 and every 3 months) for a study visit. At these study visits, you will have the following procedures done:

- A urine sample and approximately 2-3 tablespoons of blood will be drawn for the following tests:
  - Laboratory tests including kidney tests and HIV testing. You will find out the results of the HIV test during each visit.
  - Screening for sexually transmitted infections (STIs). In addition to the urine and blood sample a throat and rectal swabs will need to be done in order to screen for STIs. These collected samples and swabs will be tested to see if you have gonorrhea, Chlamydia, or syphilis. Samples will be collected as described above. Screening for STI will be done every 6 months after your entry visit.
  - Blood to be stored for future study related tests including blood levels of PrEP medications.
  - An additional sample from your throat and rectum may be taken for future study related tests.

At your study visits, you will complete a survey done on a computer that is in a location that is private so no one can see the answers to any questions you type into the computer. The survey will ask specific question about your sex life, recreational drug use, how well you took your PrEP medication and questions about your mood. You will receive risk assessment and adherence counseling. Study medication use and adverse events will be reviewed by study personnel.

Each study visit will take about 1 hour.

Additional Study Visits

If at anytime during the study you think you might have gotten an STI because someone you had sex with tells you they were diagnosed with one or you are having symptoms that you think are those of a STI or acute HIV infection you need to tell your study staff immediately so you can get an appointment to be checked. If you come for an additional visit because you think you have an STI, tests for STI will be done (blood and urine sample and rectal or throat swabs). An HIV test will be done if you think you were exposed to HIV or if you have symptoms of HIV.

If you have a positive test for HIV during the study, additional blood tests will be done to find out the amount of HIV virus in your blood, to check the HIV strain for drug resistance and to look at your immune system (T-cell count). You will be referred for HIV care.

Contact for Future Studies:

There may be other studies that are being conducted at the AVRC for which you may qualify. You may be asked to participate in one or more of these additional studies. Are you willing to be contacted for future research studies by our staff?

_____*YES* _____*NO*

Post-study Follow-up
We would like to follow-up with you after you complete the study. This is a one-time phone call 3 months after your end of study visit. We will ask about your HIV status, health insurance status, and if you were able to obtain PrEP outside of study. We will also ask you questions similar to those that you completed over the course of the study on the iPads. Are you willing to be contacted for this follow-up visit and provide additional data?

_____*YES* _____*NO*

Subject has been contacted via telephone and verbally agrees to provide additional data after completing the study:

_____*YES* _____*NO*

RISKS/DISCOMFORTS:

Participation in this study may involve some added risks or discomforts. These include:

Study drug side effects

You may experience side effects from the study medication which include but are not limited to nausea, vomiting, diarrhea, abdominal pain, rash, dizziness, body weakness, fever, weight loss, allergic reaction, elevations in liver tests and impairment in kidney function. Any side effect will be carefully evaluated and managed according to standard guidelines and may require discontinuation of the study drug.

A small number of people in this study may have these side effects or other side effects that we do not know about. However, we will screen your kidney function and overall health before you join the study. This will reduce the chances of having any side effects.

Text messaging adherence reminders

You may feel increased stigma or intrusions of privacy or confidentiality when receiving text message reminders to take your medication.

Drug Resistance

In previous studies, it was found that a few people became HIV infected despite taking the study drug. Should you become HIV infected during the course of the study, there is a very small chance that you may develop resistance to the study drug while participating in the study.

Risks of drawing blood

You may experience temporary discomfort from the blood draws. The needlesticks may cause local pain, bleeding, bruising and swelling, as well as lightheadedness, dizziness and rarely, blockage of the vein, fainting and/or a local infection.

Sexually Transmitted Infections (STIs)

You may experience some anxiety or embarrassment when being tested for sexually transmitted infections. If you are found to have a sexually transmitted disease, an appropriate referral for treatment will be made to one of several free public health clinics in your area.

Since this is an investigational study, there may be other unknown risks that are unforeseen or at this time cannot be predicted. You will be told of any significant new risks. If you have questions concerning the study, ask the study staff.

Sample Storage

As a result of your participation in this study, you are now being asked to take part in an optional part of the study involving the collection of blood and swabs for genetics testing and storage. It is up to you to decide whether to participate.

We would like your permission to store some of your blood and swab samples for future DNA research. As scientific discoveries are made, valuable research can be done in the future on samples collected today. Therefore, we ask your permission to store your DNA sample to allow for research to be done in the future.

If you agree, some of your blood, swabs, and oral specimens that are left over after all required study testing is done may be stored for future use for approved research. Your left over blood may be stored for an indefinite length of time. Because research using your left over blood will be done in the future, you will not be told the results of the research done on these samples. You may cancel your permission to store and use your left over blood at any time and still remain in this study.

Please indicate below whether or not you agree to have your blood and swabs stored, which was obtained as part of this study. All samples will be identified by a number only (your name will not be listed on the sample)

_____ (Initials) You agree that your left over samples can be used for future HIV/AIDS-related research.

_____ (Initials) You do not agree that your left over samples can be used for future HIV/AIDS-related research.

_____You agree that your left over samples can be used for future DNA-related research.
(Initials)

_____You do not agree that your left over samples can be used for future DNA-related
(Initials) research.

STORED SAMPLES

Some of your blood, swabs, and oral specimens obtained as part of this study will be stored indefinitely and may be used for approved HIV/AIDS-related research in the future. You will not be identified by name in any testing and your confidentiality will be maintained. Specimens will be identified only by an identification number (your name will not be listed on the sample). All of the individuals receiving these specimens will be scientific partners in this study. Your blood, swabs, and oral specimens and the DNA that it contains may also be used in additional research to be conducted by the University of California personnel collaborating in the research. This blood, swabs, and/or oral specimens and its derivatives may have significant therapeutic or commercial value. You consent to such uses.

The University has policies and procedures to ensure your confidentiality. We will use our best efforts to ensure that your identity and test results will not become known outside the research program, which if released, could affect your employment and ability to obtain insurance.
If you decide later that you do not want the specimens collected from you to be used for future research, you may tell this to Dr. Morris, who will use his best efforts to stop any additional studies. However, in some cases, such as if the material within your samples are found to be generally useful, it may be difficult or impossible, to stop such future research once the materials have been widely shared with other researchers. Dr. Morris, his associates, or his successors in these studies will keep your DNA specimen or the information derived from it indefinitely.

BENEFITS

There may or may not be a direct benefit to you from the procedures done as part of this study. However, information learned from this study may help the study doctor/staff learn more about different ways to help high-risk HIV negative reduce their risk of acquiring HIV.

NEW FINDINGS

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them.

REASONS FOR WITHDRAWAL FROM THE STUDY DRUGS AND/OR STUDY WITHOUT YOUR CONSENT:

You may be removed from the study without your consent for the following reasons:

- The study is canceled by the California Collaborative Treatment Group (CCTG) the sponsors, the UCSD AVRC study doctor, or the UCSD Institutional Review Board (IRB). An IRB is a committee that watches over the safety and rights of research subjects;
- You are unable to keep appointments as required by the study, including missing 2 consecutive visits before 48 weeks, 1 visit after 48 weeks or discontinuing study drug at 48 weeks or more
- You do not start the study treatment.
- You experience a high level drug toxicity
- You acquire HIV or viral hepatitis.

ALTERNATIVES TO PARTICIPATION

You may decide not to take part in this study. The alternatives to participating in this study is to receive counseling on HIV prevention and testing for sexually transmitted infections and HIV infection from your current primary care doctor. The study medication TDF/FTC could be obtained from your doctor.

COSTS TO YOU

There is no cost to you for the study-related medications, clinic visits, procedures, examinations, or laboratory tests in this study. The cost of any drugs you may need to treat other medical conditions, and any other medical costs for your treatment outside this study, will be the responsibility of you or your insurance company.

As compensation for your time and any inconvenience you may experience as a result of your participation in this study, you will receive $10 after you complete your entry and your month 1, 3, 6, 9, 12 and every 3 months study visits. You will not receive compensation for visits that are not completed. If you consent to the phone call follow-up, you will receive $10 for completing the interview.

CONFIDENTIALITY

Your research records will be confidential to the extent permitted by law. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the Federal Privacy Act, by Office for Human Research Protection (OHRP), study monitors, drug companies supplying the study drugs and their designees and the UCSD Institutional Review Board (IRB).

The University has policies and procedures to ensure your confidentiality. We will use our best efforts to ensure that your identity and test results will not become known outside the research program. Please talk with your study staff if you have any concern in this issue.

Because the University of California complies with the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and its privacy regulations, and all other applicable laws that protect your privacy, in addition to this informed consent form, you will be

asked to read and sign the attached HIPAA Authorization Form prior to your participation in this research study.

The U.S. Department of Health and Human Services (DHHS) has issued a Confidentiality Certificate to this research project to help protect your identity. This certificate means that researchers cannot be forced to release any research data in which you are identified, even under court order or subpoena, without your written consent. If we learn something that would immediately endanger you or others, we may discuss it with you, if possible, or seek help from others to protect you or others. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A Certificate of Confidentiality does not represent an endorsement of the research study by the Department of Health and Human Services or the National Institutes of Health.

RESEARCH-RELATED INJURY

If you are injured as a direct result of participation in this study, the University of California will provide any medical care you need to treat those injuries. Neither the sponsor of the study California Collaborative Treatment Group (CCTG), nor the University of California will provide any compensation to you if you are injured. You may call the UCSD Human Research Protection Program Office at (858) 455-5050 for more information about this, to inquire about your rights as a research subject, or to report research-related problems.

PROBLEMS OR QUESTIONS

Dr. [[Morris]] and/or _____ has explained this study to you and answered your questions. If you ever have questions about this research study, or in case of research-related problems, you may reach [[**Dr. Sheldon Morris at (619) 543-8080**]] or an AVRC doctor on call at (619) 543-6737 after working hours or in an emergency.

Participation in this study is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care you will receive from this institution or loss of benefits to which you are entitled.

The study purpose, procedures, possible risks and benefits as outlined in this consent have been explained to you. You have been invited to ask any questions about the study that you may have, and all your inquiries have been answered. You do not give up any of your legal rights by signing this form.

You have received a copy of this document and a copy of the "Experimental Subject's Bill of Rights" to keep.

You agree to participate.

_____

Printed Subjects Name

_____ _____
Subjects Signature Date

_____ _____
Printed Name of Person Obtaining Consent Date

_____ _____
Signature of Person Obtaining Consent Date

Subject contacted over the phone on _____
(Date)

_____
Printed Name of Person Obtaining Consent Over the Phone

_____
Signature of Person Obtaining Consent Over the Phone

16.0 APPENDICES

APPENDIX II: QUESTIONNAIRES

Domain	Assay	Header in Survey	Page	# of Q's	Schedule
HIV Literacy	HIVKQ18	HIV Knowledge	2	20	B, 48, EOS
Stigma and Disclosure	USC Survey	Stigma and disclosure	4	20	B, 48, EOS
Risk Behavior	Sexual Risk Scale	Attitude to safe sex	9	24	B
Partner Disclosure Provider Education	Milam Survey	Provider Education	11	4	B
	Anatomic Risk		12	3	B
	Modified State Form	Sexual risk survey	12	13	All
Adherence	ACTG Adherence, modified	PrEP Adherence	15	13	All except baseline
	Ira Wilson Adherence Questions	4 week medication recall	19	5	All except baseline
	Visual Analog Scale	Adherence scale	20	4	All except baseline
Intention to Adhere	VAS Intention				All visits
Depression	PHQ9	Mood scale	22	10	All
Substance Use	AUDIT	Alcohol use	23	10	B, 48, EOS
	DAST-10	Drug Use	25	10	B, 48, EOS
	SCID Screen	Drug Use	26	16	All
Access to Care	Modified USC	Access to care	27	7	B
Social Support	Modified USC	Social Support	30	6	B
Technology	Text Message Ability	Texting Knowledge	33	8	B
Sexual Compulsivity	Kalichman; Scale 1	Sexual Desire	34	9	B, EOS
	iTab/PrEP Feedback		35	15	48

iPad Header: **HIV Knowledge**	*Assay*: **HIVKQ18, BEHKA**	*# of Questions*: 20	*Time:*

Instructions: Please select the most appropriate answer.

1. **Coughing and sneezing DO NOT spread HIV or STD.**

True False Don't Know

2. **A person can get HIV or STD by sharing a glass of water with someone who has an STD or HIV.**

True False Don't Know

3. **Pulling out the penis before a man climaxes/cums keeps their partner from getting HIV or STD during sex.**

True False Don't Know

4. **Anyone can get HIV or STD if they have anal sex with a man.**

True False Don't Know

5. **Showering, or washing one's genitals/private parts, after sex keeps a person from getting HIV.**

True False Don't Know

6. **All pregnant women infected with HIV quickly show serious signs of being infected.**

True False Don't Know

7. **People who have been infected with HIV quickly show serious signs of being infected.**

True False Don't Know

8. **There is a vaccine that can stop adults from getting HIV.**

True False Don't Know

9. **People are likely to get HIV by deep kissing, putting their tongue in their partner's mouth, if their partner has HIV.**

True False Don't Know

10. **A woman cannot get HIV if she has sex during her period.**

True False Don't Know

11. **A condom that can help decrease a chance of getting HIV.**

True False Don't Know

12. **A natural skin condom works better against HIV than does a latex condom.**

True False Don't Know

13. **A person will NOT get HIV if she or he is taking antibiotics.**

True False Don't Know

14. **Having sex with more than one partner can increase a person's chance of being infected with an STD or HIV.**

True False Don't Know

15. **Taking a test for HIV less than one week after having sex will tell a person if he or she has HIV.**

True False Don't Know

16. **A person can get HIV or STD by sitting in a hot tub or swimming pool with someone who has HIV.**

True False Don't Know

17. **A person can get HIV from oral sex.**

True False Don't Know

18. **Using Vaseline or baby oil with condoms lowers the chance of getting HIV or STDs.**

True False Don't Know

19. **Is the goal of treatment to make the 'CD4 count" go up or down?**

Up Down

20. **Is the goal of treatment to make the "viral load" go up or down?**

Up Down

iPad Header: **Stigma and Disclosure**	*Assay*: **Bluthenthal**	*# of Questions*: 20	*Time:*

Instructions: The next set of questions asks about some of your feelings and opinions about HIV/AIDS. Please indicate how much you agree or disagree with the following statements:

1. People who have HIV or AIDS should be isolated from the rest of society.

1 Strongly disagree
2 Disagree
3 Neither agree or disagree
4 Agree
5 Strongly agree

8 Do not know
9 Prefer not to answer

2. People who have HIV or AIDS should only date other HIV positive people.

1 Strongly disagree
2 Disagree
3 Neither agree or disagree
4 Agree
5 Strongly agree

8 Do not know
9 Prefer not to answer

3. People who have HIV or AIDS are not sexually desirable.

1 Strongly disagree
2 Disagree
3 Neither agree or disagree
4 Agree
5 Strongly agree

8 Do not know
9 Prefer not to answer

4. People who have HIV or AIDS are more sexually promiscuous than most people.

1 Strongly disagree
2 Disagree
3 Neither agree or disagree

4 Agree
5 Strongly agree

8 Do not know
9 Prefer not to answer

5. The promiscuity of people who are gay is the reason why HIV/AIDS exists.

1 Strongly disagree
2 Disagree
3 Neither agree or disagree
4 Agree
5 Strongly agree

8 Do not know
9 Prefer not to answer

In the next questions, we will ask you personal beliefs about privacy. For each of the following statements, mark the response that best indicates your experience. On the scale, 1 is Disagree Strongly and 7 is Agree Strongly. Please be as honest as possible in your responses.

