Implementation, Evaluation, and Cost Effectiveness of a Data-to-Care Strategy to Improve HIV Continuum Outcomes for Out of Care PLWH in Ukraine

Sponsored by:

US National Institutes of Health

NCT number: NCT05821413

Co-Principal Investigators

Jill Owczarzak, PhD

The Johns Hopkins University

Kostyantyn Dumchev, MD, MPH

Ukrainian Institute on Public Health Policy

D2C Ukraine

Version 1.1

21-Mar-2023

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Study overview

In Ukraine, use of ART among people living with HIV (PLWH) has not kept pace with the number of new HIV diagnoses over the past two decades.[1] Of the approximately 250,000 estimated people living with HIV in Ukraine, only 136,105 (44%) are receiving ART.[2] The majority of those who test positive for HIV never returned to a care provider for a full assessment and enrollment in treatment. The cascade shows significant gaps: about 34,000 PLWH are diagnosed but not on ART. Drop-offs in the HIV care continuum and diminished access to HIV care persist despite scale-up of linkage to care and comprehensive case management programs for PLWH in Ukraine.[3–9] ART use rates are particularly low among HIV-positive people who inject drugs (PWID), with only 38% on ART and 28% virally suppressed.[10] At least 50% of PLWH in Ukraine acquired HIV though intravenous drug use and are likely to be active people who inject drugs (PWID).

Data-to-Care (D2C) is a high-impact public health strategy that integrates multiple sources of data such as clinical data from medical information systems, surveillance data, and ongoing case management assessments with clients to identify PLWH who are not in care, engage them in care, and manage the HIV care continuum.[11] D2C strategies complement evidence-based practices for HIV care adherence by integrating clinical and case management data at multiple points along the HIV care continuum, using systematic assessments to identify unmet needs such as substance abuse treatment and make appropriate care referrals, and using data to inform practice change and improve linkage to and retention in care. D2C strategies have been effectively implemented in jurisdictions throughout the United States[12] but are not standard of care in low- and middle-income countries (LMICs) such as Ukraine. How to effectively implement D2C strategies in these new contexts has not been studied. To address this gap, this R34 study will adapt and pilot a D2C strategy to improve HIV care outcomes among not-in-care PWID living with HIV in Ukraine.

This study's Specific Aims are:

1) **To adapt a D2C implementation strategy for Ukraine**. We will use the Dynamic Adaptation Process[13,14] to identify the individual, organizational, policy, and infrastructure factors to adapt an existing US-developed D2C strategy in Ukraine.

2) **To study preliminary effectiveness of a D2C strategy versus standard of care** on *primary outcomes* of HIV care engagement, ART initiation or re-initiation, and viral suppression among not-in-care PLWH (n=160); and *secondary outcomes* of engagement or re-engagement in ancillary services (e.g., drug treatment) and quality of life using a cluster randomized trial design.

3) **To assess the feasibility, acceptability, and implementation-related processes and outcomes of the D2C strategy** using the Consolidated Framework for Implementation Research adapted for Complex Systems (CFIR-CS)[15] and practice improvement notes, in-depth interviews with D2C implementers and participants, and quantitative D2C usage data.

    a. Determine the cost of the D2C strategy and estimate the thresholds for the intervention to be cost-effective or cost-saving.

Ukraine is well-positioned as a site to identify how D2C strategies can be implemented in LMICs. With the support of international stakeholders such as PEPFAR and USAID, the Ukrainian Ministry of Health is actively promoting the use of a medical information system (MIS) at the HIV clinic level. The MIS contains patient-level information on HIV care appointments kept, medication prescriptions, all diagnosed co-morbidities, and clinical and laboratory test results.[16] This information can be mobilized

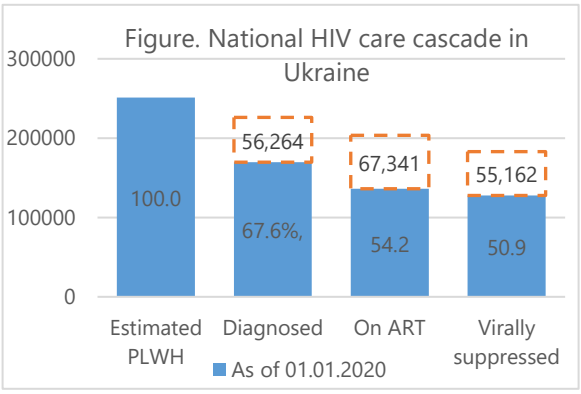
in a D2C strategy that tracks patients through the care continuum, uses data to make decisions about patient care and improve case management practices, attends to psychosocial factors that affect medication adherence (e.g., substance use), and coordinates the provision of non-clinical social services.[17] Our project is positioned to institute and test strategies for maximizing the benefits of this system to improve the HIV cascade for PLWH with history of drug use.

