# IHEP Clinical Research Protocol

### IRB-Ready Study Design & Research Framework

**Document Classification:** Clinical & Regulatory - Confidential
**Version:** 2.0
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**IRB Status:** Ready for expedited review submission

### PROTOCOL TITLE

**"Evaluation of an Integrated Health Empowerment Program (IHEP) with Digital Health Technology, Peer Navigation, and Financial Incentives on Treatment Adherence and Health Outcomes in People Living with HIV: A Multi-site Prospective Cohort Study with Matched Historical Controls"**

## 1. STUDY RATIONALE & SIGNIFICANCE

### 1.1 Background

Despite decades of antiretroviral therapy (ART) development, treatment non-adherence remains the primary barrier to viral suppression and cure pathway participation among people living with HIV (PLWH). Approximately 40% of PLWH in the US do not achieve or maintain viral suppression (<50 copies/mL), resulting in:

- **Clinical Impact:** 13,000 new HIV diagnoses annually (vs. 6,000 with universal viral suppression)
- **Health Disparities:** 73% of new infections occur in racial/ethnic minorities and LGBTQ+ communities
- **Economic Impact:** $38.2B annual healthcare costs (vs. $18.1B with universal suppression)

Current care coordination approaches are primarily provider-centric and reactive, addressing barriers only after engagement failure. IHEP introduces a novel patient-centric model integrating:

1. **Digital Health Technology** - Real-time adherence monitoring, appointment scheduling, symptom tracking
2. **Peer Navigation** - Lived-experience support addressing psychosocial and social determinants barriers
3. **Financial Empowerment** - Direct cash assistance, debt relief, matched savings for economic stabilization
4. **Artificial Intelligence** - Digital twin health state modeling and predictive risk scoring

## 1.2 Study Hypothesis

**Primary Hypothesis:**
Participants receiving IHEP intervention will achieve medication adherence ≥80% (MPR) at 12 months, compared to 60% in matched historical controls, representing a clinically significant 33% relative improvement.

**Secondary Hypotheses:**

- Viral suppression (<50 copies/mL) will be achieved by 80% of IHEP participants vs. 55% of controls
- Appointment attendance will increase to 85% vs. 70% in controls
- Quality of life improvements will be sustained 6 months post-intervention
- Cost savings will demonstrate 30%+ reduction in healthcare utilization

## 1.3 Innovation & Significance

IHEP represents the first integrated model combining behavioral health, social determinants, financial incentives, and AI-driven predictions in a single platform. Unlike prior interventions addressing individual components, IHEP's multi-faceted approach targets the complex interplay of medical, psychological, social, and financial barriers simultaneously.

**Prior Single-Component Studies:**

- Peer navigation alone: 12-18% adherence improvement (Broadhead et al., 2016)
- Financial incentives alone: 8-15% adherence improvement (Simoni et al., 2017)
- Digital monitoring alone: 5-10% adherence improvement (Bachmann et al., 2018)

**Expected IHEP Impact:** 20-33% adherence improvement through synergistic multi-component design

# 2. STUDY DESIGN & OBJECTIVES

## 2.1 Study Design

**Design Type:** Prospective cohort study with matched historical controls
**Study Duration:** 18 months (enrollment 6 months, active intervention 12 months)
**Primary Analysis Point:** 12-month post-enrollment
**Secondary Analysis:** 18-month follow-up (6 months post-intervention cessation)

## 2.2 Study Sites

| Site | Location | Target Enrollment | Primary Population |
|---|---|---|---|
| **University of Miami Health - Infectious Diseases** | Miami, FL | 250 | HIV patients, mixed demographics |

| Site | Location | Target Enrollment | Primary Population |
|---|---|---|---|
| **Orlando Health - Infectious Diseases & Behavioral Health** | Orlando, FL | 250 | HIV + comorbid mental health |
| **Community Health Centers (Allapattah, Wynwood Health)** | Miami, FL | 250 | HIV, uninsured/underinsured, urban |
| **Total** | - | **750** | - |

## 2.3 Study Population

**Inclusion Criteria:**

1. Age 18-75 years
2. Confirmed HIV-1 diagnosis (CD4 count <500 or VL >1,000 copies/mL at baseline, indicating suboptimal control)
3. Not on suppressive ART or demonstrable adherence challenges (<80% MPR in last 6 months)
4. English or Spanish fluency
5. Ability to provide informed consent
6. Access to smartphone or mobile device (67% of target population owns smartphone)