15. I prefer to keep my sexual relationships rather private.

1 Strongly disagree
2 Disagree
3 Neither agree or disagree
4 Agree
5 Strongly agree

8 Do not know
9 Prefer not to answer

16. I keep careful controls over who knows about my sexual relationships with men.

1 Strongly disagree
2 Disagree
3 Neither agree or disagree
4 Agree
5 Strongly agree

8 Do not know
9 Prefer not to answer

17. My sexual behavior is nobody's business.

1 Strongly disagree
2 Disagree
3 Neither agree or disagree

4 Agree
5 Strongly agree

8 Do not know
9 Prefer not to answer

18. If you are not careful who you ask about their HIV status, you can get very hurt.

1 Strongly disagree
2 Disagree
3 Neither agree or disagree
4 Agree
5 Strongly agree

8 Do not know
9 Prefer not to answer

19. I think very carefully before asking about someone's HIV status.

1 Strongly disagree
2 Disagree
3 Neither agree or disagree
4 Agree
5 Strongly agree

8 Do not know
9 Prefer not to answer

20. My sexual orientation is a very personal and private matter.

1 Strongly disagree
2 Disagree
3 Neither agree or disagree
4 Agree
5 Strongly agree

8 Do not know
9 Prefer not to answer

iPad Header: **Attitude to safe sex**	*Assay*: **Sexual Risk Scale**	*# of Questions*: 24	*Time:*

Instructions: Safer sex means sexual activity which reduces the risk of AIDS virus transmission. Using condoms is an example of safer sex. Unsafe, risky, or unprotected sex refers to sex without a condom, or to other sexual activity which might increase the risk of AIDS virus transmission. For each of the following items, please choose the response which best characterizes your opinion.

		Strongly Disagree	Disagree	Undecided /neutral	Agree	Strongly Agree
1.	If my partner wanted me to have unprotected sex, I would probably "give in".	**1**	**2**	**3**	**4**	**5**
2.	I may have had sex with someone who was at risk for HIV/AIDS.	**1**	**2**	**3**	**4**	**5**
3.	If I were to have sex, I would take precautions to reduce my risk for HIV/AIDS.	**1**	**2**	**3**	**4**	**5**
4.	I am at risk for HIV/AIDS.	**1**	**2**	**3**	**4**	**5**
5.	I would try and use a condom when I had sex.	**1**	**2**	**3**	**4**	**5**
6.	Condoms interfere with romance.	**1**	**2**	**3**	**4**	**5**
7.	My friends talk a lot about "safer" sex.	**1**	**2**	**3**	**4**	**5**
8.	If my partner wanted me to participate in "risky" sex and I said that we needed to be safer, we would probably end up having "unsafe" sex.	**1**	**2**	**3**	**4**	**5**
9.	Generally, I am in favor of using condoms.	**1**	**2**	**3**	**4**	**5**
10.	If a friend knew I might have sex on a date, he/she would ask if I were carrying a condom.	**1**	**2**	**3**	**4**	**5**
		Strongly Disagree	**Disagree**	**Undecided /neutral**	**Agree**	**Strongly Agree**
11.	If I had a date, I would probably not drink alcohol or use drugs.	**1**	**2**	**3**	**4**	**5**
12.	"Safer sex" reduces the mental pleasure of sex.	**1**	**2**	**3**	**4**	**5**

13.	If I thought that one of my friends had sex on a date, I would ask them if they used a condom.	**1**	**2**	**3**	**4**	**5**
14.	The idea of using a condom doesn't appeal to me.	**1**	**2**	**3**	**4**	**5**
15.	"Safer" sex is a habit for me.	**1**	**2**	**3**	**4**	**5**
16.	If my partner wanted me to participate in "risky" sex and I suggested a lower risk alternative, we would have the "safer" sex instead.	**1**	**2**	**3**	**4**	**5**
17.	The sensory aspects (smell, touch, etc.) of condoms make them unpleasant.	**1**	**2**	**3**	**4**	**5**
18.	I am determined to practice "safer" sex.	**1**	**2**	**3**	**4**	**5**
19.	My sexual experiences do not put me at risk for HIV/AIDS.	**1**	**2**	**3**	**4**	**5**
20.	Condoms are irritating.	**1**	**2**	**3**	**4**	**5**
		Strongly Disagree	**Disagree**	**Undecided /Neutral**	**Agree**	**Strongly Agree**
21.	When I socialize, I usually drink alcohol or use drugs.	**1**	**2**	**3**	**4**	**5**
22.	If a sexual partner didn't want to use condoms, we would have sex without using condoms.	**1**	**2**	**3**	**4**	**5**
23.	People can't get the same pleasure from "safer" sex as from unprotected sex.	**1**	**2**	**3**	**4**	**5**
24.	Using condoms interrupts sex play.	**1**	**2**	**3**	**4**	**5**

iPad Header: **Provider Education**	*Assay*: **Milam**	*# of Questions*: 4	*Time:*

1. Thinking about all the visits you made to your health care provider(s) during the past 3 months, how often did you receive any information (got a brochure, saw a poster, spoke with someone) about preventing transmission of HIV infection (choose only one answer)?

0 = every visit
1 = most visits
2 = some visits
3 = none of my visits
7 = Don't Know
8 = Refuse to Answer

2. In the last 6 months, how many times have you been to your health care provider for regular, scheduled visits for care that addressed HIV prevention

0 = 0 times
1 = 1 time
2 = 2 times
3 = 3 times
4 = 4 or more times
7 = Don't Know
8 = Refuse to Answer

3. Think about these visits. At how many of these visits did your care provider talk with you about you using safer sex, such as condoms?

0 = 0 visits
1 = 1 visit
2 = 2 visits
3 = 3 visits
4 = 4 or more visits
7 = Don't Know
8 = Refuse to Answer

4. Still thinking about these visits. At how many of these visits did your care provider talk with you about asking your sexual partners about their HIV status?

0 = 0 visits
1 = 1 visit
2 = 2 visits
3 = 3 visits
4 = 4 or more visits
7 = Don't Know
8 = Refuse to Answer

iPad Header: Anatomic **Baseline RIsks**	*Assay*: **Morris**	*# of Questions*: 3	*Time:*

1. Is your penis circumcised?

0 No
1 Yes

8 Do not know
9 Prefer not to answer

2. In the past month how frequently have you performed rectal douching or enema (cleaning out your rectum or colon)?

0 Never
1 Rarely (once or twice)
2 A few times (less than weekly)
3 Fairly regular (about weekly)
4 Many times (more than once a week)

8 Do not know
9 Prefer not to answer

3. For rectal douching or enemas in the past month what do you use? (check all that are apply)

0 Nothing in past month
1 Soapy water enema
2 Plain water enema
3 Saline ('Fleet') enema
4 Mineral oil enema
5 Polyethylene glycol oral (e.g. Go-Lytely)
6 Other enema type
7 Other oral colonic cleanser

8 Do not know
9 Prefer not to answer

iPad Header: **Sexual Risk Survey**	*Assay*: **Modified State form**	*# of Questions*:13	*Time:*

Instructions: The following questions ask more questions about the specific sexual activities that you have been participated in recently.

1. In the past 3 months, did you talk about safer sex with any of your sexual partners ?

5 Never
6 Rarely
7 Some of the time
8 Most of the time
9 All of the time

10 Do not know
11 Prefer not to answer

2. How many of the sexual partners that you had in the past 1 month knew that you were taking medicine to prevent HIV transmission?

0 None knew
1 Some knew
2 All knew

8 Do not know
9 Prefer not to answer

3. In the past three month who did you have sex with? (check all that are apply)

0 No sex partners
1 Men
2 Women
3 Male to female transgender
4 Female to male transgender

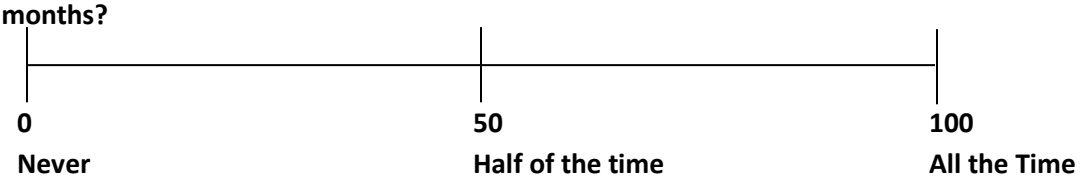
8 Prefer not to answer

4. How many male sexual partners have you had in past 3 months: _____ (if 0, skip)

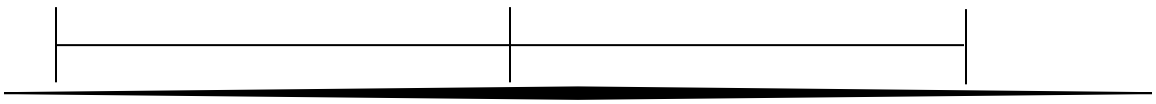
With your male partners in the past 3 months, did you

4a. Have Anal insertive (your penis in them) sex? (Y/N) (if N, skip)

How frequently did you use condoms during anal insertive (your penis in them) sex **with men in the past 3 months?**



4b. Anal receptive (their penis in you) condom use

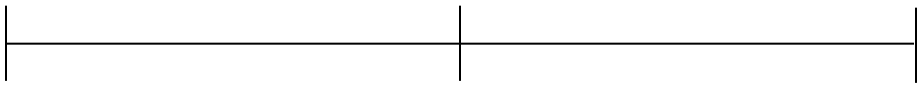


0	50	100
Never	Half of the time	All the Time

5. How many transgender sexual partners have you had in past 3 months: _____

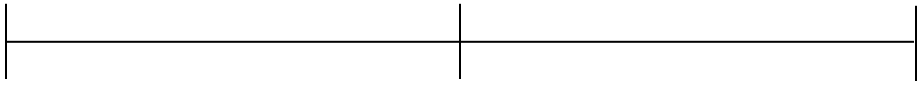
How frequently did you condoms with men in the past 3 months?

5a. Anal insertive (your penis in them) condom use



0	50	100
Never	Half of the time	All the Time

5b. Anal receptive (their penis in you) condom use

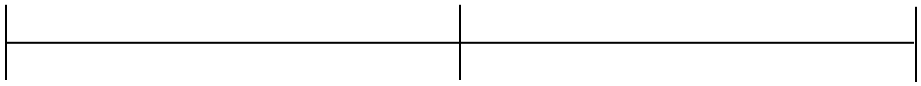


0	50	100
Never	Half of the time	All the Time

5. How many female sexual partners have you had in past 3 months: _____

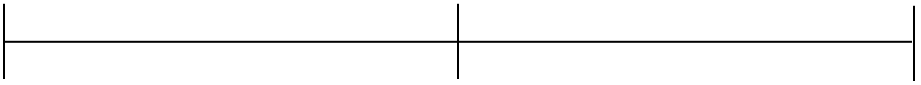
How frequently did you condoms with females in the past 3 months?

5a. Anal condom use



0	50	100
Never	Half of the time	All the Time

5b. Vaginal condom use



0	50	100
Never	Half of the time	All the Time

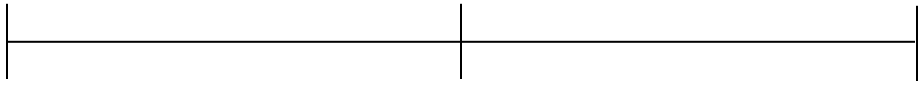
6. In the last 3 months have you

Given someone money, drugs, or items in exchange for sex?	(yes) (no)
Yourself received money, drugs, or items in exchange for sex?	(yes) (no)
Had sex with someone who injects drugs?	(yes) (no)

Had sex with someone who is HIV positive status? (yes) (no)
Had sex with someone who you did not know their HIV status? (yes) (no)

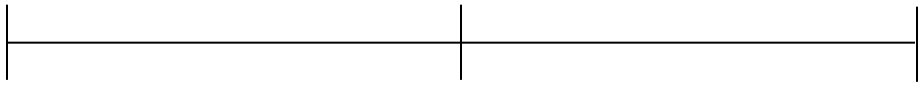
7. How frequently did you know the HIV status with partners before having sex in the past three months?
(never)
(sometimes)
(usually)
(always)

8. We are interested in your condom use if you had anal sex with someone where you did not know their HIV status or that you knew their status was HIV positive.
How frequently did you condoms (these) partners in the <u>past 3 months</u> when
8a. having Anal insertive (your penis in them) sex



0 **50** **100**
Never **Half of the time** **All the Time**

8b. when having anal receptive (their penis in you) sex



0 **50** **100**
Never **Half of the time** **All the Time**

9. Other

10. Did you inject drugs? (yes) (no)
10a. If you inject, did you share needles?
(not applicable)
(never)
(sometimes)
(usually)
(always)

11. In the past three months did you meet a sex partner through any of the following ways (check none or all that apply)

- None
- Internet
- Mobile applications
- Bath house
- Bar
- Sex Party
- Other

12. Now we want you to think about just the last month. How many male or transgender sex partners did you have in the past one month by status:

# of HIV negative (you know status because you discussed) _____
# of HIV positive (you know status because you discussed) _____
# of HIV unknown (you did not discuss HIV status) _____

13. Please estimate the number of sex acts you have with those partners that were HIV positive or unknown status:

# of unprotected anal receptive (their penis in you) acts _____
# of unprotected anal insertive (your penis in them) acts _____
# of unprotected oral sex acts _____

iPad Header: **PrEP Adherence**	*Assay*: **ACTG 4-day recall**	*# of Questions*:	*Time:*

Instructions: Most people with HIV have many pills to take at different times during the day. Many people find it hard to always remember pills:

- Some people get busy and forget to take their pills with them.

- Some people find it hard to take their pills according to all the instructions, such as “with food”, “on an empty stomach”, “every 8 hours”, or “with plenty of fluids”.
- Some people choose to skip pills to avoid side effects or to just not be taking pills that day.

We need to understand how people on PrEP are really doing with their pills. Please tell us what you are actually doing. Don’t worry about telling us that you don’t take all your pills. We need to know what is really happening, not what you think we “want to hear.”
Complete frequency of drug

1. **How many times a day are supposed to take your PrEP medication? _____**

2. **How many pills you supposed to take when you take this drug? _____**

3. **Are you currently taking any of your PrEP medication?**

No……0
Yes……SKIP TO QUESTION 6……1

4. **Why are you not taking your PrEP medication?** (CIRCLE ALL THAT APPLY)

I wanted to avoid the side effects……1
Not having sex……2
Having sex but do not think you are at risk……3
Don’t believe in these medications……4

5. **Over the last 4 days, have you not been able to take any of your PrEP medication?**

No……SKIP TO QUESTION 7……0
Yes……1

6. **The next section of the questionnaire asks about the PrEP medication that you have not been able take taking over the <u>last four days</u>. When were not able to take your medication (check all that apply)**

Yesterday……1

Day before yesterday ((2 days ago)……2

3 days ago……3

4 days ago……4

7. **PrEP medication would best be taken at the same time every day. How closely did you take the medication at about the same time over the last four days?**

Never……0
Some of the Time……1
About Half of the Time……2
Most of the Time……3
All of the Time……4

8. **Some people find that they forget to take their pills on the weekend days. Were you not able to take any of your PrEP medication last weekend—last Saturday and Sunday?**

No……0
Yes……1

9. **Including the four days you just described, when was the last time you were not able to take your PrEP medication?**

Never missed PrEP medication……0
More than 3 Months Ago……1
1—3 Months Ago……2
2—4 Months Ago……3
1—2 Weeks Ago……4
Within the Past Week……5

Instructions: For participant to complete questions 12 and 13.

