**Study Protocol**: Effectiveness and safety of Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in HIV-1 infected patients with Active illicit Substance usE (BASE)

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**Hypothesis**: People living with HIV (PWH) that use illicit substances receiving B/F/TAF will have virologic suppression similar to PWH that do not use illicit substances receiving B/F/TAF without safety concerns or treatment emergent resistance

**Abstract:**

**Description:**
Illicit substance use is a growing concern across the United States and has been linked to HIV outbreaks and viral hepatitis. Close to half of people living with HIV (PWH) struggle with a substance use disorder often leading to non-adherence of antiretroviral therapy (ART) increasing the risk of poor treatment outcomes and potential HIV transmission. Appropriate choice of ART for PWH who use illicit substances is unknown. Boosted protease inhibitor regimens are utilized for their high genetic barrier to resistance, however, concerns for drug-drug interactions with illicit substances are present. The clinical utility of an integrase strand inhibitor (INI) based regimen is unknown. We aim to assess the effectiveness and safety of bictegravir/emtricitabine/tenofovir alafenamide in PWH who actively use illicit substances.

**Eligibility:**
Eligible participants for the study will be HIV-1 infected patients at the Specialty Care Center with HIV viremia > 1000 copies/mL and ongoing substance use by urine drug screen or self-reported within 6 months. Participants must also have a creatinine clearance of 30 mL/min or greater, no tenofovir or INI HIV resistance mutations, and not be pregnant. Illicit substances will include: methamphetamine, heroin, cocaine, PCP, GHB, ketamine, or inappropriate benzodiazepine, prescription opiate, or prescription stimulant usage.

**Interventions/Evaluations:**
This is a single-center, single-arm, prospective, pilot study to evaluate the effectiveness and safety of B/F/TAF in PWH and active illicit substance use. We aim to evaluate the proportion of patients at week 24 with undetectable viral loads (<50 copies/mL). We plan to enroll 45 participants.
Secondary/exploratory endpoints include the proportion with undetectable viral loads at week 48, proportion with emergent drug resistance, change in CD4 counts, and evaluation retention in care.
Substance use throughout the study will be evaluated by the NIDA Modified-ASSIST questionnaire.
Adherence will be evaluated by refill history/percentage of days covered, ACTG Self-Report Adherence questionnaire, and FTC-TP and TDF-DP levels by dried blood spots.

**Follow-up:**
Participants will be followed up at weeks 6, 12, 24, 36, and 48. Participants will be compensated for visits completed at $20 per hour.

**Brief Description:** Illicit substance use in the United States is a growing concern across all states. Use of illicit drugs such as cocaine, heroin, methamphetamine, prescription opioids and stimulants, and 3,4-methylenedioxy-methamphetamine (Ecstacy, MDMA) among others, has remained steady in many parts of the United States [1]. In 2017, 6% of new HIV infections occurred in people who injected drugs and 3% were in gay/bisexual men who injected drugs [2]. Furthermore, injection of illicit drugs has been linked to outbreaks of HIV and viral hepatitis acquisition [3].

Of the 1.2 million PWH in the US, an estimated 48% struggles with a substance use disorder [4]. Poor antiretroviral treatment (ART) adherence and inconsistencies in retention in HIV care has been observed among PWH that use illicit drugs. Gaps in ART coverage and lack of retention to HIV care are factors that complicate successfully managing PWH who use illicit drugs, often leading to poor treatment outcomes and increased HIV transmission [5-7]. As a result, ART choice in these patients can prove challenging and often requires the selection of an ART regimen with a high genetic barrier to resistance such as protease inhibitor based ART [8-10]. Yet, concerns of drug-drug interactions between illicit drugs and ART regimens containing a protease inhibitor and/or a pharmacokinetic enhancer have been raised [11,12]. Integrase strand inhibitor (INSTI) based ART regimens are now the primary treatment option for most PLWH in the US [8]. B/F/TAF is the newest INSTI based regimen available as a generally well-tolerated, single tablet formulation that does not require the need for a pharmacokinetic enhancer and is thought to provide a high genetic barrier to resistance. In clinical trials among naïve and treatment experienced, virologically suppressed patients, B/F/TAF exhibited efficacy of 89% to 96% without any cases of newly emergent treatment resistance [13-16].

However, little is known about the effectiveness and safety of B/F/TAF in PWH who actively use illicit drugs because such patients are typically excluded from clinical trials. In this study, we aim to evaluate the effectiveness and safety of B/F/TAF among viremic patients currently using illicit drugs at the Nebraska Medicine, Specialty Care Center (SCC) in Omaha, NE.

The SCC clinic manages approximately 1300 PLWH's HIV care of which 89% is actively engaged in care. An estimated 8% to 12% of SCC's patients uses some form of illicit substance excluding nicotine, alcohol, or marijuana on a semi-regular basis.

**Objectives**:

1. *Primary*
    a. To evaluate the virologic suppression of PLWH with ongoing illicit substance use receiving B/F/TAF
2. *Secondary*
    a. Evaluate the safety of B/F/TAF in PLWH with ongoing illicit substance use
3. *Exploratory*
    a. Evaluate for the development of treatment emergent resistance in PLWH on B/F/TAF with ongoing illicit substance use
    b. To evaluate the change in CD4 after starting B/F/TAF in PLWH with ongoing illicit substance use
    c. Evaluate the retention in care of PLWH on B/F/TAF with ongoing illicit substance use
    d. Evaluate the medication adherence of PLWH on B/F/TAF with ongoing illicit substance use

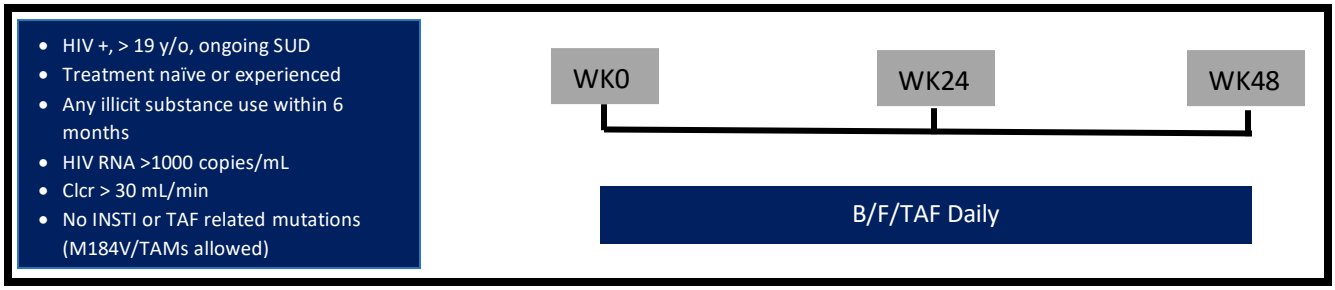
**Endpoints**:

1. *Primary*

a. Proportion of participants with ongoing illicit substance use on B/F/TAF with HIV RNA <50 copies/mL at week 24 by FDA Snapshot Algorithm

2. *Secondary*
    a. Proportion of participants who experience adverse events (grade 3 or above) at week 24 and 48
3. *Exploratory*
    a. Proportion of participants with HIV RNA <50 copies/mL at week 48 by FDA Snapshot Algorithm
        i. Reported as demographics, intention to treat, and per-protocol
    b. Proportion of participants with HIV RNA <50 copies/mL at week 48 by FDA snapshot algorithm adjusted by type of illicit substance use
    c. Proportion of participants with treatment emergent resistance at week 24 and 48
    d. Change in CD4 at week 24 and 48 from baseline
    e. Proportion of participants completing follow-up visits through weeks 24 and 48
        i. Calculated as completed study visits/total number of study visits.
    f. Adherence assessment
        i. Adherence measure
            1. Self-reported adherence questionnaire
            2. Pill counts/PDC
        ii. Tenofovir Pharmacokinetic Sampling
            1. TDF-DP and FTC-TP via DBS

**Study Design:** Prospective, single arm, open-label, pilot study




**Inclusion Criteria**:

1. Documented HIV infection
2. ≥19 years old
3. Self-reported illicit substance use or confirmed by urine drug screen within past 6 months
    a. Cocaine
    b. Heroin
    c. Methamphetamine
    d. PCP/ketamine/GHB
    e. Opiates
    f. Inappropriate use of prescription pills (opiates/benzodiazepines/stimulants) regardless of prescription
4. HIV RNA ≥ 1,000 copies/mL not presently taking B/F/TAF

5. Any CD4 count
6. Creatinine clearance >30 mL/min (Cockroft-Gault)
7. ALT and AST < 5 times the upper limit of normal
8. Willing and able to give written informed consent

**Exclusion Criteria**:

1. History of INI or TAF-related resistance mutations as defined by the IAS-USA
2. Pregnancy
3. Any concomitant use of dofetilide or known medications to reduce systemic exposure to B/F/TAF (i.e. rifamycins, carbamazepine, St. John's Wort)
4. Serious illness requiring systemic treatment (i.e. prolong intravenous treatment such as chemotherapy, extended antibiotic therapy, etc) and/or hospitalization within 30 days prior to entry

**Methods**:
After obtaining written informed consent, prospective participants will be screened with a clinical assessment (physical exam), laboratory testing (CBC, CMET, HBV/HCV serology, CD4, HIV RNA), and substance use evaluation (NIDA ASSIST) to evaluate study eligibility. Eligible patients may initiate treatment with B/F/TAF on the same day as the screening visit or start within 30 days of screening.

Post-entry evaluations will occur at weeks 6, 12 and 24, 36, and 48. Clinical and safety laboratory monitoring including blood chemistries, plasma HIV RNA levels, CD4 counts and blood sampling for ART drug quantification will take place at week 6, 24, and 48 weeks. Pregnancy testing will be performed any time pregnancy is suspected. Assessment of adverse events, adherence, ongoing substance use, and quality of life will be assessed at each visit. Adherence measures include pill counts, self-reported by visual analog scale by the ACTG Brief Adherence Self Report [17] and pharmacokinetic sampling (see below). Ongoing illicit substance use will be evaluated quarterly at week 12, 24, 36, and 48 through the NIDA ASSIST [18]. Referral for substance use counseling and/or outpatient or inpatient treatment will be offered. Additionally, the Short Form 12 survey will be utilized to evaluate quality of life and patient reported outcomes [19-21]. See schedule of events table for detail.

**Virologic Failure:**
Suspected virologic failure will be defined as plasma HIV RNA > 400 copies/mL after week 12 and will be confirmed by a repeat measurement within 28 days. Participants with confirmed virologic failure will undergo genotype resistance testing using the Genosure Prime assay. Participants with emergent INI or TAF related HIV drug resistance development will undergo ART revision but will continue to be followed on study.

**Adverse Events:**
Signs and symptoms will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [22]. All signs and symptoms grade 3 or above or any grade that led to treatment discontinuation, will be recorded on study case report forms and tracked in the REDCap data management

**Pharmacokinetic Sampling:**
Blood for PK studies will be collected at three time points while on study, week 6, 24 and 48. 4mL of K2 EDTA whole blood will be collected via venipuncture for tenofovir-diphosphate (TDF-DP) and

emtricitabine-triphosphate (FTC-TP) determination at each of the three study visits. Using a Whatman 903 Protein Saver card (DBS card), 25 microliters of whole blood from the K2 EDTA will be spotted on each circle on the card and allowed to dry for at least 3 hours. Dried DBS cards will be stored at -80$^{o}$C in plastic bags until analysis. TDF-DP and FTC-TP will be quantified from the DBS card using a 3 mm punch and LC-MS/MS [23-25]. TDF-DP and FTC-TP represent different elimination half-lives (TDF-DP: long-term - 17 days vs. FTC-TP: short-term - 35 hours), drug concentration data obtained at these three time points will help provide a collective, objective measurement of ART adherence both recent and longitudinally.

**Patient Compensation:**
Patients with receive a preloaded gift card for visit completion at a rate of $20 per hour. The anticipated time of visits is 4 hours for the first visit and 2 hours for each subsequent visit.

**Visit Spacing:**
Visit windows for the study will be +/- 3 weeks for the week 6 visit, +/- 4 weeks for the week 12 visit, and +/- 6 weeks for the weeks 24, 36, and 48 study visits.

**Data Management:**
All data collected from study visits will be kept in REDCap, a HIPPA secure database hosted by the University of Nebraska Medical Center. Questionnaires throughout the study will also be imported into REDCap.

**Study Monitoring/Safety/Futility:**
An investigational monitoring committee (IMC) comprised of an HIV clinician and HIV pharmacologist along with the study team statistician will evaluated study safety, recruitment, and futility twice throughout the course of the study. The first time point for IMC review will occur after the first 15 participants reach week 24 and with the second time point at end of study enrollment.

Additionally, the study team will perform internal audits annually to ensure all data is correctly input in the data management system, REDCap, and to ensure that all study procedures are being performed as planned.

Should a female participant become pregnant during the course of the study, they will be approached about enrollment in the Antiretroviral Pregnancy Registry. The participant will be taken off B/F/TAF and changed to a preferred Department of Health and Human Services recommended ART for use during pregnancy. A referral to obstetrics will additionally be placed and they will continue to follow on study until completion.