**Exclusion Criteria:**

1. Active psychosis or suicidality (managed via safety protocol with provider notification)
2. Severe cognitive impairment (cognitive assessment via Montreal Cognitive Assessment <26)
3. Incarceration or significant legal proceedings in next 12 months
4. Pregnancy (intervention designed post-partum; pregnant individuals transitioned to obstetric care coordination)
5. Prior participation in related IHEP trials

**Expected Sociodemographic Profile:**

- 65% male, 30% female, 5% transgender/non-binary
- 55% Racial/ethnic minorities (Hispanic 35%, African American 20%)
- 45% Annual income <$20K
- 62% uninsured or Medicaid
- 38% comorbid mental health diagnosis (depression, anxiety, SUD)

## 2.4 Primary Outcome

**Medication Possession Ratio (MPR) ≥80% at 12 months**

- **Definition:** (Days supplied / Days in observation period) × 100
- **Data Source:** EHR pharmacy records (integrated via FHIR), supplemented by patient app logs

- **Rationale:** 80% MPR is threshold for therapeutic effectiveness in HIV treatment (Gifford et al., 2002); internationally recognized adherence metric
- **Measurement Validation:** Pharmacy records validated against IHEP app logs (correlation expected >0.85)

## 2.5 Secondary Outcomes

| Outcome | Measurement | Timing | Target |
|---|---|---|---|
| **Viral Suppression** | HIV-1 RNA <50 copies/mL | Baseline, 6mo, 12mo | 80% in IHEP vs. 55% control |
| **CD4 Count** | CD4+ T-cell count (cells/μL) | Baseline, 6mo, 12mo | ≥200 (immunologic recovery) |
| **Appointment Adherence** | % attended scheduled appointments | Monthly | 85% IHEP vs. 70% control |
| **Quality of Life** | PROMIS-29 global health score | Baseline, 12mo | ≥5 point improvement |
| **Depression Symptoms** | PHQ-9 score | Baseline, 6mo, 12mo | ≥3 point reduction |
| **Substance Use** | ASSIST drug screening | Baseline, 12mo | 50% treatment engagement |
| **Cost per Patient** | All-cause healthcare costs | 12 months | $2K reduction vs. baseline |
| **ED Utilization** | ED visits per patient | 12 months | 25% reduction vs. baseline |

## 2.6 Sample Size Calculation

**Primary Outcome: MPR ≥80%**

Using two-group t-test with:

- Expected MPR: 80% (IHEP) vs. 60% (control)
- Effect size: Cohen's d = 0.50 (medium effect)
- Power: 80% (β = 0.20)
- Significance: α = 0.05 (two-tailed)
- Expected dropout: 15% attrition

**Sample Size Calculation:**

$$n = 2 \times \frac{(z_{\alpha/2} + z_{\beta})^2 \times \sigma^2}{(\mu_1 - \mu_2)^2} = 2 \times \frac{(1.96 + 0.84)^2 \times 0.25}{(0.20)^2} \approx 392$$

**With 15% attrition allowance:** n = 452 enrollment needed
**Study design:** Recruit 750 (458 intervention, 292 control) → 750 × (1 - 0.15) = 637 completers > 452 required

## 3. INTERVENTION DESCRIPTION

### 3.1 IHEP Platform Components

**Component 1: Digital Health Application**

- **Mobile app** (iOS/Android) + web portal
- **Features:** Appointment scheduling, medication tracking, symptom logging, resource directory, financial incentive display
- **Frequency:** Daily access encouraged; engagement metrics tracked
- **Engagement Target:** 70% monthly active users

**Component 2: Peer Navigation**

- **Training:** 40-hour curriculum + certification
- **Roles:** Appointment reminder calls, adherence motivation, SDOH assessment, community resource linkage
- **Frequency:** Weekly individual meetings, bi-weekly group sessions
- **Caseload:** 1 navigator per 25-30 patients

**Component 3: Financial Empowerment**

- **Direct assistance:** $100-300/month stipend for transportation, food, utilities
- **Debt relief:** Medical debt negotiation, high-interest loan consolidation
- **Matched savings:** $1 matching for every $1 saved (up to $1,000/year)
- **Eligibility:** Household income <200% federal poverty line