10. **People may miss taking their medications for various reasons. Here is a list of possible reasons why you may miss taking your medications. How often have you missed taking your medications because you:**

		Never	Rarely	Sometimes	Often
A.	**Were away from home?**	**1**	**2**	**3**	**4**
B.	**Were busy with other things?**	**1**	**2**	**3**	**4**
C.	**Simply forgot?**	**1**	**2**	**3**	**4**
D.	**Had too many pills to take?**	**1**	**2**	**3**	**4**
E.	**Wanted to avoid side effects?**	**1**	**2**	**3**	**4**
F.	**Did not want others to notice you taking medication?**	**1**	**2**	**3**	**4**
G.	**Had a change in daily routine?**	**1**	**2**	**3**	**4**
H.	**Felt like the drug was toxic/harmful?**	**1**	**2**	**3**	**4**
I.	**Fell asleep/slept through dose time?**	**1**	**2**	**3**	**4**
J.	**Felt sick/ill from side effects?**	**1**	**2**	**3**	**4**
K.	**Felt depressed/overwhelmed?**	**1**	**2**	**3**	**4**
L.	**Had problem taking pills at specified time (with meals, on empty stomach, etc.?)**	**1**	**2**	**3**	**4**
M.	**Lost medications?**	**1**	**2**	**3**	**4**
N.	**Could not obtain medications?**	**1**	**2**	**3**	**4**
O.	**Did not have sex with a HIV positive person**	**1**	**2**	**3**	**4**

P.	**Did not have sex with anyone unknown status**	**1**	**2**	**3**	**4**
Q.	**Did not have sex with anyone**	**1**	**2**	**3**	**4**

11. **In the last 30 days, how good a job did you do at taking Truvada for PrEP in the way you were supposed to?**
    - o Very poor
    - o Poor
    - o Fair
    - o Good
    - o Very good
    - o Excellent

12. **In the last 30 days, how often did you take Truvada for PrEP in the way you were supposed to?**
    - o Never
    - o Rarely
    - o Sometimes
    - o Usually
    - o Almost always
    - o Always

13. **In the last 30 days, how hard was it for you to take Truvada for PrEP in the way you are supposed to?**

    - o Extremely hard
    - o Very hard
    - o Somewhat hard
    - o Not very hard
    - o Not hard at all

iPad Header: **4 week medication recall**	*Assay*: **Ira Wilson**	*# of Questions*:	*Time:*

Instructions: Please select the most appropriate answer.

1. Thinking about the past 4 weeks, on average, *how would you rate your ability to take* all of your PrEP medication as your doctor prescribed them?

o Very poor
o Poor
o Fair
o Good
o Very good
o Excellent

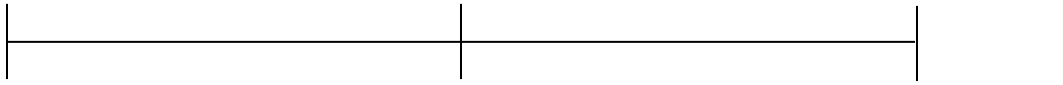
2. Thinking about the past 4 weeks, *how often did you take* all of your PrEP medication as your doctor prescribed them?

o None of the time
o A little of the time
o A good bit of the time
o Most of the time
o All of the time

3. Thinking about the past 4 weeks, *what percent of the time* were you able to take all your PrEP medications as your doctor prescribed them?

0 / 10 / 20 / 30 / 40 / 50 / 60 / 70 / 80 / 90 / 100

4. Place your finger on the bar and slide to the right to indicate your level of adherence over the past 4 weeks. Zero percent means you have taken no antiretroviral medications, 50% means you have taken half of your antiretroviral medications, 100% means you have taken every single dose of your antiretroviral medications during the past 4 weeks.



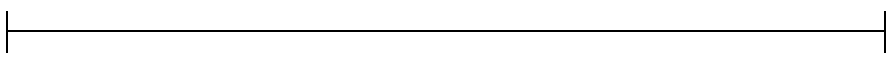
0 **50** **100**
Never **Half of the time** **All the Time**

5. Thinking about the past 7 days, *how many Truvada pills did you take*?

o All of my pills every day
o Most of my pills
o About one-half of my pills
o Very few of my pills
o None of my pills

iPad Header: **Adherence Scale**	*Assay*: **VAS; Intention**	*# of Questions*:	*Time:*

Instructions: Please put a mark on the line below indicating what percentage of the time over the <u>past 4 weeks you took your</u> PrEP medication exactly as prescribed on the pill bottle.

1. 

0 **100**

Never **All the time**

Instructions: Score | | | |

2. **Adherence Aids. Which of the following devices have you used to help you remember to take your PrEP medication:**

Not used; No devices 0
Alarm/watch 1
Calendar 2
"Post-it" reminder pad 3
Pill box 4
iTAB texting reminders 5
Other mobile phone reminder (e.g. phone app.) 6
Other—explain: 7
Other—explain: 8

Instructions: Please put a mark on the line below indicating what percentage of the time over the next 4 weeks you INTEND to take your PrEP medication exactly as prescribed on the pill bottle.

1. |——————————————————————|

0 **100**

Never **All the time**

INSTRUCTIONS TO CLINICIAN: Score: | | | |

Instructions: Please put a mark on the line below indicating what percentage of the time over the next 4 weeks you think you will actually take your PrEP medication exactly as prescribed on the pill bottle.

1. |——————————————————————|

0 **100**

Never **All the time**

INSTRUCTIONS TO CLINICIAN: Score:

iPad Header: **Mood Scale**	*Assay*: **PHQ9**	*# of Questions*:	*Time:*

TOTAL

Instructions: Over the last 2 weeks how often have you been bothered by any of the following problems?

		NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
1.	**Little interest or pleasure in doing things**	**0**	**1**	**2**	**3**
2.	**Feeling down, depressed, or hopeless**	**0**	**1**	**2**	**3**
3.	**Trouble falling or staying asleep, or sleeping too much**	**0**	**1**	**2**	**3**
4.	**Feeling tired or having little energy**	**0**	**1**	**2**	**3**
5.	**Poor appetite or overeating**	**0**	**1**	**2**	**3**
6.	**Feeling bad about yourself — or that you are a failure or have let yourself or your family down**	**0**	**1**	**2**	**3**
7.	**Trouble concentrating on things, such as reading the newspaper or watching television**	**0**	**1**	**2**	**3**
8.	**Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual**	**0**	**1**	**2**	**3**
9.	**Thoughts that you would be better off dead or of hurting yourself in some way**	**0**	**1**	**2**	**3**

		NOT DIFFICULT AT ALL	SOMEWH AT DIFFICULT	VERY DIFFICULT	EXTREMELY DIFFICULT
10.	**If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people**	**0**	**1**	**2**	**3**

iPad Header: **Alcohol Use**	*Assay*: **AUDIT**	*# of Questions*:	*Time:*

Instructions: These are some questions about your use of alcoholic beverages during the past year. By alcoholic beverages we mean beer, wine, or liquor (vodka, whiskey, brandy, etc.).

1. How often do you have a drink containing alcohol?

Never……0
Monthly or less……1
2 to 4 times a month……2
2 to 3 times a week……3

4 or more times a week.....4

2. How many drinks of alcohol do you have in a typical day when you are drinking?

1 or 2.....0
3 or 4.....1
5 or 6.....2
7, 8 or 9.....3
10 or more.....4

3. How often do you have six or more drinks on one occasion?

Never.....0
Less than monthly.....1
Monthly.....2
Weekly.....3
Daily or almost daily.....4

4. How often during the last year have you found that you were unable to stop drinking once you had started?

Never.....0
Less than monthly.....1
Monthly.....2
Weekly.....3
Daily or almost daily.....4

5. How often during the last year have you failed to do what was normally expected from you because of drinking?

Never.....0
Less than monthly.....1
Monthly.....2
Weekly.....3
Daily or almost daily.....4

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

Never.....0
Less than monthly.....1
Monthly.....2
Weekly.....3
Daily or almost daily.....4

7. How often during the last year have you had a feeling of guilt or remorse after drinking?

Never.....0
Less than monthly.....1
Monthly.....2
Weekly.....3
Daily or almost daily.....4

8. How often during the past year have you been unable to remember what happened the night before because you had been drinking?

Never 0
Less than
monthly.....1
Monthly 2

Weekly 3
Daily or almost
daily.....4

9. Have you or someone else been injured as a result of your drinking?

No 0
Yes, but not in the last year 2
Yes, during the last year 4

10. 10. Has a relative, friend, doctor, or other health worker been concerned about your drinking or suggested you cut down?

No 0
Yes, but not in the last year 2
Yes, during the last year.....4

iPad Header: **Drug Use**	*Assay*: **DAST-10**	*# of Questions*:	*Time:*

Instructions: The following questions concern your use of any illicit drug (e.g. methamphetamine, marijuana, non-prescription opiate, cocaine) during the past 12 months. Carefully read each statement and decide if your answer is "Yes" or "No". Then, circle the appropriate response “0” for “No” or “1” for “Yes”.

Please answer every question. If you have difficulty with a statement, then choose the response that is mostly right.

THESE QUESTIONS REFER TO THE PAST 12 MONTHS	**NO**	**YES**
1. Have you used drugs other than required for medical reasons?	**0**	**1**

2.	**Do you abuse more than one drug at a time?**	**0**	**1**
3.	**Are you always able to stop using drugs when you want to?**	**0**	**1**
4.	**Have you had "blackouts" or "flashbacks" as a result of drug use?**	**0**	**1**
5.	**Do you ever feel bad or guilty about your drug use?**	**0**	**1**
6.	**Does your spouse/partner (or parents) ever complain about your involvement with drugs?**	**0**	**1**
7.	**Have you neglected your family because of your use of drugs?**	**0**	**1**
8.	**Have you engaged in illegal activities in order to obtain drugs?**	**0**	**1**
9.	**Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking drugs?**	**0**	**1**
10.	**Have you had medical problems as a result of your drug use (e.g., memory loss, hepatitis, convulsions, bleeding, HIV, etc.)?**	**0**	**1**

iPad Header: **Drug Use**	*Assay*: **SCID Screen**	*# of Questions*:	*Time:*

Instructions: Please select the most appropriate answer.

1. Alcohol	No	Yes ≥ 5x	Yes ≤ 4x
2. Tobacco (e.g., cigarettes, cigars, chew, snuff)	No	Yes ≥ 5x	Yes ≤ 4x
3. Marijuana	No	Yes ≥ 5x	Yes ≤ 4x
4. Cocaine / Crack	No	Yes ≥ 5x	Yes ≤ 4x
5. Methamphetamine (i.e., crystal meth, ice glass)	No	Yes ≥ 5x	Yes ≤ 4x
6. Other Stimulants (e.g., amphetamines, ritalin)	No	Yes ≥ 5x	Yes ≤ 4x
7. Heroin	No	Yes ≥ 5x	Yes ≤ 4x
8. Other opioids (e.g., vicodin, oxycontin)	No	Yes ≥ 5x	Yes ≤ 4x
9. Sedatives (e.g., rohypnol, GHB, Quaaludes, etc.)	No	Yes ≥ 5x	Yes ≤ 4x
10. Antianxiety drugs (e.g., valium, Xanax, ativan)	No	Yes ≥ 5x	Yes ≤ 4x
11. Hallucinogens (e.g., LSD, mushrooms, acid, etc.)	No	Yes ≥ 5x	Yes ≤ 4x
12. Dissociative drugs (e.g., PCP, angel dust, ketamine)	No	Yes ≥ 5x	Yes ≤ 4x
13. Inhalants (e.g., nitrous oxide, gasoline, glue, whippits, etc.)	No	Yes ≥ 5x	Yes ≤ 4x
14. Poppers (e.g., amyl nitrate, butyl nitrate)	No	Yes ≥ 5x	Yes ≤ 4x
15. Ecstasy (i.e., MDMA, E, X)	No	Yes ≥ 5x	Yes ≤ 4x
16. Other:_____	No	Yes ≥ 5x	Yes ≤ 4x

iPad Header: **Access to care**	*Assay*: **Modified USC**	*# of Questions*:	*Time:*

Instructions: Please select the most appropriate answer.

1. When was the last time you went to a doctor?

___ Less than 3 months ago
___ 3—6 months ago
___ 6—12 months ago
___ More than a year ago

2. Has anyone helped you get into medical care? (check all that apply)

1 Nobody
2 Counselor, social worker, case manager, or other lay professional
3 Doctor, nurse, or other health care professional
4 Partner (boyfriend/husband, girlfriend/wife)
5 Family member
6 Friend
0 Don't want to answer

Barriers to Medical Care

3. Which of the following are barriers that make it difficult for you to make an appointment and see a doctor? (check all that apply)

a. Don't know how
b. My other health problems interfere
c. I don't have transportation
d. Takes too much time
e. I forget
f. Other things are more important
g. I don't think it will improve my health
h. Costs too much
i. I am worried about what other people will think or that they will judge me
j. I had a bad experience at an HIV clinic
k. I don't trust the medical system
l. I prefer alternative treatments
m. The clinic is too busy (no appointments available)
n. Worries about immigration status or deportation

4. If you have any prescription medication which of the following are barriers that make it difficult for you to take any of your MEDICATIONS? (check all that apply)

a. Don't take any medications

b. My other health problems interfere
c. I don't have transportation
d. Takes too much time
e. I forget
f. Other things are more important
g. I don't think it will improve my health
h. Costs too much
i. I am worried about what other people will think or that they will judge me.
j. I had a bad experience at an HIV clinic
k. I don't trust the medical system
l. I prefer alternative treatments
m. The pharmacy is too busy
n. Worries about immigration status or deportation
o. Don't know how

5. Have you experienced any of the following fears or concerns when trying to receive health care? (check all that apply)

a. Fears that people would find out about HIV risk behavior
b. Worries that people would find out about your sexual orientation.
c. Worries that family members or partners would be upset
d. Worries that family members or partners would be upset
e. Fears that children would be taken away
f. Concerns that health care providers would ask uncomfortable questions
g. Worries that providers would ask about drug abuse
h. Worries that providers would ask about sexual practices
i. Worries about being judged by hospital staff

Potential Facilitators to Care

6. Which of the following would help you make and keep an appointment with a doctor? (check all that apply).

a. Money, e.g. $20 at each visit
b. Food, e.g. a bag of groceries at each visit
c. Long term housing
d. Free cell phone service
e. Transportation to medical care
f. I don't need any incentives
g. TEXT message reminders
h. Phone call reminders
i. Other: _____

7. Which of the following would help you get and take your medications? (check all that apply)

a. Don't take medications
b. Money, e.g. $20 at each visit
c. Food, e.g. a bag of groceries at each visit
d. Long term housing
e. Free cell phone service
f. Transportation to medical care
g. I don't need any incentives
h. TEXT message reminders
i. Phone call reminders
j. Other: _____

iPad Header: **Social Support**	*Assay*:	*# of Questions*:	*Time:*

Instructions: For the next set of questions, please think about the different types of support you may receive. Please indicate how much you agree or disagree with the following statements.