This study addresses 3 NIDA HIV/AIDS research priority areas: developing interventions that influence organizational structure, climate, and culture to promote evidence-based practices; evaluation of adaptation processes and intervention effectiveness in real-world settings; and studies of structural approaches to improve quality and utilization of services. It will be one of the first studies to adapt and evaluate a D2C strategy in an LMIC context, which has implications for HIV policies in Ukraine and globally. The proposed research will increase understanding of the intervention, organizational, provider, and patient characteristics that facilitate successful implementation of a D2C strategy, and the key policy, infrastructure, and process factors necessary to support integration of D2C into existing clinical and case management practices. This study will also position the research team to conduct a larger RCT to determine the effectiveness of a D2C strategy in Ukraine.

Background

People living with HIV (PLWH), particularly those who use drugs, experience significant need for supportive services such as case management and substance use treatment.[18] Provision of case management, employment services, housing, and substance use treatment can link and retain HIV positive populations to HIV care and improve HIV related clinical outcomes.[19–24] A client-centered approach,[25] with the use of a multidisciplinary team[26] and coordinated care,[27,28] is the most effective strategy to providing ancillary services to HIV infected populations. For people who inject drugs (PWID), medication-assisted treatment (MAT) is highly effective in improving linkage and retention in HIV care[29–31] and health outcomes.[29,32–34] Connecting HIV-positive PWID to ancillary services such as MAT is particularly important in Ukraine, where injection drug use (primarily opiates) accounts for up to 50 percent of new HIV cases.[17,35,36]

The national HIV care cascade in Ukraine reveals large gaps between the number of people diagnosed with HIV and the number in active care, on ART, and virally suppressed.[1] Among the approximately 250,000 estimated PLWH in Ukraine, only 136,105 (54%) are receiving ART as of 01/01/2020.[37] The majority of those who test positive for HIV never returned to a care provider for a full assessment and enrollment in treatment. The cascade (see adjacent figure) shows significant gaps: about 34,000 PLWH are in care but not on ART. The latest national bio-behavioral survey data show that only 52% of PWID are in HIV care, 38% are on ART and 28% are virally suppressed.[38]



Improving access to and use of clinical and service provision data can lead to better health outcomes for PLWH who are not in care. In the United States, recipients of Ryan White funding increasingly recognize the value of multi-directional information exchanges that use HIV surveillance data, in combination with medical record data, to identify PLWH who are not in care, and intervention opportunities such as referral to HIV specialty care or supportive services.[11] A *data-to-care* approach is a public health strategy that integrates multiple sources of data to identify HIV individuals not in care, engage them in care, and manage the HIV care continuum.[39–41] A data-to-care (D2C) strategy identifies patterns in services, outcomes, and demographics that might necessitate changes to program activities in order to improve outcomes across the HIV care continuum.[42] For example, medical information systems (MIS) can be used to track patients through the care continuum and identify points of service breaks. Provider-mediated data usage involves health department staff working with providers to re-engage patients; electronic linkages coordinate between surveillance databases and medical records databases; and in direct outreach, trained staff reach out to persons who are identified as not-in-care through the surveillance system.[43]

Key features of D2C approaches are collaboration between specialists across multiple public health and health care sectors, and feedback mechanisms to monitor progress and inform practice change. D2C requires cooperation between disease investigators, epidemiologists and researchers, information technologists, and service providers (case managers, clinicians).[42] Reports can include information on patients' viral suppression, types of prescribed ART, medical visits attended and missed, and engagement in MAT programs for PWID. These reports can then be compared to benchmarks and strategies to realign resources can be developed to respond to

performance gaps, such as more targeted outreach efforts to reach specific populations or more intensive approaches to locating clients who missed appointments.