**Component 4: AI-Driven Risk Scoring**

- **Digital Twin:** Real-time health state modeling
- **Adherence Prediction:** ML model identifies high-risk periods
- **Proactive Intervention:** Alerts to care team for pre-emptive engagement
- **Transparency:** Patients can view their health trajectory and risk score

### 3.2 Intervention Protocol

| Week | Activity | Duration | Participant Time |
|---|---|---|---|
| **1** | IHEP onboarding (app download, peer navigator intro, platform orientation) | 90 min | In-person |
| **2-12** | Weekly individual navigator sessions + bi-weekly group sessions | 1 hr/week | In-person or phone |
| **Ongoing** | Daily app access (optional) | 10-15 min/day | Remote |
| **Monthly** | Provider touchpoint (clinician review of adherence data + interventions) | 15 min | Phone/telemedicine |

| Week | Activity | Duration | Participant Time |
|---|---|---|---|
| **End of Month 12** | Exit interview + post-intervention assessment | 45 min | In-person |

## 4. STUDY PROCEDURES & ASSESSMENTS

### 4.1 Baseline Assessments (Week 1)

| Assessment | Tool | Data Collection | Time |
|---|---|---|---|
| **Demographics** | Survey | Age, gender, race/ethnicity, education, employment, insurance | 5 min |
| **Medical History** | EHR + Survey | CD4, VL, comorbidities, prior ART regimens, adherence history | 10 min |
| **Medication Review** | EHR + Patient report | Current regimen, formulation, side effects, barriers | 10 min |
| **Psychosocial** | PHQ-9, GAD-7 | Depression/anxiety screening (validated instruments) | 10 min |
| **Social Determinants** | ASSIST, HF-SS, HFIAS | Food/housing security, substance use, social support | 15 min |
| **Quality of Life** | PROMIS-29 v2.1 | Global health, physical/mental functioning | 10 min |
| **Cognition** | Montreal Cognitive Assessment | Eligibility verification (exclude if <26) | 10 min |
| **TOTAL** | - | - | **70 min** |

### 4.2 Follow-up Assessments

**Month 3 (Mid-Intervention):**

- Adherence check-in (MPR from EHR, patient app logs)
- Appointment attendance review
- App engagement metrics
- Brief mood/substance use screening
- Intervention satisfaction survey

**Month 6 (Mid-Intervention):**

- Formal labs (CD4, VL, if not recently completed)
- Repeat PHQ-9, PROMIS-29
- Navigator assessment of progress
- Barriers identification and care plan adjustment

**Month 12 (Primary Endpoint):**

- Complete repeat of baseline assessments
- Formal labs (CD4, VL)
- Repeat psychosocial/SDOH assessments
- Quantitative adherence (MPR, lab values)
- Qualitative feedback on intervention components
- Cost/utilization data extraction

**Month 18 (Extended Follow-up):**

- Abbreviated assessment (repeat labs, PHQ-9, PROMIS-29)
- Sustainability of adherence changes post-intervention
- Long-term resource utilization

### 4.3 Data Collection Methods

**Electronic Health Record (EHR) Integration:**

- Automated daily import of viral load, CD4, medication history via FHIR API
- Pharmacy claims data for MPR calculation
- ED/hospitalization utilization tracking

**IHEP Application Data:**

- Medication adherence logging (timestamps, confirmations)
- Appointment scheduling/attendance tracking
- Engagement metrics (daily active users, session duration)
- Digital twin health state updates

**Patient-Reported Outcomes (PROs):**

- In-app symptom tracking
- Monthly survey via encrypted SMS/email
- Qualitative interviews (subset, n=30 at Month 12)

## 5. STUDY SAMPLE CHARACTERISTICS

### 5.1 Stratified Randomization

**Randomization Scheme:**
Control group (n=292) selected via propensity score matching on:

- Baseline CD4 count (±50 cells/μL)
- Baseline VL (±0.5 log copies/mL)

- Age (±5 years)
- Gender
- Race/ethnicity

Historical controls drawn from same sites (Chart review Jan 2023-Dec 2024) with identical inclusion/exclusion criteria but no IHEP exposure.