1. There is no one I can talk to about the important decisions in my life. (Choose one)

1 Strongly agree
2 Agree somewhat
3 Disagree somewhat
4 Strongly disagree
8 Prefer Not to Answer

2. I feel no one respects who I am. (Choose one)
1 Strongly agree
2 Agree somewhat
3 Disagree somewhat
4 Strongly disagree
8 Prefer Not to Answer

3. No one really understands my most private worries and fears. (Choose one)
1 Strongly agree
2 Agree somewhat
3 Disagree somewhat
4 Strongly disagree
8 Prefer Not to Answer

4. There is no one I can depend on to lend me $50 if I needed it for an emergency. (Choose one)
1 Strongly agree
2 Agree somewhat
3 Disagree somewhat
4 Strongly disagree
8 Prefer Not to Answer

5. I often feel isolated and alone. (Choose one)
1 Strongly agree
2 Agree somewhat
3 Disagree somewhat
4 Strongly disagree
8 Prefer Not to Answer

Cell Phone Questions at baseline

1. Do you have a cell phone?
a. Yes
b. No

2. Does your cell phone have the ability to send/receive text message?
a. Yes
b. No
c. Not sure

2a. If yes, do you send text messages?
a. Yes
b. No

ii. About how often?

a. Hourly
b. Daily
c. Weekly
d. Monthly
e. Less than monthly

2b. If yes, do you receive text messages?
a. Yes
b. No
ii. About how often?
a. Hourly
b. Daily
c. Weekly
d. Monthly
e. Less than monthly

3. Does your cell phone have the ability to send/receive instant messages? (ex. Yahoo messenger, MSN messenger, or Google chat)
a. Yes
b. No
c. Not sure

3a. If yes, do you send instant messages?
a. Yes
b. No
ii. About how often?
a. Hourly
b. Daily
c. Weekly
d. Monthly
e. Less than monthly
3b. If yes, do you receive instant messages?
a. Yes
b. No
ii. About how often?
a. Hourly
b. Daily
c. Weekly
d. Monthly
e. Less than monthly
4. Can your cell phone run applications (apps)?
a. Yes
b. No
c. Not sure

4a. If yes, do you use them?
a. Yes

b. No

5. Can your cell phone access the internet?
a. Yes
b. No
c. Not sure

5a. If yes, do you ever browse the internet or use search engines on your phone?
a. Yes
b. No

6. Does your cell phone have the ability to send/receive email?
a. Yes
b. No
c. Not sure

6a. If yes, do you send emails on your phone?
a. Yes
b. No

6b. If yes, do you receive emails on your phone?
a. Yes
b. No

7. How long have you had the same cell phone number?
a. 0-3 months
b. 3-6 months
c. 6 months – 1 year
d. 1-5 years
e. More than 5 years

8. Has your cell phone service been disconnected in the last 6 months?
a. Yes
b. No

iPad Header: **Sexual Desire**	*Assay*: **Kalichman**	*# of Questions*:	*Time:*

	NOT AT ALL LIKE ME	**SOMEWHAT LIKE ME**	**OFTEN LIKE ME**	**VERY MUCH LIKE ME**
1. I like wild "uninhibited" sexual encounters.	**1**	**2**	**3**	**4**

2.	**The physical sensations are the most important thing about having sex.**	**1**	**2**	**3**	**4**
3.	**I enjoy the sensations of intercourse without a condom.**	**1**	**2**	**3**	**4**
4.	**My sexual partners probably think I am a "risk taker".**	**1**	**2**	**3**	**4**
5.	**When it comes to sex, physical attraction is more important to me than how well I know the person.**	**1**	**2**	**3**	**4**
6.	**I enjoy the company of "sensual" people.**	**1**	**2**	**3**	**4**
7.	**I enjoy watching "X-rated" videos.**	**1**	**2**	**3**	**4**
8.	**I have said things that were not exactly true to get a person to have sex with me.**	**1**	**2**	**3**	**4**
9.	**I am interested in trying out new sexual experiences and sensations.**	**1**	**2**	**3**	**4**

iPad Header:	*Assay*: **iTAB PrEP Feedback**	*# of Questions*:	*Time:*

Scale #1-3

(1) Extremely unsatisfied

(2) Somewhat unsatisfied

(3) Neither unsatisfied nor satisfied

(4) Somewhat satisfied

(5) Extremely satisfied

1. How would you rate your overall satisfaction of participating in this study?
2. How satisfied were you with the medication education that you received at your first study visit?
3. Overall, how satisfied were you with the text messaging intervention?

Scale #4-11

(1) Not helpful

(2) A little helpful

(3) Somewhat helpful

(4) Very helpful

(5) Extremely helpful

4. How helpful was participating in this study?
5. How helpful was the medication education that you received at your first study visit?
6. How helpful was the overall text messaging intervention for your medication adherence?
7. How helpful were the text messages that reminded you to take your medications?
8. How helpful were the text messages that praised you for taking your medications?
9. How helpful were the text messages that asked you why you missed a medication dose?
10. How helpful were the text messages that told you how adherent you were in the past week?
11. How helpful were the text messages that told you how adherent you would be when you took your next dose?

Scale #12-13

(1) Not at all

(2) A little bit

(3) Moderately

(4) Quite a bit

(5) Very much

12. Overall, this experience was pleasant.

13. A text messaging intervention could be helpful to me in the future.

Scale #14-15

(1) Strongly disagree

(2) Disagree

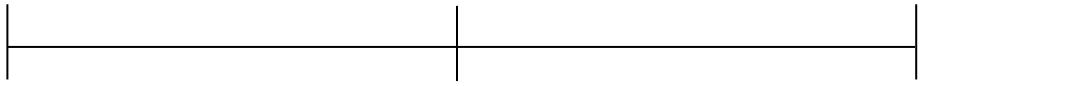
(3) Neither disagree nor agree

(4) Agree

(5) Strongly agree

14. I would use a test messaging intervention like this again.
15. I would opt to continue receiving the text message intervention if offered.

16. Place your finger on the bar and slide to the right to indicate how effective you think PrEP is in preventing HIV. Zero percent means PrEP will not prevent HIV infection and 100% means PrEP will always prevent HIV infection.



0	50	100
Never	Half of the time	All the Time

16.0 APPENDICES

APPENDIX III: VITAMIN D SUB-STUDY PROTOCOL

Effect of Vitamin D Supplementation on Bone Turnover Markers during Tenofovir-Emtricitibine Pre-Exposure Prophylaxis in Men Who Have Sex with Men

A Sub-study of CCTG 595

California Collaborative Treatment Group (CCTG)

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Substudy Version 1.0
3 September 2014

CONTENTS

SITES PARTICIPATING IN THE STUDY

University of California at San Diego (UCSD)
University of Southern California (USC)
Harbor-University of California at Los Angeles (UCLA) Medical Center

GLOSSARY OF TERMS

AE	adverse event
AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy or treatment
ARV	antiretroviral or antiretroviral drug
BMD	bone mineral density
BTM	bone turnover marker
CCTG	California Collaborative Treatment Group
CDC	Centers for Disease Control and Prevention
CrCl	creatinine clearance
CRF	case report form
CTX	C-terminal telopeptide or carboxy-terminal collagen crosslinks (a marker of bone resorption)
CVD	cardiovascular disease
DAERS	DAIDS Adverse Event Reporting System
DHHS	Department of Health and Human Services (US)
EAE	expedited adverse event
EC	ethics committee
FDA	Food and Drug Administration (US)
FTC	emtricitabine
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
IRB	institutional review board
ITT	intent to treat
IU	international unit
LFT	liver function tests

MI	myocardial infarction
MVI	multivitamin
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
P1NP	total procollagen type 1 N-terminal propeptide (a marker of bone formation)
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
PTH	parathyroid hormone
QD	once daily
SAE	serious adverse event
SID	study identification number
SOE	schedule of events
SOP	standard operating procedure
TDF	tenofovir disoproxil fumarate (Viread)
ULN	upper limit of normal
WBC	white blood cell count
WHO	World Health Organization

SCHEMA

CCTG 595 Vitamin D Sub-study

Effect of Vitamin D Supplementation on Bone Turnover Markers during Tenofovir-Emtricitibine Pre-Exposure Prophylaxis in Men Who have Sex with Men

DESIGN	CCTG 595 is an open-label clinical trial of the effect of text messaging intervention vs. standard of care on adherence to Truvada (tenofovir-emtricitibine) as PrEP in MSM at increased risk of HIV infection. This sub-study is a matched case-control study, in which cases prospectively take vitamin D3 4000 IU/day beginning at week 24 of PrEP.
DURATION	Subjects will be followed for 6 months (24 weeks)
SAMPLE SIZE	50 eligible subjects will receive vitamin D and will be compared to 50 matched control subjects from CCTG 595 who are not participating in this sub-study.
POPULATION	HIV-negative men aged ≥18 years initiating CCTG 595, who are not taking bisphosphonates and do not have a history of osteoporosis, fragility fracture, or kidney stones, or use of tenofovir prior to entry into CCTG 595
REGIMEN	Vitamin D3 4000 IU/day from week 24 through 48 of PrEP with Truvada
ENDPOINTS	Primary endpoint will be changes in bone turnover markers from week 24 through week 48 in the vitamin D intervention group as compared to age- and BMI-matched controls
ANALYSIS	A sample size of 44 subjects per group will provide 80% power to detect a 20% change in P1NP means from week 24 through week 48 between matched cases and controls using a paired t-test with a two-sided $\alpha = 0.05$. To account for attrition, a sample size of 100 is proposed, including 50 vitamin D treated cases and 50 matched controls from CCTG 595.

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

Supplementation with vitamin D 4000 IU/day will significantly blunt the increases in BTMs that occur after initiation of PrEP with Truvada.

1.2 Primary Objective

To compare the change in P1NP levels from week 24 through week 48 among subjects (cases) who receive vitamin D 4000 IU/day to the change in levels seen in matched unsupplemented controls.

1.3 Secondary Objectives

1.3.1 To compare the change in CTX levels from week 24 through week 48 among subjects who receive vitamin D 4000 IU/day to the change in levels seen in matched unsupplemented controls.

1.3.2 To compare the change in PTH level from week 24 through week 48 among subjects who receive vitamin D 4000 IU/day to the change in levels seen in matched unsupplemented controls.

1.3.3 To compare vitamin D levels at week 48 among subjects who receive vitamin D 4000 IU/day and matched unsupplemented controls.

1.3.4 To demonstrate the change in P1NP, CTX, PTH, and vitamin D levels from baseline to week 24 in both cases and controls.

2.0 INTRODUCTION

2.1 Background and Rationale

Current HIV treatment guidelines recommend combination antiretroviral therapy with three active ARVs and 7 of the 9 currently recommended initial combination regimens for ART-naïve patients include tenofovir disoproxil fumarate (TDF) [1]. While treatment with TDF-containing antiretroviral treatment (ART) regimens have proven durable, tolerable, and effective, TDF has well described toxicities, including greater loss of bone mineral density (BMD) in the first 48 weeks after ART initiation and an increased risk for fragility fracture [2-4]. The FDA recently approved TDF given with emtricitabine (FTC) as a single daily fixed dose combination (FDC) pill (Truvada (TDF/FTC)) for Pre-Exposure Prophylaxis (PrEP) to prevent HIV acquisition for persons with increased risk for HIV infection. In studies evaluating the efficacy of TDF/FTC for PrEP, daily use has been shown to significantly reduce BMD [5,6] albeit to a lesser extent than that seen during initial treatment for HIV. Although TDF-containing PrEP has not yet been associated with increased fracture risk, reduced BMD is nonetheless a concern for patients and providers of PrEP. Thus, strategies are needed to attenuate or prevent BMD loss, particularly when TDF-containing PrEP will be given for prolonged periods of time. The mechanism by which TDF induces BMD loss is unclear but appears to be mediated

through a reduction in PTH levels and PTH-controlled calcium and phosphate metabolism [7]. Additional data from ATN 063 suggest that TDF induces a state of functional vitamin D deficiency [8]

Recently, Overton and colleagues reported a dramatic reduction in the magnitude of BMD loss during initial therapy of HIV infection with vitamin D (4000 IU/day) and calcium supplementation [9] when co-administered with efavirenz/TDF/FTC ART. The amount of BMD loss at the hip measured by DXA over 48 weeks with vitamin D-calcium was approximately half that seen with placebo (-1.5% vs. -3.2%, respectively, $p< 0.001$), and was reduced to levels that would be expected with ART that does not contain TDF. Notably, the median daily vitamin D intake was low for the cohort (120 IU/day) while calcium intake approached recommended daily intake (810mg). Thus, these data provide a strong rationale to study prophylactic administration of daily oral supplemental vitamin D in subjects receiving PrEP with Truvada.

In ACTG 5280, vitamin D-calcium supplementation prevented the increase in parathyroid hormone (PTH) and blunted the increase in bone turnover markers (BTMs), including P1NP (a marker of bone formation) and CTX (a marker of bone resorption). Importantly, there was a good correlation between changes in DXA-measured BMD over time and changes in BTMs, particularly with P1NP. The percentage change of P1NP at week 48 correlated with the percentage change in total hip BMD ($r=-0.32$, $p=0.01$) as well as the change in lumbar spine BMD ($r=-0.37$, $p=0.002$) [Overton ET, unpublished data]. Due to the difficulties and expense of performing DXA scans in a clinical trial, P1NP levels are proposed as the primary outcome measure for this pilot trial.
CCTG 595 is an open-label clinical trial of the effect of a text messaging intervention vs. standard of care on adherence to Truvada as PrEP in MSM at increased risk for HIV infection (ClinicalTrials.gov Identifier: NCT01761643). Approximately 1/3 of the planned 400 subjects have been enrolled as of April 2014. Study sites include University of California at San Diego, University of Southern California, and Harbor-UCLA Medical Center.

Rationale for use of vitamin D dose: The dose of vitamin D (4000 IU/day) in this protocol carries little risk for the study subjects. This dose was without adverse effects in a more ill population, namely the HIV-infected subjects in ACTG 5280 (see above). Generally, vitamin D supplementation is well tolerated and safe. Dosages up to 10,000 IU daily in healthy adults is considered safe and the current upper U.S. Dietary Reference Intake of 2,000 IU daily is considered to be well below the actual physiologic requirements [10,11]. The Institutes of Medicine guideline considers 4000 IU/day to be the safe upper limits for daily intake for adults http://www.iom.edu/Reports/2010/dietary-reference-intakes-for-calcium-and-vitamin-D/DRI-values.aspx. Several studies have focused specifically on the safety of chronic daily administration of 4000 IU [12-14]. In these studies, 228 adult subjects received 4000 IU/day vitamin D with excellent tolerability, no toxicity, and a concomitant increase in 25 (OH) vitamin D levels ranging from 39-51 ng/mL. No abnormalities in serum calcium or urinary calcium excretion were noted.

In this study supplemental calcium will not be used because: a) in ACTG 5280, calcium intake among untreated HIV-infected subjects was generally adequate [9]. It can be anticipated that the largely healthy HIV-uninfected subjects in CCTG 595 will have levels of intake that are higher than the diseased population in ACTG 5280. This suggests supplemental calcium will not be required for 4000 IU/d vitamin D's beneficial effects,

particularly in the CCTG 595 subjects; b) there is concern that multiple additional pills a day may influence adherence with the primary intervention used in CCTG 595.

3.0 STUDY DESIGN

CCTG 595 is an open-label clinical trial of the effect of a text messaging intervention vs. standard of care on adherence to Truvada as PrEP in MSM at increased risk for HIV infection (ClinicalTrials.gov Identifier: NCT01761643). Eligible subjects for this matched case control substudy will receive vitamin D 4000 IU/day for 24 weeks, from week 24 through week 48. In CCTG 595, plasma from participants are being collected and stored at entry and every 12 weeks. These plasma samples will be used to measure P1NP, CTX, PTH, and vitamin D levels in both cases and controls at entry, week 24, and week 48.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.1.1 All subjects must meet CCTG 595 inclusion criteria.