International and Ukrainian institutions have made significant investments to increase data quality and use to improve HIV outcomes for key populations. The Public Health Center of the Ministry of Health of Ukraine (PHC) in collaboration with the Network of PLWH funded by PEPFAR actively promotes the use of a nationwide Medical Information System (MIS) at the clinic level. The MIS contains patient-level information on HIV care appointments kept, medication prescriptions, all diagnosed co-morbidities, and clinical and laboratory test results. It also includes information on new and previously detected HIV cases. The MIS is also used by NGOs that provide social and medical support for PLWH, allowing for tracking treatment and patient pathways across service sectors and institutions. MIS use has been extended to all regions of Ukraine.[16] PHC created a division to provide support MIS users and developed webinars and other materials to train a wide range of service provider cadre to use the system.[16] PHC is currently working to add new features (such as MAT and hepatitis treatment monitoring) and to expand the use of MIS to facilitate patient tracking and analysis of data on cascade and quality of care indicators at the clinic and oblast (regional) levels.[17] The Ukrainian Institute on Public Health Policy (UIPHP—see Study Team, below) evaluated outcomes of national ART optimization (scale-up of dolutegravir-based regimens) using the MIS data (ART OPTI project). PEPFAR, other international donors, and the PHC recognize the role that effective use of data will play in achieving 90-90-90 targets.

International and Ukrainian institutions have made significant commitments to increasing the quality of HIV/AIDS services, strengthening the capacity of Ukrainian institutions to improve the continuum of HIV services for key populations, and improving access to MAT. USAID and PEPFAR both currently support efforts to improve HIV case finding, primarily through increased HIV testing and initial linkage to care. Moreover, Ukraine has expanded availability of and access to MAT, a critical component of successful retention and care for PWID.[20–23,44–48] Our proposed D2C strategy complements these efforts and leverages the expansion of MAT in Ukraine by identifying out-of-care HIV-positive PWID and linking them with HIV and other services, including MAT. The D2C intervention would be a valuable amendment that would increase the cost-benefit ratio of any case-management intervention by timely identifying patients who need it most.

A planning grant (R34) is the ideal mechanism for this developmental project. It will allow the research team to establish the feasibility of a D2C for PWID in Ukraine and develop the tools, protocols, and management structure for implementing a full-scale trial. It will also produce important planning information on the cost of implementing a D2C in Ukraine and allow us to determine under what conditions a D2C may be a reasonable investment in Ukraine. Finally, the proposed analytic strategy will inform sample size estimation for a larger trial and determine whether ordinal logistic regression, and more specifically mixed proportional odds models, may be suitable for modeling movement along the HIV care continuum among PWID.

The **scientific premise** of this project is strong. Only 29% of HIV-infected PWID in Ukraine are virally suppressed; of PWID who are on ART, only about 74% are undetectable.[49] Connecting PLWH who are diagnosed to comprehensive case management and ancillary services can improve outcomes along the HIV care continuum. Clinical and service provision data, including viral suppression, ART prescription, medical visits, and engagement in other services, can be used to improve health outcomes for HIV-positive PWID. This D2C intervention extends current efforts to improve the availability and use of data by assessing clients with standardized, validated assessments on a range

of health and social factors that contribute to engagement in care and using this information to create individualized treatment plans and implement practice change.

INNOVATION

Maximize the utility of new data systems: This project leverages a resource with widespread support from policy makers, funders, and providers. We will institute and test strategies for maximizing the benefits of an MIS to improve the HIV cascade for PWID through data collection, data analysis, and program improvement.

Link clinical and case management data: The proposed D2C strategy prioritizes active review of not-in-care lists and contacting not-in-care individuals to engage them in HIV care and case management. We will develop a mechanism within the MIS to actively monitor and identify individuals who have fallen out of care or at risk for falling out, such as missed visits (which can indicate factors in individuals' lives that may interfere with their ability to remain in care and predict long-term mortality among persons initiating HIV care).[50,51]

Systematically identify client needs: The proposed data-to-care intervention will integrate an acuity tool into case management. This tool will allow case managers to systematically assess client needs in multiple domains (substance use, mental health, housing, quality of life) over time, develop client-centered treatment plans, and monitor treatment goals tailored to the specific needs of HIV-positive PWID.

Transfer best practices through Implementation Science: D2C strategies are recognized by the Centers for Disease Control and Prevention as a key component of high impact prevention efforts. The WHO recognizes the potential role of digital health information health systems strengthening[52] and calls for an increase in high-quality research on the integration of health data into health care systems, particularly in low and middle income countries.[53] Rigorous Implementation Science research is necessary to guide the adaption of highly complex interventions such as D2C into new contexts, such as LMICs, for maximum effectiveness and sustainability. Our proposed use of the Dynamic Adaptation Process and Consolidated Framework for Implementation Science will yield critical information on the organizational, policy, provider, client, and structural factors necessary for successful D2C implementation.