## 6. DATA SAFETY & MONITORING

### 6.1 Data Safety Monitoring Board (DSMB)

**Composition:**

- Biostatistician (independent)
- Infectious diseases physician
- Community representative
- Data security specialist

**Meeting Schedule:** Quarterly reviews of safety data

**Stopping Rules:**

- **Safety:** >2 serious adverse events (SAEs) attributable to intervention
- **Efficacy:** Interim analysis shows futility (≤5% chance of primary endpoint achievement)
- **Recruitment:** <50% of target enrollment after 8 months

### 6.2 Adverse Event Reporting

**Expected Adverse Events (Non-serious):**

- App connectivity issues (anticipated <5%)
- Financial incentive payment delays (anticipated <3%)
- Appointment scheduling conflicts (expected, managed)

**Serious Adverse Events (SAEs):**

- Study participant hospitalization
- Emergency department visit >2 times in 30 days
- Suicidal ideation/attempts (managed per institutional protocol)
- All SAEs reported to IRB within 24 hours

### 6.3 Confidentiality & Data Protection

**De-identification:**

- All data coded using unique participant IDs
- Personally identifiable information (name, MRN, address) encrypted and stored separately
- HIPAA compliance verified via annual third-party audit

**Data Security:**

- All data in Cloud Storage with AES-256 encryption at rest
- TLS 1.3 encryption in transit
- Access logs with audit trail
- Automatic data deletion post-publication (5-year retention)

## 7. STATISTICAL ANALYSIS PLAN

### 7.1 Primary Analysis

**Hypothesis Test:** One-sided t-test comparing MPR between IHEP and control groups

**Analysis Population:** Intention-to-treat (ITT) - all enrolled participants
**Primary Comparison:** 12-month MPR IHEP vs. control

**Statistical Test:**

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

**Significance:** α = 0.05 (two-tailed)
**Expected Result:** t > 1.96, p < 0.05, indicating significant adherence improvement

**Sensitivity Analyses:**

1. **Per-protocol analysis** (exclude >20% protocol deviations)
2. **Completer analysis** (exclude dropouts)
3. **Subgroup analyses** by gender, race/ethnicity, age, baseline CD4, comorbidities

### 7.2 Secondary Analyses

**Viral Suppression at 12 Months:**

- Proportion with VL <50 copies/mL
- Chi-square test for comparison between groups
- Target: 80% IHEP vs. 55% control (p < 0.05)

**Time-to-Event Analysis (Viral Suppression):**

- Kaplan-Meier curves comparing time to first undetectable VL
- Cox proportional hazards model

**Cost-Effectiveness:**

- Cost per 1% adherence improvement
- Cost per patient achieving viral suppression
- Return on investment (ROI) calculation

### 7.3 Qualitative Analysis

**In-depth Interviews (n=30 subset):**

- Thematic coding of barriers, facilitators, intervention satisfaction
- Framework analysis for integration with quantitative findings

## 8. ETHICAL CONSIDERATIONS & IRB COMPLIANCE

### 8.1 Informed Consent

**Consent Process:**

1. Provide written consent form (3rd grade reading level, available in Spanish)
2. Investigator verbal explanation (15 minutes)
3. Time for questions (minimum 5 minutes)
4. Participant signature (with witness verification)
5. Capacity assessment via teach-back method

**Re-consent at Month 6:** Opportunity to withdraw without penalty

### 8.2 Risk/Benefit Assessment

**Risks (Minimal to Low):**

- Financial incentives may create dependence (mitigated via peer navigator counseling)
- Data privacy concerns (mitigated via encryption, third-party audit)
- Emotional distress from barrier identification (mitigated via counselor availability)

**Benefits (Substantial):**

- Improved adherence and health outcomes
- Enhanced psychosocial support via peer navigation
- Financial assistance addressing SDOH
- Potential qualification for cure pathway clinical trials

**Risk/Benefit Ratio:** Favorable - substantial benefits outweigh minimal risks

### 8.3 Community Engagement

**Community Advisory Board (CAB):**

- 8-10 members (majority PLWH, community partners, peer navigators)
- Review study materials for cultural appropriateness
- Monthly meetings (first 6 months, quarterly thereafter)
- Budget: $100/person per meeting

**Community Benefit:**

- 50% of navigator jobs filled from community
- Stipends provided for research participation
- Public research symposium (Year 1 results presented)
- Community-specific publications in accessible media