4.2 Exclusion Criteria

4.2.1 All subjects must meet CCTG 595 exclusion criteria.

4.2.2 Current or prior use of bisphosphonate therapy.

4.2.3 Current use of vitamin D supplements greater than 400 IU/day.

4.2.4 Current use of androgenic hormones or growth hormones.

4.2.5 History of nephrolithiasis (kidney stones).

4.2.6 History of fragility fracture.

4.2.7 No use of tenofovir prior to entry into CCTG 595

4.3 Study Enrollment Procedures

Once a candidate for study entry has been identified, details will be carefully discussed with the subject. The subject will be asked to read and sign the approved protocol consent form. Participation in this substudy is not required for continued participation in CCTG 595.

5.0 STUDY TREATMENT

5.1 Study Product Formulation and Preparation

Vitamin D capsules will be supplied as 2000 IU capsules and will be taken as two capsules once daily. Store at 15°-30°C (59°-86°F). Do not expose to excessive heat or moisture.

5.2 Concomitant Medications

All concomitant medications will be recorded on existing CRFs for CCTG 595, with particular attention to vitamin D content of dietary supplements. Use of >400 IU of vitamin D3 in any dietary supplement (such as a multivitamin) will be prohibited.

6.0 CLINICAL AND LABORATORY EVALUATIONS

These will be performed as per the main study. All assays on subjects and controls will be performed on stored samples already being collected by the main study.

The only additional evaluation that will be performed will be calculating the average daily dietary intake of vitamin D and calcium from food. The participants will be asked to recall food items eaten over the last 3 days at the week 36 visit, and the calculator used in the ACTG 5280 study, which is adopted from the USDA database, will be used to quantify vitamin D and calcium intake.

7.0 CLINICAL MANAGEMENT

Instructions are provided only for toxicities related to study therapy (vitamin D). The grading system for drug toxicities is located in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), located at the Division of AIDS Regulatory Support Center Web Site: http://RSC.tech-res.com/safetyandpharmacovigilance.

For toxicities attributed to vitamin D, investigators may discontinue therapy.

7.1 Toxicity

The general guidelines presented below apply to toxicities that are not specifically addressed in section 7.2.

Grade 1 or 2
Subjects who develop a Grade 1 or 2 AE or toxicity may continue vitamin D without alteration of the dosage. For subjects experiencing Grade 1 or 2 AEs who choose to discontinue vitamin D, the site investigator should contact the protocol chair, and encourage the subject to complete other aspects of CCTG 595.

NOTE: If subjects discontinue study therapies due to experiencing Grade 1 or 2 AEs, this should be noted in the CRF as the reason for discontinuation.

Grade 3
If the investigator has evidence that the AE was NOT caused by vitamin D, dosing may continue. Subjects who develop a Grade 3 AE or toxicity thought to be related to vitamin D, should have vitamin D withheld. The subject should be reevaluated weekly until the AE returns to Grade ≤2 or baseline, at which time the study therapies may be reintroduced, at the discretion of the site investigator or according to standard practice.

If the same Grade 3 AE recurs within 4 weeks of restarting treatment, vitamin D must be permanently discontinued. However, if the same Grade 3 AE recurs after 4 weeks, the management scheme outlined above may be repeated.

Subjects experiencing a Grade 3 AE requiring permanent discontinuation of vitamin D should be followed weekly until resolution of the AE and should be encouraged to complete the follow-up protocol study evaluations.

Grade 4
Subjects who develop a Grade 4 symptomatic AE or toxicity will have vitamin D permanently discontinued. Subjects experiencing a Grade 4 AE requiring permanent discontinuation of vitamin D should be followed weekly until resolution of the AE and encouraged to complete the follow-up protocol study evaluations.

7.2 Specific Management

7.2.1 Kidney Stones

Subjects who develop signs and symptoms consistent with urinary tract obstruction should have further evaluation. Subjects with evidence of a new kidney stone on study will be taken off vitamin D but continue to be followed on study.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Permanent Treatment Discontinuation

- Drug-related toxicity
- Requirement for prohibited concomitant medications
- Subject develops a kidney stone (see section 7.3.1).
- Completion of treatment as defined in the protocol.
- Request by subject to discontinue treatment.
- Discontinuation of PrEP for any reason
- Clinical reasons believed serious by the physician, even if not addressed in the toxicity section of the protocol.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample size justification

In ACTG 5280, administration of vitamin D-calcium resulted in a significant reduction in

the magnitude of the rise in BTMs P1NP and CTX [9]. Because of more consistent association with changes in BMD with P1NP, this will be used as the primary surrogate marker to reflect bone health. Data on TDF effects on P1NP levels in the absence of HIV infection (e.g. during PrEP) are not available. In A5280, at week 24 P1NP increased by 60% with placebo and 36% with vitamin D-calcium ($p<0.001$). If we anticipate that supplementation with vitamin D results in a decrease of similar magnitude from week 24 to week 48, then the expected intervention effect size is in the range of 24%. The SD of the change in P1NP at month 6 for the vitamin D-calcium group was 63%, but it is anticipated that the variability of P1NP levels in this study will be much less than that in HIV infected subjects undergoing a variety of pro- and anti-inflammatory changes after initiation of ART as in A5280. If we anticipate that in the absence of vitamin D supplementation that P1NP will increase by 20% and those receiving vitamin D will experience a reduction of this amount at week 48, then with an SD of the change in P1NP of 40%, a sample size of 44 cases and 44 controls will provide 80% power to detect a significant difference in the change in P1NP from week 24 to week 48 between cases and controls using a paired t-test with a two-sided $\alpha=0.05$. In order to account for attrition, a sample size of 100 is proposed, consisting of 50 vitamin D treated cases and 50 matched controls.

9.2 Analyses

All analyses are ITT, unless specified otherwise. Evaluable subjects will be individuals who agree to participate in the vitamin D substudy. The primary endpoint analysis will use a paired t-test to compare the changes in P1NP levels from week 24 to 48 weeks between cases and matched controls. Secondary endpoint analyses will include comparison of changes in 25-OH vitamin D levels, PTH, and CTX and will be analyzed analogously to the primary endpoint. If parametric assumptions fail, the corresponding non-parametric test will be applied, in this case, the Wilcoxon signed rank test. Sensitivity analyses will include linear regression models that adjust for possible confounding covariates, such as dietary intake.

Matching: Concurrent controls who are not enrolled in the vitamin D substudy who are reporting supplementation with $\leq$ 400 IU of vitamin D/day will be matched 1:1 by randomization arm in the CCTG 595 main study (text messaging arm vs. standard of care), age (± 5 years), race/ethnicity, season of study entry, and BMI (± 3 kg/m^2).

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16.0 APPENDICES

APPENDIX IV: VITAMIN D SUB-STUDY SAMPLE OF INFORMED CONSENT

CALIFORNIA COLLABORATIVE TREATMENT GROUP (CCTG)

SAMPLE INFORMED CONSENT

Study Title

CCTG 595 Substudy: Effect of Vitamin D Supplementation on Bone Turnover Markers during Tenofovir-Emtricitibine Pre-Exposure Prophylaxis in Men Who Have Sex with Men

INTRODUCTION

You are being asked to take part in this research study because you are HIV-negative and are sexually active with men and are at ongoing risk for acquiring HIV. You are taking a medication (tenofovir-emtricitibine, also known as Truvada), to reduce risk of HIV infection but which may affect your bone health.

This study is sponsored by the California HIV Research Program and receives additional funding from Gilead Sciences, the makers of Truvada. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to see if taking vitamin D will help prevent the bone loss that sometimes happens when people are taking PrEP with Truvada. The risks seen with this vitamin D treatment are the same that you would encounter when taking this dose of this vitamin outside of the study.

Vitamin D, which is a nutritional supplement important for bone health, will be provided by the study.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Screening and Entry

If you would like to be in this sub-study, you will already be participating in CCTG 595

when you are asked to participate in this substudy after you have been taking Truvada for 24 weeks. Specifically for this study:

- You will be asked questions about your medical history and any medications and vitamin/mineral supplements you are taking or have taken within the last 30 days.
- You will be asked questions about your dietary intake.
- Blood already being drawn as part of the main study will be used to measure the amount of vitamin D as well markers of bone formation and breakdown (P1NP, CTX, and PTH) in your blood. The results of these tests will not be available until after the end of the study.

If you do not enroll into the study:

If you decide not to take part in this study or if you do not meet the eligibility requirements, this will not affect your participation in the main CCTG 595 study.

Study Visits

No additional study visits are required by this sub-study. Bottles of vitamin D at a dose of 4000 units per day (supplied as two 2000 unit capsules) will be dispensed to you at your regular week 24 visit and your week 36 visit. You will be asked to bring your bottles of study medications with you to each of your regular visits.

If You Have to Stop Taking Vitamin D Early or You Have to Stop the Study Early

If you stop taking vitamin D or leave the vitamin D sub-study early due to side effects, you may be asked to come to the clinic for an additional study visit.

- You will have a brief physical exam.
- You will be asked about your health and any changes in your medicines since your last visit.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 50 people will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this sub-study for about 24 weeks (about 6 months). This will be from your regular week 24 visit until your regular week 48 visit. After completion of this sub-study, you will continue with the main study.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- You are not able to attend the study visits as required by the study.
- The study is stopped or canceled.
- You are not able to take vitamin D as required by the study.
- Your primary care physician no longer thinks that participating in the study is in your best interest.

The study doctor may also need to take you off vitamin D without your permission if:

- Continuing vitamin D may be harmful to you.
- You need a treatment that you may not take while on the study.
- You develop a fragility fracture. (A fragility fracture is a fracture that occurs after any fall from a standing height or less. Our bodies should be able to sustain a fall from this height, without a fracture, unless there is some underlying cause like osteoporosis. The spine, wrist, and hip are the most common sites for fragility fractures.)
- You develop a kidney stone.

If you must stop taking vitamin D before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

IF I HAVE TO PERMANENTLY STOP TAKING STUDY-PROVIDED VITAMIN D, OR ONCE I LEAVE THE STUDY, HOW WOULD DRUGS BE PROVIDED?

<u>During the study:</u>

If you must permanently stop taking study-provided vitamin D before your study participation is over, the study staff will discuss other options that may be of benefit to you.

<u>After the study:</u>

After you have completed your study participation, the study will not be able to continue to provide you with vitamin D that you received on the study. If continuing to take vitamin D or similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

<u>Risks of PrEP</u>

The drug used in this study, Tenofovir-Emtricitibine, also known as Truvada, may have side effects, as listed in the CCTG 595 consent form.

Risks of Vitamin D

- High calcium levels in the blood (muscle weakness, headache, indifference, loss of appetite, nausea/vomiting, bone pain, calcium deposits in the tissues of the body, kidney disease, high blood pressure, and irregular heartbeats)
- High calcium levels in urine (kidney stone disease and kidney failure)

NOTE: With the doses of vitamin D provided in the study, the risk of having high calcium in blood or urine is low.

If you have questions concerning side effects of vitamin D, please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with any of the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Participant's Legally Authorized Representative (print) (As appropriate)	Participant's Legally Authorized Representative's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date

Appendix V: Multivitamin Supplement Comparisons

	Multivitamin Supplement					
	Calcium and Vitamin D content					
References	Drug Facts and Comparisons					
	Dietary Supplements Database (http://dietarysupplements.nlm.nih.gov)					
Manufacturer/ Brand	**Product**	**servings**	**Calcium/ serving (mg)**	**VitD/serving (IU)**		
21st Century	Multi Vitamin and Multi Mineral Diabetes formula	3 tablets	1500	400.00		
4Life	CM Super Calcium & Magnesium Superiority	3 tablets	2000	400.00		
	Multiplex Vitamin & Mineral Formula	2 tablets	100	400.00		
	RiteStart Men	2 tablets	225	400.00		
	RiteStart Women	2 tablets	1100	400.00		
	Transfer Factor	2 tablets	200	400.00		
Alacer	Emergen C Immune Defense Drink Mix	1 packet	50	100.00		
	EmerGen-C Kids Multi (various flavors)	1 packet	63	400.00		
Albertsons	Calcium + D	2 tablets	1200	400.00		
Alcon	I Caps MV Major	4 tablets	330	400.00		
American Health	Chewy Bears Multi Vitamin with Calcium 250mg	2 bars	250	400.00		
	More Than a Multiple (with or without iron)	3 tablets	500	400.00		
	Nutri-Mega	2 capsules	400	400.00		
Amerifit	Estoven Plus Multi-Vitamin	1 capsule	200	1000.00		
	Estroven PM	1 capsule	60	800.00		
	Estroven Maximum Strength	1 capsule	100	400.00		
AmeriSciences	Childrens Chewable	1 tablet	20	400.00		
	Mens Master-Multi	2 packets	540	400.00		
	Osteo	1 tablet	175	300.00		
	Sleep	4 tablets	250	150.00		
	Womens Master-Multi	1 packet	585	400.00		

AN	Active Womans Formula	3 tablets	400	400.00		
	Prenatal Plus	4 tablets	800	400.00		
Anselmo	Super Multis	3 tablets	105	800.00		
Atkins	Basic 3	3 tablets	50	200.00		
	Barefoot Coral Calcium Plus	3 tablets	250	400.00		
Azur Pharm	Natalle-ez	1 tablet	100	400.00		RX only
Bayer	Citracal Plus Bone Density Builder	2 tablets	600	400.00		
	Citracal Plus Heart Health	1 tablet	315	250.00		
	Citracal UltraDense Calcium Citrate Petites	2 caplets	630	400.00		
	Citracal UltraDense Calcium Citrate Tablets	2 tablets	400	400.00		
	Citracal UltraDense Calcium Citrate Plus with Magnesium	2 tablets	500	250.00		
Belvedere	Healthy Day Multi	1 tablet	100	400.00		
	One a Day	1 tablet	20	200.00		
Bionatures	Advanced Mega Multi	6 capsules	400	400.00		
	Bone Support	3 capsules	500	200.00		
	Coral Calcium Plus - 1000mg	1 tablet	715	200.00		
Biotics	Aqueous Multi-Plus	1 tablet	25	400.00		
	Bio-Multi Plus (all types)	3 tablets	200	400.00		
BodyTech	Tech X Lite	1 packet	300	240.00		
	Tech X Mass Gainer	1 packet	500	200.00		
Breckenridge	Multifol Tablets	1 tablet	125	400.00		
	Vinate GT	1 tablet	200	400.00		RX only
	Vinate II	1 tablet	200	400.00		RX only
	Vinate-M	1 tablet	200	400.00		RX only
	Vinate Calcium	1 tablet	125	400.00		RX only
	Multifol Plus	1 tablet	100	400.00		RX only
Bronson Laboratories	Calcium 600mg with Vitamin D	4 tablets	125	500.00		
	Therapeutic Vitamin & Mineral Formula	1 tablet	100	400.00		