**Schedule of Procedures:**
See Addendum A

**Questionnaires:**
See Addendum's B-C

**Study Follow-up/Labs**:

| Intervention Type | Entry/WK0 | WK6 | WK12 | WK24 | WK36 | WK48 |
|---|---|---|---|---|---|---|
| **Laboratory** | CBC/CMET<br>HIV RNA<br>CD4<br>HBV/HCV serologies<br>Urine Pregnancy | CMET<br>HIV RNA<br>Urine Pregnancy | Urine Pregnancy | CBC/ CMET<br>HIV RNA<br>CD4<br>Urine Pregnancy | Urine Pregnancy | CBC/ CMET<br>HIV RNA<br>CD4<br>Urine Pregnancy |
| **Safety** | | X | X | X | X | X |
| **Adherence Questionnaire** | | X | X | X | X | X |
| **Substance use Questionnaire** | X | | X | X | X | X |
| **PRO Questionnaire** | X | | | X | | X |
| **PHARMACOKINETIC SAMPLING** | | X | | X | | X |
| **Physical Exam** | X | | | X | | X |

**Sample Size Justification:**
The sample size justification is based on the estimation of a confidence interval for a single proportion. We are interested in estimating the precision of determining the proportion of PLWH with ongoing illicit substance use on B/F/TAF with HIV RNA <50 copies/mL at week 24. It is proposed that this proportion could range from .60 to .80 depending on how adherent patients are to the therapy. It is also uncertain how many eligible patients will continue on treatment through week 24.
The table below provided estimates of precision (with 95% confidence) based on the number of patients who complete 24 weeks of therapy and the proportion who achieve HIV RNA <50 copies/mL.

| Confidence Level | Sample size | CI Width | Proportion HIV RNA <50 | Lower limit | Upper limit |
|---|---|---|---|---|---|
| 0.95 | 20 | 0.45 | 0.6 | 0.36 | 0.81 |
| 0.95 | 20 | 0.42 | 0.7 | 0.46 | 0.88 |
| 0.95 | 20 | 0.38 | 0.8 | 0.56 | 0.94 |
| 0.95 | 25 | 0.40 | 0.6 | 0.39 | 0.79 |
| 0.95 | 25 | 0.38 | 0.7 | 0.49 | 0.87 |
| 0.95 | 25 | 0.34 | 0.8 | 0.59 | 0.93 |
| 0.95 | 30 | 0.37 | 0.6 | 0.41 | 0.77 |
| 0.95 | 30 | 0.35 | 0.7 | 0.51 | 0.85 |
| 0.95 | 30 | 0.31 | 0.8 | 0.61 | 0.92 |

| | | | | | |
|---|---|---|---|---|---|
| 0.95 | 35 | 0.34 | 0.6 | 0.42 | 0.76 |
| 0.95 | 35 | 0.32 | 0.7 | 0.52 | 0.84 |
| 0.95 | 35 | 0.29 | 0.8 | 0.63 | 0.92 |
| 0.95 | 40 | 0.32 | 0.6 | 0.43 | 0.75 |
| 0.95 | 40 | 0.30 | 0.7 | 0.54 | 0.83 |
| 0.95 | 40 | 0.27 | 0.8 | 0.64 | 0.91 |

This is a pilot study to estimate the efficacy (i.e. HIV RNA <50 copies/mL at week 24) of B/F/TAF in PLWH with ongoing illicit substance usage. A sample size of 30 produces a two-sided 95% confidence interval with a width equal to 0.35 when the sample proportion of patients who achieve HIV RNA <50 copies/mL at week 24 is 0.70. The sample size will be increased to 45 patients to account for an estimated attrition of ~50%.

**Data analysis [26, 27]:**
Statistical analysis will be performed using GraphPad Prism, SAS as well as IBM SPSS software. Descriptive summaries will be presented using means, medians, standard deviations, and ranges for continuous variables and frequencies and percentages for categorical variables. Patients achieving HIV RNA <50 copies/mL at week 24 will be presented as a proportion and 95% confidence interval. Counts and percentages will be used to describe safety assessment, retention and adherence of B/F/TAF in HIV infected patients with ongoing illicit substance usage. Adherence will also be evaluated with summary statistics of drug levels measured in patients at the 24 week visit. A logistic regression model may be considered to investigate the effect of adherence on the 24 week outcome.

**References**


1. Substance Abuse and Mental Health Services Administration (2018). Results from the 2017 National Survey on Drug Use and Health. Rockville, MD: Substance Abuse and Mental Health Services Administration.
2. Centers for Disease Control and Prevention. HIV Surveillance Report, 2017; vol. 29. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published November 2018. Accessed [December 2018].
3. Peters, P.J., et al., *HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014-2015.* N Engl J Med, 2016. **375**(3): p. 229-39.
4. Hartzler, B., et al., *Prevalence and Predictors of Substance Use Disorders Among HIV Care Enrollees in the United States.* AIDS Behav, 2017. **21**(4): p. 1138-1148.
5. Meyer, J.P., A.L. Althoff, and F.L. Altice, *Optimizing care for HIV-infected people who use drugs: evidence-based approaches to overcoming healthcare disparities.* Clin Infect Dis, 2013. **57**(9): p. 1309-17.
6. Kamarulzaman, A. and F.L. Altice, *Challenges in managing HIV in people who use drugs.* Curr Opin Infect Dis, 2015. **28**(1): p. 10-6.
7. Shubber, Z., et al., *Patient-Reported Barriers to Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis.* PLoS Med, 2016. **13**(11): p. e1002183.
8. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at

http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Section "What To Start." [December 2018]. [F-1 – F-42]
9. Dierynck, I., et al., *Binding kinetics of darunavir to human immunodeficiency virus type 1 protease explain the potent antiviral activity and high genetic barrier.* J Virol, 2007. **81**(24): p. 13845-51.
10. El Bouzidi, K., et al., *HIV-1 drug resistance mutations emerging on darunavir therapy in PI-naive and -experienced patients in the UK.* J Antimicrob Chemother, 2016. **71**(12): p. 3487-3494.
11. Gruber, V.A. and E.F. McCance-Katz, *Methadone, buprenorphine, and street drug interactions with antiretroviral medications.* Curr HIV/AIDS Rep, 2010. **7**(3): p. 152-60.
12. Bracchi, M., et al., *Increasing use of 'party drugs' in people living with HIV on antiretrovirals: a concern for patient safety.* AIDS, 2015. **29**(13): p. 1585-92.
13. Gallant, J., et al., *Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial.* Lancet, 2017. **390**(10107): p. 2063-2072.
14. Sax, P.E., et al., *Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial.* Lancet, 2017. **390**(10107): p. 2073-2082.
15. Daar, E.S., et al., *Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial.* Lancet HIV, 2018. **5**(7): p. e347-e356.
16. Molina, J.M., et al., *Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial.* Lancet HIV, 2018. **5**(7): p. e357-e365.
17. Giordano TP, Guzman D, Clark R, Charlebois ED, Bangsberg D. Measuring adherence to antiretroviral therapy in a diverse population using a visual analogue scale. HIV Clin Trials. 2004;5:74–79.
18. U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse. National Institute on Drug Abuse (NIDA) – Modified Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), Version 2.0 [March 2012]. Available from: http://www.nida.nih.gov/nidamed/screening/nmassist.pdf.
19. Ware, J., Jr., Kosinski, M., & Keller, S. D. (1996). A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care, 34*(3), 220-233. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8628042.
20. Gandek, B., Ware, J. E., Aaronson, N. K., Apolone, G., Bjorner, J. B., Brazier, J. E., . . . Sullivan, M. (1998). Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol, 51*(11), 1171-1178. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9817135.
21. Jenkinson, C., Layte, R., Jenkinson, D., Lawrence, K., Petersen, S., Paice, C., & Stradling, J. (1997). A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *J Public Health Med, 19*(2), 179-186. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9243433.
22. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading

the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf
23. Castillo-Mancilla JR, Zheng JH, Rower JE et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS Res Hum Retroviruses*. 2013;29:384-90.
24. Castillo-Mancilla J, Seifert S, Campbell K et al. Emtricitabine-triphosphate in dried blood spots as a marker of recent dosing. *Antimicrob Agents Chemother*. 2016;60:6692-7.
25. Zheng JH, Rower C, McAllister K et al. Application of an intracellular assay for determination of tenofovir-diphosphate and emtricitabine-triphosphate from erythrocytes using dried blood spots. *J Pharm Biomed Anal*. 2016;122:16-20.
26. Fleiss, J. L., Levin, B., Paik, M.C. 2003. Statistical Methods for Rates and Proportions. Third Edition. John Wiley & Sons. New York.
27. Newcombe, R. G. 1998. 'Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods.' Statistics in Medicine, 17, pp. 857-872.

**Addendum A: Schedule of Events**

| BASE Data Collection Chart | | | | | | |
|---|---|---|---|---|---|---|
| **Variable** | **Baseline/Screening** | **W6** | **W12** | **W24** | **W36** | **W48** |
| | | | | | | |
| ***Patient Information*** | | | | | | |
| PID | X | X | X | X | X | X |
| Name | X | | | | | |
| Age | X | | | | | |
| Height | X | | | | | |
| Weight | X | | | X | | X |
| Race | X | | | | | |
| Ethnicity | X | | | | | |
| Education | X | | | | | |
| Gender | X | | | | | |
| ART Exp | X | | | | | |
| Housing | X | | | | | |
| Income | X | | | | | |
| Reported Illicit Substance or UDS Result | X | | | | | |
| Baseline/Archived Resistance | X | | | | | |
| | | | | | | |
| ***Clinical Information*** | | | | | | |
| CBC | X | | | X | | X |
| Creatinine | X | X | | X | | X |
| AST | X | X | | X | | X |
| ALT | X | X | | X | | X |
| HBV c Ab | X | | | | | |
| HBV s Ab | X | | | | | |
| HBV s Ag | X | | | | | |
| HCV Ab | X | | | | | |
| HIV RNA | X | X | | X | | X |
| CD4 | X | | | X | | X |
| CD4% | X | | | X | | X |
| CD4/CD8 | X | | | X | | X |
| Pregnancy (if applicable) | X | X | X | X | X | X |
| Emergent Resistance | | X | | X | | X |
| | | | | | | |
| ***Safety/AE Assessment*** | | X | X | X | X | X |
| | | | | | | |
| ***Physical Exam*** | X | | | X | | X |

| | | | | | | |
|---|---|---|---|---|---|---|
| ***Questionnaire*** | | | | | | |
| ACTG Adherence | | X | X | X | X | X |
| NIDA ASSIST | X | | X | X | X | X |
| SF-12 Survey | X | | | X | | X |
| | | | | | | |
| ***Lab Collection*** | | | | | | |
| DBS Card Collection | | X | | X | | X |

**Addendum B: Adherence Questionnaire – adapted from ACTG Visual Analog Scale**

## BASE Study: ACTG Adherence

Name: Visit Week:

DOB: Participant ID:

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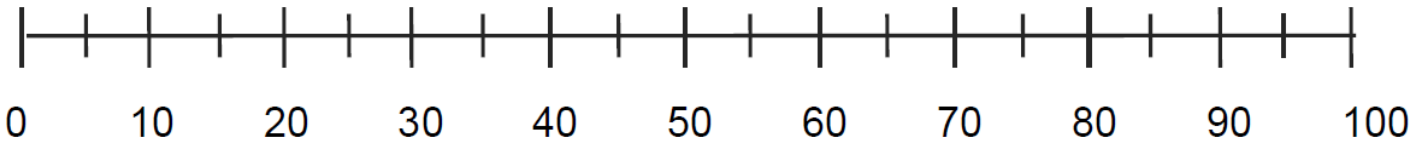
**Reported Adherence**

We understand that many people on anti-HIV medications find it very difficult to take them regularly. We would like to know HOW MUCH of your anti-HIV medications you have taken DURING THE LAST MONTH.

Please put a cross (**X**) on the line below at the point showing your best guess about how much of your
anti-HIV medication you have taken **in the last month.** We would be surprised if this was 100% for most people.

For example: **0%** means you have taken **none** of your anti-HIV medication.
**50%** means you have taken **half** your anti-HIV medication.
**100%** means that you have taken **every single dose** of your anti-HIV medication in the past month.




Self-reported adherence score: _____

**Addendum C: Substance Use Questionnaire – adapted from NIDA-ASSIST**

## BASE Study: NIDA ASSIST

Name: Visit Week:

DOB: Participant ID:

**NIDA Quick Screen:**

**In the past year, how often have you used the following?**

| Alcohol | Never | Once or twice | Monthly | Weekly | Daily or Almost Daily |
|---|---|---|---|---|---|
| • Men (≥5 drinks/day) | | | | | |
| • Women (≥4 drinks/day) | | | | | |
| Tobacco Products | | | | | |
| Prescription Drugs for Non-Medical Reasons | | | | | |
| Illegal Drugs | | | | | |

**NIDA Modified Screen:**

1. **In your lifetime, which of the following substances have you ever used?**

| Cannabis (marijuana, pot, grass, hash, CBD, etc.) | Yes | No |
|---|---|---|
| Cocaine (coke, crack, etc.) | | |
| Prescription stimulants (Ritalin, Concerta, Dexedrine, Adderall, diet pills, etc) | | |
| Methamphetamine (speed, crystal meth, Tina, ice, etc) | | |
| Inhalants (nitrous oxide, glue, gas, paint thinner, "poppers", etc.) | | |
| Sedatives or sleeping pills (Valium, Ativan, Xanax, Librium, Rohypnol, GHB, etc) | | |
| Hallucinogens ( LSD, acid, mushrooms, PCP, Special K, ecstasy, etc) | | |
| Street opioids (heroin, opium, etc) | | |
| Prescription opioids (fentanyl, oxycodone [Oxycontin, Percocet], methadone, Buprenorphine, oxymorphone, hydrocodone [Vicodin]) | | |
| Other – specify: | | |