Project Team and Relevant Experience

This project brings together a strong team of multidisciplinary researchers with expertise in HIV research in Ukraine, linkage to care programs, implementation science, and qualitative and quantitative methodologies. An **existing partnership between Johns Hopkins School of Public Health (JHSPH) and the Ukrainian Institute on Public Health Policy (UIPHP)** will allow efficient implementation by avoiding start-up delays common to de novo research programs. Our collaborative portfolio includes 2 NIH-funded studies that explore drug use, social networks, and HIV risk (R21 DA044807) and stigma among HIV-positive women who use drugs (R21TW011060). The study will be led by Principal Investigators **Jill Owczarzak, PhD** and **Konstantin Dumchev, MD, MPH. Owczarzak** is an Associate Professor in the Department of Health, Behavior, and Society (HBS) at JHSPH. She is an expert in qualitative research methods and implementation science and served as the PI of 4 Ukraine-based, NIH-funded studies related to gender and access to care (R21DA040969); drug use practices, social networks, and place (R21 DA044807), stigma, gender, and HIV care (R21TW011060); and the development of evidence-based interventions for PWID (R01 DA033644).[54–58] **Dumchev** is the Director of UIPHP. He conducts research on substance use and

HIV/AIDS, including epidemiology, estimation, and program effectiveness. He served as a Site PI for the HPTN 074 trial (UM1AI068619) of an integrated case management intervention aimed at improving linkage to care and ART initiation among PWID.[34,59] During his work as a Strategic Information Advisor at CDC, he managed the development of the concept and terms of reference for the MIS. He continues to consult the PHC on further MIS development. Dr Dumchev has developed the Simple Treatment Monitoring Application (STMA), an electronic medical records system. STMA was widely used by MAT and HIV clinics,[2,36,60] and is now being gradually replaced by MIS. Relevant ongoing projects include IMPACT (R01DA043125), integrating MAT into primary care using tele-education and Quality Improvement interventions, and MEDIUM (U01DA045384), implementing mental health services into MAT clinics. **Brian Weir, PhD** is an HIV prevention researcher with expertise in the design and analysis of quantitative research and in economic cost-effectiveness analysis.[61–65] **Christopher Hoffmann, MD** brings expertise in implementation science research on the improvement of HIV and TB outcomes in low and middle income settings.[66–69] **Tetiana Kiriazova, PhD** is a Senior Researcher at UIPHP and is an expert on linkage to HIV and addiction care for PWID, prisoners and other populations domestically[9,70,71] and internationally,[72] and stigma towards key populations.[73]

All study key personnel have current Good Clinical Practice and Human Subject Protection trainings certificates.

Approach

Overview of a Data-to-Care Strategy D2C strategies incorporate surveillance and other data into multiple points along the HIV care cascade, including **Patient Identification and Outreach**, **Case Management**, **and Health and Social Service Use**. **Patient Identification and Outreach** encompasses: (1) using data within the HIV-specific reporting systems (such as eHARS in the US) to identify those patients who meet the not-in-care criteria (e.g., patients registered as HIV-positive who had no HIV medical visits in a calendar year[76]); (2) generating regular reports that list patients who meet the criteria; and (3) providing clinic-based providers with this list (including patient contact information).[39,40,43] This information is then shared with case managers, disease intervention specialists, or linkage-to-care coordinators (depending on the implementation context), who then use available contact information to establish contact with the client and initiate engagement in care activities. After contact is made between the client and service provider (linkage-to-care specialist, case manager), through **Case Management**, care coordinators use Acuity Tools and other needs assessments to identify unmet needs, potential barriers to care, and referral pathways. *Acuity Tools complement rather than supplant ongoing case management programs* to assess mental health, substance use, social support, intimate partner violence, financial stability, housing situation, legal issues, dental care, and sexual health. *Acuity Scores*, derived from the Acuity Tool, determine the frequency and intensity of case management engagement with clients and the types of service referrals clients need.[41,42,77] [**See table at right.**] For example, a client that keeps appointments as scheduled, is stably housed, has been in drug recovery for a year, and has no history of mental illness would be categorized as Level 1: Self-Management and receive face-to-face contact with a case manager once every 6 months. Clients who decline to take medication, exhibit significant risk behaviors, do not follow up on referrals, and have multiple medical diagnoses would be categorized as Level 4: Intensive Case Management and would have monthly face-to-face and weekly phone contact with a case manager. **Health and Social Service Data** are tracked in data management systems, including *clinical patient data* (CD4, viral load, ART initiation and re-initiation, co-morbid diagnoses

and medications); and *process data* (enrollment in services, HIV care appointments made and kept, referrals, contact attempts).