Brookstone	BP Prenate	1 tablet	100	425.00		RX only
Canopy Roads Pharmaceuticals	CRNatal	1 tablet	100	425.00		RX only
Carlson	Cardi-Rite	4 tablets	400	400.00		
	Kids Chewable Vitamins with Minerals	1 tablet	50	400.00		
	Liquid Cal Mag	1 gelcap	200	500.00		
	Mini-Gel Vitamins & Minerals	6 gelcaps	1000	1200.00		
	Mini-Multi Vitamins & Minerals	1 tablet	20	400.00		
	Super-1-Daily Vitamins & Minerals	1 tablet	50	400.00		
	Super-2-Daily Vitamins & Minerals	2 tablets	50	600.00		
Centrum	Regular	1 tablet	200	400.00		
	Performance	1 tablet	100	400.00		
	Silver	1 tablet	200	400.00		
	Women's Silver	1 tablet	500	800.00		
	Men's Silver	1 tablet	250	600.00		
	Chewable	1 tablet	108	400.00		
	Cardio	1 tablet	54	200.00		
	Advanced	1 tablet	162	400.00		
	Ultra Men's Formula	1 tablet	210	600.00		
	Ultra Women's Formula	1 tablet	500	800.00		
	Kids Complete Chewable (various)	1 tablet	108	400.00		
Country Life	Chewable Adult Multi	8 wafers	480	400.00		
	Daily Total One	2 wafers	40	400.00		
	Life Essential Lfe Caps	8 caps	320	400.00		
	Max for Men	4 tablets	200	400.00		
	Daily Multi Sorb	2 tablets	50	400.00		
	Liquid Multi	30ml	50	400.00		
	Life Superior Multiple	3 wafers	200	100.00		
Cyclin	VITa-PMS Plus	1 tablet	167	17.00		
Cypress	Calcium 600 with D	1 tablet	600	200.00		
	Calvite P & D	1 tablet		120.00		
	Prenatal AD	1 tablet	200	400.00		RX only
	Prenatabs CBF	1 tablet	200	400.00		RX only
	Prenatab FA	1 tablet	200	400.00		RX only
	Prenatal 19 (Regular & Chewable)	1 tablet	200	400.00		RX only
	Prenatabs OBN	1 tablet	200	400.00		RX only
	Trinate	1 tablet	200	400.00		RX

						only
	PrenaFirst	1 tablet	200	400.00		RX only
Cytosport	Cytogainer (all flaviors)	6 scoops	500	200.00		
	Muscle Milk (all flavors)	240ml	1000	600.00		
Douglas Labs	FM Support Pack	1 packet	250	50.00		
	Pro-PCA Fuel	4 scoops	250	200.00		
	Ulta-Ostivone	4 capsules	600	200.00		
ETHEX	NutriSpire Tablets	1 tablet	200	400.00		
	Prenatal MR 90 FE	1 tablet	250	400.00		RX only
	NatalCare PIC Forte	1 tablet	250	400.00		RX only
	Advanced NatalCare	1 tablet	200	400.00		RX only
	Ultra NatalCare	1 tablet	200	400.00		RX only
	NatalCare GlossTabs	1 tablet	200	400.00		RX only
	Advanced-RF NatalCare	1 tablet	200	400.00		RX only
	Prenatal Z Advance formula	1 tablet	200	400.00		RX only
	Prenatal RX 1	1 tablet	200	400.00		RX only
	NataTab CFe	1 tablet	200	400.00		RX only
	NataTab FA	1 tablet	200	400.00		RX only
	CareNatal DHA	1 tablet	200	400.00		RX only
	NatalCare Three	1 tablet	200	400.00		RX only
	Prenatal MTR with Selenium	1 tablet	200	400.00		RX only
	NatalCare Plus	1 tablet	200	400.00		RX only
	NatalCare PIC	1 tablet	125	400.00		RX only
	Cal-Nate	1 tablet	125	400.00		RX only
	NatalCare RX	1 tablet	100	200.00		RX only
Everett	Vitafol Caplets	1 caplet	125	400.00		
	Vitafol-PN Caplets	1 caplet	125	400.00		
	Vitafol-OB Caplets	1 caplet	125	400.00		
	Calcifolic-D Wafers	1 wafer	125	300.00		
	Vitafol-OB+DHA	1 tablet	100	400.00		Rx

Freeda	Yelets Teenage Formula	1 tablet	60	400.00		
	Monocaps	1 tablet	50	400.00		
	Vitalets Chewables	1 tablet	80	200.00		
	Quintabs-M	1 tablet	30	400.00		
	Ultra-Freeda with Iron	1 tablet	83	133.00		
	Ultra-Freeda	1 tablet	83	133.00		
	Fem-Cal	1 tablet	80	100.00		
	Fem-Cal Citrate	1 tablet	60	80.00		
	KPN Prenatal with Extra Calcium	1 tablet	333	133.00		
	A-Free Prenatal	1 tablet	333	133.00		
Future Biotics	Calcium Essentials	6 caps	900	100.00		
	Hair Skin and Nails	6 tablets	1200	400.00		
	MV Teen	3 capsules	100	400.00		
	PMSharmony	8 tablets	600	200.00		
	Pressure Lo	4 tablets	1000	300.00		
	Vegetarian Super Multi	6 tablets	400	400.00		
	Vitomegamen	3 tablets	100	400.00		
	Vitomegawomen	3 tablets	100	400.00		
GNC	ActiveCal	2 tablets	1000	200.00		
	Calcimate Plus 800mg	4 caps	800	800.00		
	Calcium Citrate Plus 800	2 caps	400	400.00		
	Chewable Calcium 600	1 tablet	600	200.00		
	Coral Calcium	4 capsules	800	400.00		
	Kids Multibite Plus minerals Chewable	2 tablets	30	400.00		
	Kids Vitamin Chews	1 tablet	150	400.00		
	Mega Men Sport	4 capsules	400	400.00		
	Mega Teen	3 tablets	100	400.00		
	Mens Mega Men	4 tablets	400	400.00		
	Mens Mega Men 50 PLUS	2 capsules	200	400.00		
	Men's Mega Multi Time Release	2 tablets	200	1600.00		
	Multi Mega Minerals	2 tablets	1000	400.00		
	Multi-Gel	2 gelcaps	200	400.00		
	Natural Brand Fantastic Fiber	10gm	250	400.00		
	Preventron	4 tablets	60	400.00		
	Solotron (with or without)	1 tablet	60	400.00		
	Solotron Platinum	2 tablets	200	400.00		
	Teen Chewable Mega Teen	2 tablets	100	400.00		
	Ultra Mega Gold (with or without iron)	2 tablets	100	400.00		
	Ultra Mega Green	2 capsules	50	400.00		
	Ultra Mega Timed Release	2 tablets	100	400.00		
	Ultra Mega Two Timed Release (with or without iron)	2 tablets	50	400.00		
	Women's Mega Multi Time Release	2 tablets	200	1600.00		

	Women's Prenatal without Iron	2 tablets	500	400.00		
	Womens Ultra Mega	2 capsules	500	400.00		
Garden of Life	Living Calcium Advanced	3 capsules	500	300.00		
	Living Multi Optimal Womens formula	6 capsules	400	200.00		
	Vitamin Code 50 & Wiser Women	4 capsules	50	1000.00		
	Vitamin Code Men	4 capsules	20	400.00		
GlaxoSmithKline	Geritol Complete	1 tablet	148	400.00		
	Fiber Choice Chewable	1 tablet	100	50.00		
	Os-Cal Ultra	1 caplet	600	500.00		
	Os-Cal Chewable	1 caplet	500	600.00		
	Oscal-D	1 caplet	500	200.00		
	Oscal Extra D	1 caplet	500	600.00		
	Oscal 500 + D	1 tablet or 1 chewable	500	400.00		
Goldline	Therapeutic Tablets	1 tablet	400	400.00		
	Calcarb 600 with Vitmain D	1 tablet	600	200.00		
	Oyst-Cal-D	1 tablet	200	125.00		
	Health HNS Fat Cutter	4 tabs	600	400.00		
	Healthy N Fit Nutri Pack	1 tablet	1000	400.00		
Hawthorne	ICAR Prenatal Therapy	1 tablet	600	200.00		RX only
Health Sense	Once Daily	1 tablet	400	400.00		
	Complete Senior	1 tablet	200	400.00		
Hero Nutritionals	Vegetarian Calcium with Vitamin D	1 gummie	125	100.00		
Integrative Therapeutics	Vitaline Total Formula 3	1 tablet	500	400.00		
Integrity	Stuart Prenatal	1 tablet	200	400.00		RX only
Irwin Naturals	Kids Supervitamin	1 softchew	150	400.00		
	Super Calcium	3 capsules	1000	400.00		

	Mens Living Green Lig-Gel Multi	3 gelcaps	50	400.00		
	Liqui-Gel Multi	4 capsules	100	200.00		
Ivax	Certagen Tablets	1 tablet	162	400.00		
	One-Tablet-Daily with Minerals	1 tablet	162	400.00		
	Generix-T	1 tablet	58	400.00		
	Prenatal S	1 tablet	200	400.00		
Jarrow Formulas	All Capsule Health Pak	1 packet	500	200.00		
	Bone-Up	6 capsules	1000	400.00		
KAL	Enhanced energy	3 tablets	300	400.00		
	Amino-Max	2 tablets	1000	200.00		
	Beyond Calcium Ipriflavone	5 tablets	1000	400.00		
	Bone Meal	4 tablets	1000	400.00		
	Cal Citrate Plus	4 tablets	1000	400.00		
	Enhanced Energy Teen Complete	1 tablet	100	400.00		
	High Potency Soft Multiple	2 capsules	200	400.00		
	Mega Vita-Min	1 tablet	50	400.00		
	Multi-Four Plus	4 tablets	500	400.00		
	Multi-Max 1	1 tablet	50	400.00		
	Multiple Energy	4 tablets	500	400.00		
	MultiSaurus DinoSours	1 packet	50	200.00		
	Vita Mom Advanced	3 tablets	600	200.00		
Kenwood/Bradley	Kenwood Therapeutic Liquid	5ml	250	133.00		
Kirkland Signature	Calcium 500mg + D	2 tablets	1000	400.00		
	Calcium Chews 500mg + D + K	2 chews	1000	400.00		
	Calcium Citrate, vitamin D, Magnesium & Zinc	2 tablets	500	250.00		
	Childrens Chewable Multivitamin	1 tablet	200	400.00		
	Daily Multivitamin Pack with Energy Boosting Nutrients	1 pack	1200	400.00		
	Daily Multivitamin with Lutein	1 tablet	162	400.00		
	Mature Multi Vitamins & Minerals	1 tablet	200	400.00		
	Premium Performance Multivitamin with Lycopene & Lutein	1 tablet	165	400.00		
Laser	Lactocal-F	1 tablet	200	400.00		RX only
Leiner	One Daily Mens Health Formula	1 tablet	210	400.00		

Life Enhancements	3-way Calcium complex (Womens Health)	2 capsules	500	400.00		
	BioEnhance with DNAble	4 capsules	1000	50.00		
Life Extension	Childrens Formula Life Extension Mix	2 tablets	100	400.00		
	Mix with Extra Niacin Without Copper	4 tablets	100	400.00		
	LifePlus Daily Biobasics	1 scoop	500	300.00		
	Liquimins Ca; Mag Zinc	1.25ml	1200	400.00		
	Longs Womnes Multivitamin/Multimineral.Herbs	2 tablets	500	400.00		
	MD Select Advanced Breast support	2 capsules	225	400.00		
Major	Certavite with Lutein	1 tablet	162	400.00		
	Certavite with Lutein	1 tablet	160	400.00		
	High Potency	1 tablet	60	400.00		
	Thera	1 tablet	400	400.00		
	Calcium 600-D	1 tablet	600	200.00		
	Oyster Shell Calcium 500 + D	1 tablet	500	200.00		
	Oyster Shell Calcium with D	1 tablet	400	125.00		
	Prenatal Plus	1 tablet	200	400.00		
Marmel	Marnatal-F Plus	1 tablet	250	400.00		RX only
McNeil	Viactiv	1 caplet	200	400.00		
	Viactiv for Teens	1 tablet	500	200.00		
	Viactiv Calcium plus Vitamin D and K	1 chew	500	100.00		
	Viactiv Flavor Glides	1 glide	500	100.00		
	Viactiv Multi Vitamin Flavor Glides	1 glide	200	400.00		
	Viactiv Multivitamin Chocolate Milk	8oz	200	400.00		
Michaels Neuropathic	Childrens Chewables	4 wafers	200	400.00		
	JUST ONE Multivitamin	1 tablet	50	400.00		
	Vision Factors	6 tablets	150	100.00		
Miller	Ragus	1 tablet	193	133.00		
	Complere	1 tablet	150	133.00		
	Sclerex	1 tablet	8	67.00		

	Theramill Plus	1 tablet	67	33.00		
	Theramill Forte	1 capsule	67	33.00		
Mission	Calcet Plus	1 tablet	160	400.00		
	Fosfree	1 tablet	175	150.00		
	Citracal	1 caplet	315	200.00		
	Citracal Plus	1 caplet	300	125.00		
	Calcet	1 tablet	200	100.00		
	Citracal Prenatal 90 + DHA	1 tablet	200	400.00		RX only
	CitraNatal 90 DHA	1 tablet	200	400.00		RX only
	Citracal Prenatal + DHA	1 tablet	125	400.00		RX only
	CitraNatal DHA	1 tablet	125	400.00		RX only
	CitraNatal Rx	1 tablet	125	400.00		RX only
	Prenatal F.A	1 tablet	50	400.00		
	Prenatal HP	1 tablet	50	400.00		
	Prenatal	1 tablet	50	400.00		
Natrol	My Favorite Multiple	4 tablets	200	400.00		
	My Favorite Multiple with Coral Calcium and Zeanthin	2 capsules	250	400.00		
Naturade	Head Start Nutritional Breakfast drink	240ml	200	100.00		
	Power Shake	1 scoop	280	400.00		
	Ribo-tein Vital	1 scoop	280	400.00		
	Super Weight Gain	4 scoops	30	200.00		
Natural Factors	Big Friends Childrens Chewable (various flavors)	1 tablet	65	400.00		
	Calcium & Magnesiuim Citrate with D	4 tablets	1000	400.00		
	Mens 50 Plus MultiStart	4 tablets	400	200.00		
	Mens MultiStart	4 tablets	400	100.00		
	MulitFactors Womens 50 Plus	3 Capsules	200	1000.00		
	MultiStart prenatal	3 capsules	500	50.00		
	Super Multi Iron Free	1 tablet	125	400.00		
	Ultra Multi Plus	1 tablet	125	400.00		
	Womens MultiStart	3 tablets	500	200.00		
	Womens Plus MultiStart	3 tablets	500	200.00		
Nature Made	Women's Multi for Her	1 tablet	250	1000.00		
	Men's Multi for Him	1 tablet	162	1000.00		
	Women's Multi for Her 50+	1 tablet	250	1000.00		
	Men's Multi for Him 50+	1 tablet	162	1000.00		
	Advanced High Absorption Calcium with 100mg Phytonutrients	2 tablets	500	200.00		