2. **In the past 3 months, how often have you used the substances you mentioned (first drug, second drug, etc)?**

| Frequency (Points listed in box) | Never | Once/Twice | Monthly | Weekly | Daily or Almost Daily |
|---|---|---|---|---|---|
| Cannabis (marijuana, pot, grass, hash, CBD, etc.) | 0 | 2 | 3 | 4 | 6 |
| Cocaine (coke, crack, etc.) | 0 | 2 | 3 | 4 | 6 |
| Prescription stimulants (Ritalin, Concerta, Dexedrine, Adderall, diet pills, etc) | 0 | 2 | 3 | 4 | 6 |
| Methamphetamine (speed, crystal meth, Tina, ice, etc) | 0 | 2 | 3 | 4 | 6 |
| Inhalants (nitrous oxide, glue, gas, paint thinner, "poppers", etc.) | 0 | 2 | 3 | 4 | 6 |
| Sedatives or sleeping pills (Valium, Ativan, Xanax, Librium, Rohypnol, GHB, etc) | 0 | 2 | 3 | 4 | 6 |
| Hallucinogens ( LSD, acid, mushrooms, PCP, Special K, ecstasy, etc) | 0 | 2 | 3 | 4 | 6 |
| Street opioids (heroin, opium, etc) | 0 | 2 | 3 | 4 | 6 |
| Prescription opioids (fentanyl, oxycodone [Oxycontin, Percocet], methadone, Buprenorphine, oxymorphone, hydrocodone [Vicodin]) | 0 | 2 | 3 | 4 | 6 |
| Other – specify: | 0 | 2 | 3 | 4 | 6 |

3. **In the past 3 months, how often have you a strong desire or urge to use (first drug, second drug, etc)?**

| Frequency (Points listed in box) | Never | Once/Twice | Monthly | Weekly | Daily or Almost Daily |
|---|---|---|---|---|---|
| Cannabis (marijuana, pot, grass, hash, CBD, etc.) | 0 | 3 | 4 | 5 | 6 |
| Cocaine (coke, crack, etc.) | 0 | 3 | 4 | 5 | 6 |
| Prescription stimulants (Ritalin, Concerta, Dexedrine, Adderall, diet pills, etc) | 0 | 3 | 4 | 5 | 6 |
| Methamphetamine (speed, crystal meth, Tina, ice, etc) | 0 | 3 | 4 | 5 | 6 |
| Inhalants (nitrous oxide, glue, gas, paint thinner, "poppers", etc.) | 0 | 3 | 4 | 5 | 6 |

| | | | | | |
|---|---|---|---|---|---|
| **Sedatives or sleeping pills (Valium, Ativan, Xanax, Librium, Rohypnol, GHB, etc)** | **0** | **3** | **4** | **5** | **6** |
| **Hallucinogens ( LSD, acid, mushrooms, PCP, Special K, ecstasy, etc)** | **0** | **3** | **4** | **5** | **6** |
| **Street opioids (heroin, opium, etc)** | **0** | **3** | **4** | **5** | **6** |
| **Prescription opioids (fentanyl, oxycodone [Oxycontin, Percocet], methadone, Buprenorphine, oxymorphone, hydrocodone [Vicodin])** | **0** | **3** | **4** | **5** | **6** |
| **Other – specify:** | **0** | **3** | **4** | **5** | **6** |

4. **In the past 3 months, how often has your use (first drug, second drug, etc) lead to health, social, legal or financial problems?**

| **Frequency (Points listed in box)** | **Never** | **Once/Twice** | **Monthly** | **Weekly** | **Daily or Almost Daily** |
|---|---|---|---|---|---|
| **Cannabis (marijuana, pot, grass, hash, CBD, etc.)** | **0** | **4** | **5** | **6** | **7** |
| **Cocaine (coke, crack, etc.)** | **0** | **4** | **5** | **6** | **7** |
| **Prescription stimulants (Ritalin, Concerta, Dexedrine, Adderall, diet pills, etc)** | **0** | **4** | **5** | **6** | **7** |
| **Methamphetamine (speed, crystal meth, Tina, ice, etc)** | **0** | **4** | **5** | **6** | **7** |
| **Inhalants (nitrous oxide, glue, gas, paint thinner, "poppers", etc.)** | **0** | **4** | **5** | **6** | **7** |
| **Sedatives or sleeping pills (Valium, Ativan, Xanax, Librium, Rohypnol, GHB, etc)** | **0** | **4** | **5** | **6** | **7** |
| **Hallucinogens ( LSD, acid, mushrooms, PCP, Special K, ecstasy, etc)** | **0** | **4** | **5** | **6** | **7** |
| **Street opioids (heroin, opium, etc)** | **0** | **4** | **5** | **6** | **7** |
| **Prescription opioids (fentanyl, oxycodone [Oxycontin, Percocet], methadone, Buprenorphine, oxymorphone, hydrocodone [Vicodin])** | **0** | **4** | **5** | **6** | **7** |
| **Other – specify:** | **0** | **4** | **5** | **6** | **7** |

5. **In the past 3 months, how often have you failed to do what was normal expected of you because of your use (first drug, second drug, etc)?**

| Frequency (Points listed in box) | Never | Once/Twice | Monthly | Weekly | Daily or Almost Daily |
|---|---|---|---|---|---|
| Cannabis (marijuana, pot, grass, hash, CBD, etc.) | 0 | 5 | 6 | 7 | 8 |
| Cocaine (coke, crack, etc.) | 0 | 5 | 6 | 7 | 8 |
| Prescription stimulants (Ritalin, Concerta, Dexedrine, Adderall, diet pills, etc) | 0 | 5 | 6 | 7 | 8 |
| Methamphetamine (speed, crystal meth, Tina, ice, etc) | 0 | 5 | 6 | 7 | 8 |
| Inhalants (nitrous oxide, glue, gas, paint thinner, "poppers", etc.) | 0 | 5 | 6 | 7 | 8 |
| Sedatives or sleeping pills (Valium, Ativan, Xanax, Librium, Rohypnol, GHB, etc) | 0 | 5 | 6 | 7 | 8 |
| Hallucinogens ( LSD, acid, mushrooms, PCP, Special K, ecstasy, etc) | 0 | 5 | 6 | 7 | 8 |
| Street opioids (heroin, opium, etc) | 0 | 5 | 6 | 7 | 8 |
| Prescription opioids (fentanyl, oxycodone [Oxycontin, Percocet], methadone, Buprenorphine, oxymorphone, hydrocodone [Vicodin]) | 0 | 5 | 6 | 7 | 8 |
| Other – specify: | 0 | 5 | 6 | 7 | 8 |