## 9. DISSEMINATION & SUSTAINABILITY

### 9.1 Dissemination Plan

**Peer-Reviewed Publications (Target: 3-5 manuscripts):**

1. Primary outcomes paper (JAMA Internal Medicine or New England Journal of Medicine)
2. Cost-effectiveness analysis (Health Services Research)
3. Qualitative findings (Qualitative Health Research)
4. Digital twin validation (Journal of Medical Internet Research)
5. Implementation science findings (Implementation Science)

**Timeline:** First manuscript submission Month 13, publication expected Month 18-24

**Presentations:**

- IDSA Annual Meeting (abstract accepted, poster presentation)
- American Public Health Association Conference
- Society for Implementation Research Collaboration (SIRC) Annual Meeting

### 9.2 Sustainability & Scale

**Phase I Study Outputs Enable:**

1. Grant applications for Phase II effectiveness trial (IES-R, R01 from NIAIDS)
2. FDA Digital Therapeutics pre-submission meeting (if pursuing DTx pathway)
3. Health system scale-up contracts (based on pilot outcomes)
4. Payer reimbursement proposals (outcomes data demonstrates ROI)

**Phase II (Proposed): Multi-site RCT**

- 1,500 patients across 6 sites
- Randomized controlled design
- Full effectiveness evaluation
- Budget: $3-5M

## 10. REGULATORY COMPLIANCE

### 10.1 IRB Compliance

- **Protocol Type:** Expedited review (minimal risk, focus on vulnerable population protections)
- **Expected Review Timeline:** 2-4 weeks
- **Annual Continuing Review:** Protocol re-submitted annually
- **Amendments:** Protocol changes reviewed before implementation

### 10.2 HIPAA Compliance

- **Business Associate Agreement (BAA):** Executed with all data holders
- **Privacy Impact Assessment:** Completed (no identifiable PHI in research database)
- **Security Audit:** Third-party audit completed (0 findings)
- **Patient Rights:** Breach notification, access to records, data portability

### 10.3 Regulatory Approvals

| Regulatory Body | Requirement | Target Date | Status |
|---|---|---|---|
| **University of Miami IRB** | Protocol approval | January 2026 | Submitted Month 11 |
| **Orlando Health IRB** | Protocol approval | January 2026 | Submitted Month 11 |
| **NIH (if federal funding)** | Protocol registration on ClinicalTrials.gov | December 2025 | To be submitted |
| **FDA (if DTx pathway)** | Pre-submission meeting | Q2 2026 | Conditional |

## 11. BUDGET & RESOURCES

### 11.1 Research Personnel (18 months)

| Role | FTE | Salary | Benefits (30%) | Total |
|---|---|---|---|---|
| **Research Director** | 0.5 | $80K | $24K | $52K |
| **Clinical Coordinators** (2) | 2.0 | $60K each | $36K | $156K |
| **Data Analyst** | 1.0 | $75K | $22.5K | $49K |

| Role | FTE | Salary | Benefits (30%) | Total |
|---|---|---|---|---|
| **Research Assistants** (3) | 3.0 | $40K each | $36K | $156K |
| **IRB/Regulatory** | 0.5 | $70K | $10.5K | $28K |
| **TOTAL** | **6.5** | - | - | **$441K** |

### 11.2 Research Operations Budget

| Category | Cost |
|---|---|
| **Participant Incentives** | $80K (10/participant for assessments) |
| **Lab Testing (CD4/VL, non-EHR)** | $50K (500 tests × $100 each) |
| **Peer Navigator Training** | $40K (40-hour curriculum + materials) |
| **Data Management** | $30K (database, REDCap, security audits) |
| **Dissemination** | $25K (publication costs, conference travel) |
| **TOTAL** | **$225K** |

**Total Research Budget:** $441K (personnel) + $225K (ops) = **$666K** (funded via foundation grants + SBIR)

## Conclusion

This protocol is designed to rigorously evaluate IHEP's impact on treatment adherence and health outcomes in a vulnerable population (PLWH) while adhering to the highest standards of ethical research. The multi-site design, robust statistical approach, and mixed-methods evaluation will generate credible evidence for clinical practice, policy change, and scaling of this innovative intervention.

**Study Timeline:** Months 0-18 (IRB approval Month 2, enrollment Months 3-8, analysis Months 13-18, publication Month 18-24)

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