	Calcium Magnesium Zinc with Vitamin D	1 tablet	333	200.00		
	Calcium Plus soy	1 tablet	500	200.00		
	Calcium with Vitamin D	1 tablet	600	200.00		
	Diabetes Health Pack	1 packet	200	400.00		
	Essential 50+	1 tablet	200	400.00		
	Essential Balance Compete Multi Vitamin/Mineral	1 tablet	100	400.00		
	Essentail Daily	1 tablet	450	400.00		
	Essential Man 50+	1 tablet	450	400.00		
	Essential multi Plus Energy	1 tablet	50	200.00		
	Essential Woman 50+	1 tablet	250	400.00		
	Man with Lycopene	1 tablet	100	400.00		
	Maximin Pack	1 packet	850	800.00		
	Mens Pack	1 packet	350	400.00		
	Multi Complete with Iron & Calcium	1 softgel	100	1000.00		
	Multi for Her with Iron & Calcium	1 softgel	100	1000.00		
	Multi Prenatal Premium	1 tablet	200	400.00		
NatureSmart	Disney Princess Complete Multivitamin Chewable Tablet	1 tablet	100	400.00		
	Winnie the Pooh Chewables	1 tablet	100	400.00		
	Gummies (Finding Nemo, Winnie the Pooh, etc)	1 gummies	100	400.00		
Natures Best	Hardcore Pack	1 packet	1100	400.00		
	Zero Carb Isopure	1 scoop	300	100.00		
Nature's Bounty	Theravim-M	1 tablet	40	400.00		
	Multi-Day plus Minerals	1 tablet	162	400.00		
	Mega VM-80	1 tablet	19	400.00		
	Absorbable Calcium 1220 + D	2 softgels	1200	200.00		
	Calcium 500mg with Vitamin D	4 tablets	120	500.00		
	Calcium 600 + Vitamin D with Soy Isoflavones	2 tablets	100	400.00		
	Chewable Calcium Wafers Plus Vitamin D	2 wafers	200	200.00		
	Coral Calcium 1000mg Plus Vitamin D and Magnesium	2 tablets	370	400.00		
	Green Source	3 tablets	250	400.00		
	Hair Skin and Nails Formula	3 tablets	830	100.00		
	High Potency Vitamin D 1000IU	1 tablet	120	1000.00		
	Multi-Day Weight Trim with Green Tea EGCG	1 tablet	300	400.00		
	Oystercal-D Calcium 500mg with Vitamin D3	1 tablet	500	400.00		
	Pre-Natal Formula	1 tablet	200	400.00		
	Prescriptive Formulas Optimal Mens	1 packet	712	200.00		
	Prescriptive Formulas Optimal Womens	1 packet	975	525.00		

	Soy Protein shake Powder	30gm	900	40.00		
	Ultra Man Time Release	2 tablets	200	200.00		
	Ultra Vita-Min	1 tablet	60	400.00		
	Ultra Woman	2 tablets	500	400.00		
	Vitmain D 2000IU	1 tablet	1500	2000.00		
Natures Life	Antioxidant Soft Multi	2 sofgels	200	400.00		
	Great Greens	3 tablets	250	800.00		
	Green Pro-96 Multi	1 tablet	50	200.00		
	One Daily Vegetarian Multiple	1 capsule	20	400.00		
	Prenatal Multiple	6 capsules	1000	200.00		
	Soft Gelatin Multiple	2 softgels	200	400.00		
	Stress Soft Multi	2 softgels	200	400.00		
	Ultra Mega Vite Multi	1 tablet	100	400.00		
Natures Plus	Adults Chewable MultiVitamin and Minerals	1 tablet	10	400.00		
	Adults Chewable Vitamin D3 1000IU	1 tablet	80	1000.00		
	Adults Dental Care Probiotic Lozenges	1 lozenges	150	400.00		
	Adults Multi-Vitamin Chewable	1 tablet	10	400.00		
	Childrens Chewable Dental Probiotic (various flavors)	2 tablets	300	400.00		
	Bone Power - Calcium with Boron	4 softgels	1000	200.00		
	Dyno Vites Sustained Release	2 tablets	50	1000.00		
	Golden Years	6 tablets	300	400.00		
	Especially Yours Women's Multiple	3 tablets	150	400.00		
	Liquid Bone Power	15ml	1000	200.00		
	Liquid Calcium	15ml	1000	40.00		
	Love Bites Childrens Chewable	1 tablet	20	400.00		
	Mega Force Tablets for Men Only	3 tablets	25	400.00		
	Nutri-Genic Softgels for Sensitive People	2 softgels	50	400.00		
	Nutri-Genic Tablets for Sensitive People	2 tablets	50	400.00		
	Power Teen for Her Chewable	2 tablets	100	500.00		
	Power Teen for Him Chewable	2 tablets	50	500.00		
	Power-Plex sustained release MultiVitamin and Mineral	1 tablet	26	400.00		
	Regeneration Liquid Sunshine	60ml	200	400.00		
	Regeneration Multivitamin and mineral Softgels	3 softgels	100	400.00		
	Source of Life Adults Chewable Multi	2 wafers	100	400.00		
	Source of Life Animal Parade Liquid	30ml	20	200.00		
	Source of Life GOLD Mini-Tablets	3 tablets	250	400.00		
	Source of Life Gold tablets	3 tablets	250	400.00		
	Source of Life Gold Vcaps (Vegan)	9 caps	250	1000.00		
Natures Secret	womens Whole Body Daily Multivitamin	2 softgels	100	400.00		

Natures Sunshine	Super Supplemental Vitamins and Minerals without Iron	4 tablets	400	600.00		
Natures Way	Alice Iron-Free Multivitamin	3 tablets	250	400.00		
	Alive Mens Multivitamin & Mineral	3 tablets	250	800.00		
	Alive Womens Multivitamin & Mineral	3 tablets	500	1000.00		
	BoneSoy	2 tablets	400	133.00		
	Coral Calcium	3 capsules	600	200.00		
	Natures Way Alive	3 tablets	250	400.00		
	Once Daily Women's 50 +Ultra Potency	1 tablet	500	1000.00		
	Once Daily Men's 50 +Ultra Potency	1 tablet	100	1000.00		
	Alive Once Daily Energy 50 +	1 tablet	100	1000.00		
New Chapter	Every Womans Daily	1 tablet	10	400.00		
	Bone Strength Take Care	3 tablets	680	800.00		
	Every Man	3 tablets	8	400.00		
	Every Woman	3 tablets	25	400.00		
	Every Woman II	6 tablets	75	400.00		
	Only One	1 tablet	2	400.00		
	Perfect Prenatal	3 tablets	30	400.00		
	Unbound Energy	3 tablets	5	1000.00		
New Phase	Complete Menopause Support	4 capslets	800	400.00		
Nnodum Pharmaceuticals	Inatal Advance	1 tablet	200	400.00		RX only
	Inatal Ultra	1 tablet	200	400.00		RX only
North Star	Daily Defense Plus	3 capsules	200	200.00		
	Ultimate Bionic Plus	1 packet	500	400.00		
Novato	Multivitamin Plus	1 tablet	200	400.00		
	Super Multivitamins	2 capsules	50	400.00		
Now Foods	Full Spectrum Minerals	2 tablets	1000	200.00		
	ADAM Superior	3 capsules	350	400.00		
	Bone Calcium	4 tablets	1000	200.00		
	Daily Vits Vitamin	1 tablet	150	100.00		
	Calcium Citrate	2 tablets	600	100.00		
	Eco-Green Multi Vitamin	2 capsules	50	100.00		
	Full Spectrum Minerals	2 tablets	1000	200.00		
	Kids Vit Chewable (various flavors)	2 tablets	40	200.00		

	Liquid Cal Mag	15ml	500	400.00		
	Liquid Multi Gels	2 gelcaps	100	400.00		
	Magnesium & Calcium	3 tablets	400	200.00		
NSI	Prenatal Plus	6 capsules	1300	400.00		
	Synergy Basic Multi Vitamin Version 2	2 capsules	20	700.00		
	Synergy Mens Multi Vitamin Version 2	8 capsules	50	700.00		
	Synergy Multi Vitamin Version 10	6 capsules	500	1000.00		
Nutrilite	Cal Mag D	4 tablets	1000	400.00		
	Daily Multivitamin and Multimineral	1 tablet	200	400.00		
Nutrition Now	Calcium Soft Chews	1 softchew	500	100.00		
	Rhino Beanie Vites	2 tablets	4	100.00		
	Rhino Calcium	1 tablet	250	100.00		
	Rhino Wigglers	1 wiggler	2	400.00		
One A Day	Essential Multi	1 tablet	45	400.00		
	Men's Health	1 tablet	210	400.00		
	Men's 50+	1 tablet	120	400.00		
	Women's	1 tablet	450	800.00		
	Maximum	1 tablet	162	400.00		
	Complete Chewable (Flintstones, Bugs Bunny, Scooby Doo, etc	1 tablet	100	400.00		
	Gummies (Flintstones, Bugs Bunnies, etc	1 gummie	100	400.00		
	Energy	1 tablet	250	400.00		
	Active	1 tablet	110	400.00		
	Cholesterol Plus	1 tablet	200	400.00		
	Daily Multivitamin Vital Body and Cells Formula	1 tablet	200	400.00		
	Joint and Bone Vitality	1 tablet	250	67.00		
	Men's Pro Edge	1 tablet	200	800.00		
	Menopause Formula	1 tablet	300	800.00		
	Women's Prenatal	1 tablet	300	400.00		
	Women's Active Mind & Body	1 tablet	300	800.00		
	Women's Active Metabolism	1 tablet	300	800.00		
	Weight Smart	1 tablet	300	400.00		
	Carb Smart	1 tablet	200	400.00		
	Today	1 tablet	240	400.00		
	Science Daily	1 tablet	250	400.00		
	Nutrilite	1 tablet	200	400.00		
	Teen Advantage for Her	1 tablet	300	800.00		
	Teen Advantage for Him	1 tablet	200	400.00		
Optimox	Gynovite Plus	1 tablet	83	67.00		

Optimum Nutrition	OptiMen	3 tablets	200	300.00		
	OptiWomen	2 capsules	150	600.00		
	Nutrition Serious Mass	2 scoops	590	200.00		
Perque	Life Guard	2 tablets	50	400.00		
	Bone Guard Forte 20	4 capsules	500	400.00		
	Life Guard Chewables	1 chewable	50	200.00		
	Mito Guard 100 Plus	1 tablet	50	200.00		
Pfizer	Myadec	1 tablet	162	400.00		
	Caltrate 600-D	2 tablets or softchews	1200	800.00		
	Caltrate 600-D Plus minerals	2 tablets or softchews	1200	800.00		
Pharmanex	Bone Formula	2 tablets	250	50.00		
	Life Essentials	1 tablet	100	200.00		
	LifePak Kosher	1 packet	250	200.00		
	LifePak Prenatal	1 packet	325	200.00		
	LifePak Prime Anti Aging Formula	1 packet	500	300.00		
	LifePak Teen	1 capsule	250	200.00		
	LifePak Women	1 packet	500	200.00		
	Nutrimmune chews	1 chewtab	250	50.00		
	Vitox	2 capsules	250	200.00		
Pharmaton	Ginsana Gold Formula	2 softgels	200	400.00		
Pharmics	O-Cal FA	1 tablet	200	400.00		RX only
PhysioLogics	MultiLogics Iron-Free Once Daily	1 capsule	92	400.00		
	OsteoLogic Pro	2 tablets	400	150.00		
	Phytotality Daily Multivitamin + Minerals	3 tablets	252	400.00		
	Ultra MultiLogics for Men High Potency	2 tablets	200	400.00		
	Ultra Multillogics for Women High Potency	2 tablets	500	600.00		
Precision Engineered	Milk and Egg Protein Powder	1 scoop	600	140.00		
	Muscle Weight Gainer	5 tbs	1100	200.00		
	ProtoPlex Deluxe	3 scoops	600	200.00		

Prevention	Age-Defying Multivitamin & Mineral for Men 50 Plus	2 tablets	250	400.00		
	Diabetic Support MultiNutrient	2 tablets	240	400.00		
	High Potency Multivitamin & Mineral for Women	1 tablet	250	400.00		
Prime Marketing	Thera-M with Minerals	1 tablet	40	400.00		
	Complete Tablets	1 tablet	162	400.00		
	Prenatal	1 tablet	200	400.00		
Pure Encapsulations	Nutrient 950 (various formulations)	6 capsules	300	800.00		
	PureBears	2 tablets	100	400.00		
	Daily Multi	3 capsules	200	200.00		
Puritans Pride	ABC PLUS SENIOR with Lutein & Lycopene	1 tablet	200	400.00		
	Absorbable Calcium with Vitamin D	2 capsules	1000	100.00		
	Adult Chewable Multi-Vitamin	1 chewtab	10	400.00		
	Calcium Magnesium with D	3 tablets	1000	400.00		
	Childrens Chewable Animal Chews (various formaltions)	1 chewtab	125	200.00		
	Childrens Chewable Multivitamin	1 chewtab	50	400.00		
	Complete One	1 tablet	54	400.00		
	Daily 3 Multiple with Cholesterol Regulators	3 capsules	106	800.00		
	Formula 100 with Beta Carotene	1 tableet	100	400.00		
	Green Source	3 tablets	750	400.00		
	High Potency Calcium 600 + Vitamin D	2 tablets	1200	400.00		
	Iron Free green Source	3 tablets	252	400.00		
	Mega Vita Gel	2 softgels	200	400.00		
	Mega Vita Min for Seniors	2 tablets	200	400.00		
	Mega Vita Min for Women	2 tablets	500	400.00		
	Mega Vita min for Women Timed Release	2 tablets	510	400.00		
	Mega Vita Min	1 capsule	15	400.00		
	Multi-Day Plus Minerals	1 tablet	162	400.00		
	Multi-Day Take One Green Tea Formula	1 tablet	300	400.00		
	Potent 75 Super VM	1 tablet	50	400.00		
	Prenatal Complex	4 capsules	1300	400.00		
	Puritron	6 tablets	800	400.00		
	Super All Day Nutricom Powder	15gm	500	400.00		
	Ultra Vita-Mam Time Release for Men	2 tablets	200	200.00		

	Ultra Vita-Min VM-33	1 tablet	60	400.00		
	Vita-min Complete Formula 1	6 tablets	800	200.00		
	Whole Food Concentrate	3 capsules	500	400.00		
Quantum	Mega 1 Daily Iron Free	1 capsule	25	200.00		
	Natures Daily Multi Vitamin	1 tablet	50	400.00		
	Complete Super Vitamin Multi	1 tablet	50	400.00		
Radiance	Absorbable Calcium with Vitamin D	2 softgels	1000	100.00		
	Calcium 600 + Vitamin D	2 tablets	1200	250.00		
	Coral Calcium 500 Plus	2 capsules	370	400.00		
	Green Source Multivitamins and minerals	3 tablets	250	400.00		
	Mega Vita Gel	2 softgels	200	400.00		
	Mega Vita Min for women	2 tablets	500	400.00		
	Mega Vita Min High Potency 9 time Release	2 tablets	500	400.00		
	Prenatal Vitamin	1 tablet	200	400.00		
	Skin, Hair & Nails Formula	3 tablets	834	100.00		
	Ultra Vita Man High Potency Timed Release	2 tablets	200	200.00		
	Vanilla Soy Protein shake	30gm	200	200.00		
Rainbow Light	Active Health Teen Multi	3 tablets	200	100.00		
	Active Senior Multivitamin	1 tablet	200	400.00		
	Advanced Nutritional System	6 tablets	240	400.00		
	Complete Menopause Support	4 tablets	1000	400.00		
	Everyday Calcium with Enzymes	4 tablets	1200	200.00		
	Just Once Iron Free Safe Guard multivitamin	1 tablet	30	400.00		
	Just Once Food Based Calcium	1 tablet	500	200.00		
	Mens One Multivitamin	1 tablet	50	400.00		
	Nutritional Systems NutriStars	2 tablets	40	50.00		
	Prenatal One Multivitamin	1 tablet	200	400.00		
	Womens Nutritional System	6 tablets	1000	400.00		
	Womens One Multivitamin	1 tablet	200	400.00		
	Womens Whole Nutrition Liquid Multi	2 softgels	100	400.00		
	Mens Whole Nutrition Liqiud Multi	2 softgels	100	400.00		
Reliv	RelivClassic	2 scoops	1000	400.00		
	RelivNow for kids	2 scoops	1000	400.00		
	Simplicity	1 scoop	500	200.00		
Rexall-Sundown	Complete Daily with Lutein	1 tablet	162	400.00		
	SunVite	1 tablet	162	400.00		
	Daily Multi Caplets	1 caplet	162	400.00		
	Complete Energy	1 caplet	100	400.00		