6. **Has a friend or relative or anyone else ever expressed concern about your use (first drug, second drug, etc)?**

| Frequency (Points listed in box) | No, never | Yes, but not in the past 3 months | Yes, in the past 3 months |
|---|---|---|---|
| Cannabis (marijuana, pot, grass, hash, CBD, etc.) | 0 | 3 | 6 |
| Cocaine (coke, crack, etc.) | 0 | 3 | 6 |

| | | | |
|---|---|---|---|
| **Prescription stimulants (Ritalin, Concerta, Dexedrine, Adderall, diet pills, etc)** | **0** | **3** | **6** |
| **Methamphetamine (speed, crystal meth, Tina, ice, etc)** | **0** | **3** | **6** |
| **Inhalants (nitrous oxide, glue, gas, paint thinner, "poppers", etc.)** | **0** | **3** | **6** |
| **Sedatives or sleeping pills (Valium, Ativan, Xanax, Librium, Rohypnol, GHB, etc)** | **0** | **3** | **6** |
| **Hallucinogens ( LSD, acid, mushrooms, PCP, Special K, ecstasy, etc)** | **0** | **3** | **6** |
| **Street opioids (heroin, opium, etc)** | **0** | **3** | **6** |
| **Prescription opioids (fentanyl, oxycodone [Oxycontin, Percocet], methadone, Buprenorphine, oxymorphone, hydrocodone [Vicodin])** | **0** | **3** | **6** |
| **Other – specify:** | **0** | **3** | **6** |

7. **Have you ever tried and failed to control, cut down or stop using (first drug, second drug, etc)?**

| **Frequency (Points listed in box)** | **No, never** | **Yes, but not in the past 3 months** | **Yes, in the past 3 months** |
|---|---|---|---|
| **Cannabis (marijuana, pot, grass, hash, CBD, etc.)** | **0** | **3** | **6** |
| **Cocaine (coke, crack, etc.)** | **0** | **3** | **6** |
| **Prescription stimulants (Ritalin, Concerta, Dexedrine, Adderall, diet pills, etc)** | **0** | **3** | **6** |
| **Methamphetamine (speed, crystal meth, Tina, ice, etc)** | **0** | **3** | **6** |
| **Inhalants (nitrous oxide, glue, gas, paint thinner, "poppers", etc.)** | **0** | **3** | **6** |
| **Sedatives or sleeping pills (Valium, Ativan, Xanax, Librium, Rohypnol, GHB, etc)** | **0** | **3** | **6** |
| **Hallucinogens ( LSD, acid, mushrooms, PCP, Special K, ecstasy, etc)** | **0** | **3** | **6** |
| **Street opioids (heroin, opium, etc)** | **0** | **3** | **6** |
| **Prescription opioids (fentanyl, oxycodone [Oxycontin, Percocet], methadone, Buprenorphine, oxymorphone, hydrocodone [Vicodin])** | **0** | **3** | **6** |
| **Other – specify:** | **0** | **3** | **6** |

8. **Have you ever used any drug by injection (non-medical use only)?**
   - ☐ No, never
   - ☐ Yes, but no in the past 3 months
   - ☐ Yes, in the past 3 months

9. **Substance use grading**

| Substance Involvement Score | Total (SI Score) | Risk Level |
|---|---|---|
| **Cannabis (marijuana, pot, grass, hash, CBD, etc.)** | | |
| **Cocaine (coke, crack, etc.)** | | |
| **Prescription stimulants (Ritalin, Concerta, Dexedrine, Adderall, diet pills, etc)** | | |
| **Methamphetamine (speed, crystal meth, Tina, ice, etc)** | | |
| **Inhalants (nitrous oxide, glue, gas, paint thinner, "poppers", etc.)** | | |
| **Sedatives or sleeping pills (Valium, Ativan, Xanax, Librium, Rohypnol, GHB, etc)** | | |
| **Hallucinogens ( LSD, acid, mushrooms, PCP, Special K, ecstasy, etc)** | | |
| **Street opioids (heroin, opium, etc)** | | |
| **Prescription opioids (fentanyl, oxycodone [Oxycontin, Percocet], methadone, Buprenorphine, oxymorphone, hydrocodone [Vicodin])** | | |
| **Other – specify:** | | |

**SI risk Level**

| Level of risk associate with SI score for Illicit or nonmedical prescription drug use | |
|---|---|
| **0-3** | **Lower Risk** |
| **4-26** | **Moderate Risk** |
| **27+** | **High Risk** |

**Addendum D: Patient Reported Outcomes – adapted from SF-12**

## BASE Study: SF-12

Name: Visit Week:
DOB: Participant ID:

1. In general would you say your health is:
   ☐ Excellent
   ☐ Very good
   ☐ Good
   ☐ Fair
   ☐ Poor

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

   Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:
   ☐ Yes, limited a lot
   ☐ Yes, limited a little
   ☐ No, not limited at all

   Climbing several flights of stairs:
   ☐ Yes, limited a lot
   ☐ Yes, limited a little
   ☐ No, not limited at all

3. During the past week, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

   Accomplished less than you would like:
   ☐ Yes
   ☐ No

   Were limited in the kind of work or other activities:
   ☐ Yes
   ☐ No

4. During the past week, have you had any of the following problems with your work or other regular daily activities as a result of your emotional health problems (such as feeling depressed or anxious)?

   Accomplished less than you would like:
   ☐ Yes
   ☐ No

   Didn't do work or other activities as carefully as usual:
   ☐ Yes
   ☐ No

5. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?
   ☐ Not at all
   ☐ A little bit
   ☐ Moderately
   ☐ Quite a bit
   ☐ Extremely

6. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week:

   Have you felt calm and peaceful:
   ☐ All the time
   ☐ Most of the time
   ☐ A good bit of the time
   ☐ Some of the time
   ☐ A little of the time
   ☐ None of the time

   Did you have a lot of energy:
   ☐ All the time
   ☐ Most of the time
   ☐ A good bit of the time
   ☐ Some of the time
   ☐ A little of the time

☐ None of the time

Have you felt downhearted and blue:
☐ All the time
☐ Most of the time
☐ A good bit of the time
☐ Some of the time
☐ A little of the time
☐ None of the time

7. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
   ☐ All the time
   ☐ Most of the time
   ☐ A good bit of the time
   ☐ Some of the time
   ☐ A little of the time
   ☐ None of the time

**PCS-12 (Physical Score): _____**

**MCS-12 (Mental Score): _____**

**Scoring available at: http://orthotoolkit.com/sf-12/**

**Addendum E: Qualitative Sub-Study**

**Study Protocol**: Engagement in HIV Care and On-going Substance Use: A Qualitative Sub-Study of Perspectives from BASE Study Participants

**Investigators:** Josh Havens, Liam Heerten-Rodriguez, Jason Coleman, Susan Swindells

**Objectives:**
We aim to qualitatively examine BASE study participants for their experiences and perspectives of BASE study participation impact on engagement in HIV care, treatment adherence, and ongoing substance/mental health.

**Brief Description:**
Illicit substance use in the United States is a growing concern across all states. Use of illicit drugs such as cocaine, heroin, methamphetamine, prescription opioids and stimulants, and 3,4-methylenedioxy-methamphetamine (Ecstacy, MDMA) among others, has remained steady in many parts of the United States[1]. Of the 1.2 million PWH in the US, an estimated 48% struggles with a substance use disorder[2]. Poor antiretroviral treatment (ART) adherence and inconsistencies in retention in HIV care has been reported among PWH that use illicit drugs [3-5]. Gaps in ART coverage and lack of retention to HIV care are factors that complicate successfully managing PWH who use illicit drugs, often leading to poor treatment outcomes and increased HIV transmission[6-8].

The BASE study is a single-arm, pilot study assessing the efficacy and safety of bictegravir/emtricitabine/tenofovir alafenamide, B/F/TAF) over a total of 48 weeks (NCT03998176). At present, roughly 40% of the allotted 45 patients have given consent for BASE study participation with the initial participant's now reaching week 24. Historically, approximately half of the currently enrolled BASE participants have remained out of HIV care and struggled with adherence and ongoing substance use. The study team have been surprised to observe that many of these participants are more engaged in care and not missing study visits. Further, the same participants have reportedly remained adherent to antiretroviral therapy for the first time in years, and some have reduced or ceased their substance use since study enrollment.

In order to examine the underlying reasons for this behavior change, we propose a qualitative study in the form of in-depth, face-to-face interviews with BASE study participants to evaluate the impact of BASE study participation on their treatment adherence, motivations for engagement in HIV care, on-going substance use, mental health, stigma, and access to the necessary support systems.

***Hypothesis:***

BASE study participation positively impacted the participant's treatment adherence, motivations for engagement in care for HIV, substance use disorders, and mental health.

***Objectives:***

1. Primary: Determine BASE participant perspectives on how study participation impacted their engagement in HIV care and treatment adherence.
2. Secondary: Determine BASE participant perspectives on how study participation impacted their on-going substance use, mental health, and access to necessary support systems.

***Study Design:***

Overview

This study will be a prospective qualitative study design with interest in examining patient perspectives on the impact of BASE study participation on the following topical domains: treatment adherence, motivations for engagement in HIV care, on-going substance use, mental health, stigma, and access to the necessary support systems. We plan to use a semi-structured, in-depth face-to-face interview to evaluate the topical domains previously listed among participants enrolled in the Phase IV trial in the United States (Effectiveness and safety of Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in HIV-1 infected patients with Active illicit Substance usE [BASE]; NCT 03998176). The anticipated timeframe for in-depth interviews is near the BASE week 48 visit window (42 to 60 weeks).

Sample Size/Justification

A sample size of 10 to 15 participants is typically understood to be a sufficient amount to develop themes within a given group. However, we aim to sample roughly half of the BASE participants (20-25) or until thematic saturation is achieved.

***Participants:***

Inclusion Criteria

This study will include participants currently enrolled in the BASE study at the Specialty Care Center in Omaha, NE. We will attempt to balance the enrollment by gender and sociodemographic diversity. A summary of BASE inclusion criteria is below:

9. Inclusion Criteria
    a. Current participant in the BASE study
    b. Willing and able to give written informed consent (not severely experiencing psychiatric condition or severely under the influence of illicit substances compromising ability to understand and provide consent)
    c. English speaking

Exclusion Criteria

1. None

**Study Procedures**

Recruitment

Research providers (primary investigator or study team provider) who have already had contact with the participants through the BASE study conduct will identify and directly contact potential study participants during a BASE study visit. If the participant is interested in participating in the qualitative

sub-study, study description and obtaining consent would take place in-person at the Specialty Care Center with a subsequent qualitative study visit scheduled in the future.

All study interactions with potential or enrolled participants will be conducted in a private room at the Specialty Care Center.

Consent Process

Written informed consent will be obtained for all participants wishing to enroll in the qualitative sub-study. Written informed consenting will be conducted by research providers (primary investigator or study team provider) prior to any interviewing procedures. All consenting will take place at the Specialty Care Center in a private room. All consenting study team members are CITI trained and the consenting study team member will sign off on the consent.

Study Implementation

After consent has been given, each sub-study participant will be interviewed using a semi-structured, in-depth interview guide. The interview guide (Appendix A) contains a listing of open-ended questions with subsequent sub-question probes to elicit participant experiences and perspectives regarding each core topic.

Topics to be explored within the in-depth interviews include:

1. Living with HIV
2. Living with a substance use disorder
3. Engagement in HIV care
4. Views and experiences with study participation

All in-depth interviews will be conducted by a trained interviewer in qualitative research. Interviews will be conducted in English. All interviews will be audio-recorded and transcribed by study team members for data analysis.

Only one in-depth interview will be conducted for each participant. We expect the interviews to be 1 to 2 hours in length. All interviews will take place in a private room. Since participants are enrolled in the BASE study in a rolling fashion, each participant may hit the week 48 study visit window at different time points. Thus, we expect the timeframe for qualitative interviews to take up to 6 months to allow for at least half of BASE participants reaching week 48.

Interview transcripts will be coded through a qualitative software, QSR NVivo. Within each topic of interest, a thematic analysis approach will be utilized toward the coded transcripts. The study team will examine the emerging themes from the data analysis.

All study data including participant contact information will be collected and stored on University of Nebraska Medical Center (UNMC), secure-servers with password-protected files. All interview forms, audio-records, and transcripts will be identified only by the participants BASE patient identification number.

**Data Management and Security**

Data Storage

All data collection forms will be coded with the participants BASE study identification number. Patient identification numbers are stored securely on a UNMC, secure-server and also within REDCap hosted by UNMC. All study records will be will stored on a UNMC, secure-server until publication.

Confidentiality

All participants are provided a National Institutes of Health, Certificate of Confidentiality (CoC), for their participation within the BASE study. The CoC has already been applied for and approved prior to BASE study initiation.

**Study Risks**

Participants within this qualitative study may potentially become embarrassed, frustrated, or uncomfortable with the sensitive questions asked of them during in-depth interviewing regarding their HIV diagnosis, on-going substance use, stigma, etc. Those experiencing psychological distress will be offered a referral for counseling or psychiatric evaluation, including in the emergency room if needed.