	Vitamins to Go Maximum	1 tablet	777	525.00		
	Daily Multi 50+	1 tablet	162	400.00		
	Osteo Bi-Flex Plus Calcium With Vitamins C and D	3 caplets	500	400.00		
Rite Aid	Whole Source Mature Adult Multivitamin/Mineral	1 tablet	165	400.00		
	Calcium Soft Chews	1 softchew	500	100.00		
	600mg Calcium Plus Vitamin D	1 tablet	600	200.00		
	Central Vite	1 tablet	162	30.00		
River's Edge	VitaPhil	1 tablet	100	400.00		RX only
Rugby	Advance Formula Cerovite	1 tablet	162	400.00		
	Cerovite Jr. Chewables	1 tablet	108	400.00		
	VITa-PMS	1 tablet	21	17.00		
	Calcium 600-D	1 tablet	600	200.00		
	Oysco 500 + D	1 tablet	500	200.00		
	Oysco D	1 tablet	400	125.00		
	Prenavite	1 tablet	200	400.00		
Schiff	Childrens chewables	1 chewtab	20	200.00		
	Guided Minerals Multi Minerals Complex	3 tablets	1200	400.00		
	Hair, Skin and Nails with MSM	2 tablets	170	800.00		
	Prime Years Multi Vitamin	1 softgel	100	400.00		
	Prostrate Health	2 capsules	29	400.00		
	Single Day Antioxidant Rich	1 tablet	10	400.00		
	Super Calcium 1200 with Vitamin D	2 softgels	1200	400.00		
	Sustained Release Single Day Multi Vitamin	1 tablet	25	400.00		
	Vegetarian Multiple with Beta Carotene	2 capsules	200	400.00		
Shaklee	Vita-Lea Iron Formula High Potency Multivitamin & Mineral	2 tablets	450	200.00		
	OsteoMatrix	4 capsules	1000	400.00		
	Vita-Lea Gold Vitamin K Formula high Potency Multivitamin & Mineral	2 tablets	450	400.00		
	Chewable Cal Mag Plus	4 chewtabs	1000	200.00		
	Cinch 3-in-1 Inch Loss Plan Boost	3 tablets	300	260.00		
Sciele Pharma	OptiNate	1 tablet	200	400.00		RX only
Solaray	Iron Free Spectro Multi-Vita-Min	6	500	400.00		

		capsules				
	Mens Golden Multi-Vita-Min	3 capsules	75	400.00		
	Multi-Vita Mega-Mineral Multi-Vita-Min	4 capsules	420	400.00		
	Once Daily High Energy Multi-Vita-Min	1 capsule	10	400.00		
	Once Daily Softgel with Lutein Multi-Vita-Min	1 softgel	25	400.00		
	Provide Multi-Vita-Min	2 softgels	200	400.00		
	Spectro 50 Plus Multi-Vita-Min	4 capsules	200	800.00		
	Spectro Energy Multi-Vita-Min	4 capsules	250	800.00		
	Spectro Kid Multi-Vitamin	2 tablets	200	400.00		
	Spectro Man Multi-Vita-Min	4 capsules	200	400.00		
	Spectro Woman Multi-Vita-Min	4 capsules	400	800.00		
	Twice Daily Multi-Vita-Min	2 capsules	200	400.00		
	Vegetarian Spectro Multi-Vita-Min	6 capsules	500	400.00		
	VitaPrime for Men Multi-Vita_min	4 capsules	400	400.00		
	VitaPrime for Women Multivitamin and Multimneral	4 capsules	400	400.00		
	Womens Golden Multi-Vita-min	3 capsules	75	400.00		
	YumAid Multi-Vita-Min Punch	1tsp	50	400.00		
Solgar	Adv Proanthocyanidin Complex	2 capsules	170	800.00		
	Calcium Magnesium with Vitamin D	5 tablets	1000	400.00		
	Earth Source Multi-Nutrient	3 tablets	250	400.00		
	Female Multiple	3 tablets	400	400.00		
	Formula V VM-75 Multivitamin with Chelated Minerals	2 capsules	20	400.00		
	Formula VM-2000	2 tablets	50	400.00		
	Formula VM-Prime for Adults 50 Plus Iron Free	1 tablet	20	400.00		
	Iron Free Formula VM-75	1 tablet	20	400.00		
	Kangavites Complete Childrens Formula	2 tablets	128	200.00		
	Male Multiple	3 tablets	400	400.00		
	Omnium Multiple Vintamin and Mineral Formula Iron Free	2 tabletws	25	200.00		
	Prenatal Nutrients	4 tablets	1300	400.00		
Source Naturals	Advanced One Multiple (witn and without Iron)	1 tablet	50	400.00		
	Advanced Triple Boron with Calcium 1000mg	2 capsules	500	400.00		
	Calcium & Magnesium 300mg	1 tablet	200	500.00		

	Calcium Hydroxyapatite	2 tablets	600	500.00		
	Calcium Night 150mg	2 tablets	300	100.00		
	Calcium 200mg	1 tablet	200	500.00		
	Elan Vital Multiple	6 tablets	200	400.00		
	Life Defense	4 tablets	95	200.00		
	Life Force	4 capsules	100	1000.00		
	Mega Kid	1 wafer	20	200.00		
	Mens Life Force	3 tablets	100	400.00		
	Mothers Choice	4 tablets	615	400.00		
	Spirulina	2 tablets	106	400.00		
	Ultra	6 tablets	125	400.00		
	Womens Life Force	3 tablets	200	400.00		
Sundown	Advanced SunVite	1 tablet	162	400.00		
	Calcium 600 + D	1 capsule	600	200.00		
	Calcium Oyster Shell 1000mg	3 tablets	1000	400.00		
	Complete Daily with Lutein	1 caplet	162	400.00		
	Daily Multi & Min	1 caplet	162	400.00		
	Daily Multiple 50+ Iron Free with Lutein & Lycopene	1 caplet	200	400.00		
	Multiple Complete Womens	1 caplet	250	400.00		
	Naturals Prenatal Formula	1 tablet	200	400.00		
	One Daily Multiple for Women	1 caplet	400	400.00		
	Prenatal Vitamin and Mineral Formula	1 tablet	200	400.00		
	Vitamins to Go Womens	1 packet	660	125.00		
Super Nutrition	Calcium Blend	3 tablets	1000	1000.00		
	Longevity	1 tablet	68	400.00		
	Menopause Multiple Blend	8 tablets	750	500.00		
	Mens Blend	3 tablets	300	500.00		
	Simply One Prenatal	1 tablet	210	500.00		
	Simply One - One Per Day	1 tablet	33	400.00		
	Simply Perfect Kids	4 tablets	120	400.00		
	Super Blend	4 tablets	500	500.00		
Ther-RX	PrimaCare Softgel	1 softgel	400	400.00		RX only
	PrimaCare Advantage	1 softgel	250	230.00		RX only
	PrimaCare ONE	1 capsules	150	170.00		RX only
Thompson	Adult Plex	3 tablets	300	400.00		
	All in One Multivitamin Iron Free	1 capsule	100	400.00		
	Coachs Formula with Enzymes	2 tablets	333	133.00		
	Mega 80	1 tablet	45	600.00		
	Multi Formula for Women	2 capsules	300	200.00		
	Multi Vitamins with Minerals	2 tablets	170	200.00		
	Nuplex with Iron	1 tablet	120	400.00		

	Prenatal Formula	2 tablets	68	610.00		
	Teenplex Multivitamin	2 tablets	200	400.00		
TwinLab	Daily One Caps (with or without Iron)	1 capsule	25	400.00		
	Dr. Greene Childrens (various flavors)	1 tablet	100	400.00		
	Dr. Greene Healthy Bone Formula	1 tablet	500	200.00		
	Dr. Greene Pre-Natal formula	2 capsules	500	400.00		
	Dualtabs Mega Vitamin and Mineral formula	2 tablets	500	200.00		
	Allergy Multi Caps	2 capsules	333	133.00		
	Animal Friends Kids Chewable (various flavors)	1 chewable	100	400.00		
	Bone Support with Ostivone	4 tablets	1500	800.00		
	Cal Quick Liquid	5ml	500	100.00		
	Calcium 500 with Magnesium & Vitamin D	1 tablet	500	200.00		
	Calcium Citrate Chewable	4 wafers	1000	400.00		
	Pre-Natal Care	2 capsules	400	400.00		
	Womens Ultra Daily	4 capsules	510	400.00		
Usana	Active Calcium	4 tablets	800	400.00		
	Body Rox Active Calcium Chewable	4 chewtabs	800	400.00		
	Essentials Usanimals	1 tablet	75	100.00		
	HealthPak	1 packet	335	1000.00		
VegLife	MultiVeg Energy	4 tablets	34	400.00		
	MultiVeg Energy with Lutein and Iron	3 capsules	50	800.00		
	SpectroVeg High Energy	6 tablets	500	400.00		
	Vegan Cal-Mag Citrate Plus Vitamin D	3 tablets	500	200.00		
	Vegan Kids	2 tablets	30	400.00		
	Vegan One Multi with Iron	1 tablet	50	400.00		
	Vital Teen Boys	2 capsules	150	800.00		
	Vital Teen Girls	2 capsules	150	1000.00		
Vitabase	Active Mans Formula	1 tablet	50	400.00		
	Childrens Multiple Liquid	30ml	200	220.00		
	Coral Calcium 1000mg	1 capsule	250	200.00		
	Hair, Skin & Nails Liquid	3 liquicaps	300	200.00		
	Kids Chewable Calcium	2 chewtabs	200	200.00		
	PreNatal Plus	4 tablets	800	400.00		
	Super Calcium & Magnesium	3 tablets	1000	200.00		
	Super Softgel Formula	2 softgels	200	400.00		

Vitaline	Total Formula	1 tablet	100	400.00		
	Total Formula 2	1 tablet	100	400.00		
	Maximum Red	1 tablet	83	67.00		
Vitamin Shoppe	1 Daily	1 tablet	100	400.00		
	Ultimate Man	2 tablets	200	1000.00		
	Ultimate Woman	2 tablets	500	1000.00		
	Calcium Citrate	2 tablets	333	204.00		
Vitamin World	Bone Reinforcer with Hydroxyapatite	4 tablets	1200	400.00		
	Calcium Magnesiun with D	3 tablets	1000	400.00		
	Coral Calcium 500mg Plus Vitamin D	2 capsules	370	400.00		
	Daily 3 Multiple with Chloesterol Regulators	3 capsules	106	800.00		
	Green Source	3 tablets	250	400.00		
	Spirulina Soy protein Drink	1 scoop	300	400.00		
	Thervim M	1 tablet	40	400.00		
	Ultra Vita Man timed release	2 tablets	200	200.00		
Whole Health	Cal-Mag Calcium & Magnesium Citrates 1400mg	4 tablets	1000	400.00		
	Childrens Chewable Multivitamin	2 chewtabs	55	400.00		
	GreenHealth Natural Multi	2 capsules	50	100.00		
	HerHealth	4 capsules	780	600.00		
	HisHealth	3 capsules	272	400.00		
	Prenatal Health	4 tablets	1000	220.00		
	Super Multi Plus	3 tablets	400	400.00		
Whole Source	Mature Adults Multi Mineral with Herbs	1 tablet	165	400.00		
Windmill	Ezcal 2000 + D (regular tablets & chewables)	1 tablet	1000	400.00		
Women's Health America	ProCycle Gold	1 tablet		100.00		
Wonder Labs	Mulitvitamin/Multimineral with Beta Carotene & Lycopene	1 tablet	162	400.00		
	Pure coral Calcium 2500mg	3 capsules	2500	200.00		
Xanodyne	Duet DHA	1 tablet	200	400.00		RX

						only
	Duet Chewable	1 tablet	100	400.00		RX only

Appendix VI: Dietary calcium and vitamin D intake calculator

Questionnaire adapted from Rapid
Vit D data from USDA database from NDS

INSTRUCTIONS

Use the excel spreadsheet to calculate the average daily dietary intake of calcium and vitamin D from food.
Please ask the participant to recall food items eaten over the last 3 days.
Ask the participant about each food item in column "B" and record how many servings (size of each serving detailed in spreadsh eet) he/she ate over the last 3 days
Enter the number of servings in column "C". The total amount of calcium and vitamin D from that food item will be automatically calculated in the spreadsheet and di
The total DAILY intake of calcium and vitamin D (an average of the 3 day intake) will be automatically calculated and displayed in row 65: these are the numbers to t
Upload the spreadsheet using the File Exchange Utility located on the FSTRF website (www.fstrf.org)

Food	servings	Calcium/serving (r	VitD/serving (mcg)	CA Total (mg)	D Total (IU)
Milk/yogurt/cheese					
cheese (1 oz or 6 tbsp)		200	0.09	0	0
cottage cheese (1/2cup)		50	0.03	0	0
custard, pudding, cream pie (1/2 cup)		150	1.43	0	0
ice cream, frozen yogurt, milkshake (1 cup)		200	1.26	0	0
yogurt (1 cup)		388	0.03	0	0
butter (1 tbsp)		100	0.20	0	0
milk (1 cup)		300	2.50	0	0
latte or mocha latte (1 cup)		220	2.00	0	0
café au lait (1 cup)		99	2.00	0	0
cappucchino (1 cup)		250	2.00	0	0
Fortified orange juice (1 cup)		350	2.50	0	0
soy milk, unfortified (1 cup)		10	0.00	0	0
soy milk, fortified (1 cup)		300	2.50	0	0
cream soup/sauce (1 cup)		200	0.18	0	0
macaroni and cheese (1 cup)		250	0.23	0	0
pizza (1 slice)		250	0.03	0	0
quiche (1 slice)		250	1.01	0	0
Fruits /Vegetable				0	0
broccoli or cooked greens (1/2 cup)		100	0.00	0	0
other vegetables (1/2 cup)		30	0.00	0	0
fruit (1/2 cup or 1 small)		30	0.00	0	0
Bread/Cereal/Rice/Pasta				0	0
bread (1 slice)		20	0.00	0	0
calcium enriched bread (1 slice)		102	0.00	0	0
cereal (1 oz)		20	0.94	0	0

smoked eel (1oz)		0.89	0	0
herring (1oz)		11.54	0	0
canned salmon with bones (3oz)	150	9.91	0	0
canned sardines with bones (3oz)	400	3.91	0	0
shrimp (3oz)	100	3.04	0	0
oysters (7-9)	100	9.36	0	0
tofu (2.5x2.5x1 inch)	100	0.00	0	0
peanuts (1/2 cup)	30	0.00	0	0
egg (1)	30	0.56	0	0
Fat/Sugar/Alcohol			0	0
cake (1 slice)	40	0.12	0	0
beer (12 oz)	10	0.00	0	0
cola (12 oz)	10	0.00	0	0
chocolate (1 oz)	50	0.00	0	0
TOTAL INTAKE PER DAY			**0**	**0**