**Study Benefits**

There are no direct benefits to the participants. Possible societal benefits involve informing medical providers on engaging patients with on-going substance use disorders and HIV infection.

**Participant Compensation**

Participants will be reimbursed with Visa cash cards at a rate of $20/hour.

**Study Management**

The primary investigator will oversee all aspects of the study including obtaining informed consent, data collection, and analysis. The study team will identify 1 to 2 doctoral or post-doctural students to assist in the study conduct. All planned interviews and data analysis will be conducted by the University of Nebraska Omaha (UNO), School of Health and Kinesiology faculty or staff under the guidance of Dr. Jason Coleman. All interviewers will have CITI certifications and training in qualitative research.

**References**


1. Substance Abuse and Mental Health Services Administration (2018). Results from the 2017 National Survey on Drug Use and Health. Rockville, MD: Substance Abuse and Mental Health Services Administration.
2. Hartzler B, Dombrowski JC, Crane HM, et al. Prevalence and Predictors of Substance Use Disorders Among HIV Care Enrollees in the United States. *AIDS Behav.* 2017;21(4):1138-1148.
3. Colasanti J, Stahl N, Farber EW, Del Rio C, Armstrong WS. An Exploratory Study to Assess Individual and Structural Level Barriers Associated With Poor Retention and Re-engagement in Care Among Persons Living With HIV/AIDS. *J Acquir Immune Defic Syndr.* 2017;74 Suppl 2:S113-S120.

4. Mimiaga MJ, August Oddleifson D, Meersman SC, et al. Multilevel Barriers to Engagement in the HIV Care Continuum Among Residents of the State of Rhode Island Living with HIV. *AIDS Behav.* 2019.
5. Pecoraro A, Royer-Malvestuto C, Rosenwasser B, et al. Factors contributing to dropping out from and returning to HIV treatment in an inner city primary care HIV clinic in the United States. *AIDS Care.* 2013;25(11):1399-1406.
6. Kamarulzaman A, Altice FL. Challenges in managing HIV in people who use drugs. *Curr Opin Infect Dis.* 2015;28(1):10-16.
7. Meyer JP, Althoff AL, Altice FL. Optimizing care for HIV-infected people who use drugs: evidence-based approaches to overcoming healthcare disparities. *Clin Infect Dis.* 2013;57(9):1309-1317.
8. Shubber Z, Mills EJ, Nachega JB, et al. Patient-Reported Barriers to Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis. *PLoS Med.* 2016;13(11):e1002183.

**Appendix A**

**Interview Question Guide: BASE Participants**

PID:_____ Date: _____

***Introduction*:**

Thank you for the opportunity to speak with me today. Please note that this conversation is confidential. We are interested in hearing your opinions and experiences regarding how your participation in the BASE study impacted your motivations for engaging in medical care, your substance use, your mental health and you overall quality of life. May I start by asking you about your experience living with HIV…

***Living with HIV***

1. What has your experience been like living with HIV?
    a. Probe: When were you first diagnosed?
    b. Probe: What experiences did you have coping with your HIV diagnosis?

2. What support systems did you initially have or currently have for coping with your HIV diagnosis?
    a. Probe: friends, family, partner, support groups, etc

3. What were you initially told about HIV treatment?
    a. Probe: What feelings did you have regarding the need for life-long treatment?
    b. Probe: What feelings did you have knowing there was no cure for HIV infection?

4. What experiences have you had with stigma or discrimination because you are living with HIV?
    a. Probe: Friends, family, partner, work

5. What is the hardest part of living with HIV?
    a. Probe: Taking life-long medicine, coming to medical visits, dealing with stigma, worry of health, cost of care, etc.

***Living with a substance use disorder***

1. What has your experience been like living with a substance use disorder?
    a. Probe: When did you first use an illicit drug and how has your substance use impacted your well-being?
    b. Probe: What experiences did you have coping with your substance use?

2. What support systems did you initially or currently have for coping with your substance use disorder?
    a. Probe: friends, family, partner, support groups, etc

3. In what ways has your substance use disorder affected your life?

a. Probe: Medically, relationships, financial, etc.

4. What experiences have you had with stigma or discrimination because you have a substance use disorder?
    a. Probe: Friends, family, partner, work

5. What are your experiences with receiving help for your substance use disorder?
    a. Probe: Describe your experiences with trying to stop or reduce your substance use.
    b. Probe: How many times have your tried to stop or reduce your substance use?
    c. Probe: What have been the challenges with stopping or reducing your substance use?

***Engagement in HIV care***

1. What does being engaged in HIV care mean to you?
    a. Probe: Would you describe your engagement in HIV care prior as good or bad? Why?

2. Tell us your experiences with coming to clinic appointments.
    a. Probe: What barriers have kept you from coming to your appointments?

3. What are your views on what has kept you from coming to your clinic appointments?
    a. Probe: Medication non-adherence, substance use, homelessness, etc

4. What interventions have helped you to come to your clinic appointments?
    a. Probe: acute sickness, concern for your health, transportation assistance, gift cards, etc.

5. What experiences have you had with stigma or discrimination when coming to an HIV clinic appointment?
    a. Probe: What are you feelings about the impact of HIV control (U=U) on stigma related to HIV infection or substance use disorders?
    b. Probe: What have been your experiences during interactions with medical service providers?
    c. Probe: Would you describe your experiences with various types of healthcare providers (medical [both HIV providers and non-HIV providers], mental health, etc) as different? Why?

***Views and experiences with study participation***

1. How did you hear about the BASE study?
    a. Probe: What motivated you to enroll?
    b. Probe: What interested you most about the study?

2. What concerns did you have about participating in the BASE study?
    a. Probe: Privacy, stigma, legal concerns

3. Tell us about your experiences with BASE study participation.
    a. Probe: Would you describe your experience as positive or negative? Why?

4. How has participating in the BASE study impacted your ability to come to your clinic appointments?
    a. Probe: What are your feelings of your medical care during participation of the BASE study?
    b. Probe: What factors have increased or decreased your ability to come to your clinic appointments during the course of the BASE study?

5. How has participating in the BASE study impacted your ability to take your medicine?
    a. Probe: What factors have increased or decreased your ability to adhere to prescribed medications during the course of the BASE study?

6. What experiences have you had with stigma or discrimination because you participated in the BASE study?
    a. Probe: Medical providers, friends, family, partner, work

7. How has participating in the BASE study impacted your substance use disorder?
    a. Probe: Compared to before study participation, would you describe your substance use better or worse? Why?

8. In what ways has your participation in BASE helped you cope or not cope with your HIV diagnosis or substance use disorder?

*Closing*

1. Is there anything else that you feel is important for us to know that we haven't already asked about?