Study Sites Consistent with PEPFAR priorities, we will partner with large HIV clinics in four high burden regions: Dnipro, Poltava, Odesa and Kyiv City. We will select 4 sites from the list of clinics that will match the following criteria: (a) at least current 150 patients registered with injecting drug use (IDU) mode of transmission; (b) current provision of case management (Steps Toward Health or other interventions, described below); (c) MIS is fully operational and all patients are entered; (d) administration approval for the site and its clinicians to participate.

Acuity Scale Levels

Management Level	Point Range	Health Status/Medical Condition	Frequency
Level 1: Self-Management	25-35	Client is medically stable and is able to manage supportive needs without assistance.	Face to Face at least once every 6 months for reassessment no phone contact indicated
Level 2: Basic Management	36-60	Client is medically stable and is able to manage supportive needs with minimal assistance	Face to Face every 6 months with at least one phone contact every 3 months
Level 3: Moderate Management	61-84	Client is at-risk of becoming medically unstable without assistance and support systems are not adequate to meet client's immediate needs without support	Face to Face a minimum of every 3 months with at least one phone contact monthly
Level 4: Intensive Management	85-100	Client is medically unstable and in need of comprehensive support for medical and supportive needs	Face to Face at least once a month with phone contacts weekly

Specific Aim 1: Adapt a D2C implementation strategy for Ukraine

We will use the Dynamic Adaptation Process (DAP)—phases I (Exploration) and 2 (Preparation)—to guide the adaptation of a D2C strategy for Ukraine.[13] The DAP considers the multilevel context of service delivery and engages multiple stakeholders, which is appropriate for a complex structural intervention such as a D2C. Project activities for Aim 1 will include baseline in-depth interviews with service providers, clinic directors, PLWH who inject drugs, and other key stakeholders who will be involved in adapting and implementing the D2C strategy; MIS data module and extraction protocol development; and finalizing the D2C strategy.

Provider Baseline Interviews We will conduct baseline in-depth interviews (n=32 with case managers, nurses, and agency directors who will implement the D2C intervention. Directors (n=4) may not have regular, direct contact with clients but can provide an overall view of various systems that may impact access to treatment services and implementation of the D2C strategy, including policies and how they are put into practice, admission requirements, and health care and treatment organization. They can provide key insight into institutional processes and organizations.[78] Case Managers/nurses/social workers (n=28) have regular, direct contact with clients within the social service and health care systems, and can provide practical, detailed information about program and policy implementation.[79,80] All participants will engage in a full consent process.

Provider Inclusion criteria and screening: (1) 18 years of age or over; (2) being an employee of an organization that currently conducts case management among PLWH; (3) speak either Ukrainian or Russian; and (4) able to consent and willing to participate.

Provider Sampling plan and recruitment: Interview participants will be all case managers and directors of D2C intervention implementation sites that have agreed to participate in this research project.

Provider Baseline Interview Content: Interviews will focus on current practices with respect to providing and coordinating services to PLWH, existing communication efforts/strategies, and how data is currently collected and used within case management. All interviews will also explore:

- current referral processes, patient prioritization, client load, and client profiles
- client counseling and continuing care services;

- policies that may create barriers to the delivery of the D2C intervention, patient care coordination and current related public health interventions;
    - existing programs or other innovations to improve services or outcomes for PLWH and PWID;
    - critical barriers to care for an D2C program to address and the feasibility of addressing them;[81]
- perceived client satisfaction, barriers to treatment, and general environmental features that may facilitate or undermine clients' efforts to access services.

PLWH Baseline Interviews (n=20). In-depth, qualitative interviews will be used to understand HIV-positive PLWH access to, use of, and perceived needs for services related to their HIV, drug use, mental and physical health, and social needs, and inform the D2C strategy based on participant needs and available resources.

PLWH Inclusion criteria: 1) being at least 18 years old, living in one of the study cities; 2) having received an HIV diagnosis; 3) having self-reported injecting drugs in the previous year; 4) speak either Ukrainian or Russian; and 5) able to consent and willing to participate.

PLWH Sampling plan and recruitment: We will interview 10 participants from each study city (n=20). 10 interviews in each city will allow us to obtain a breadth of perspectives on PLWH access to health care and other services and reasons why people do not link to care and why they may disengage in care. Due to its formative nature, we will target HIV-positive PLWH both in and out of treatment and employ purposive sampling to obtain a broad range of possible experiences in terms various characteristics:

- demographic (e.g., age, marital/partner status, socioeconomic status);
- behavioral (e.g., type of drugs injected, number of years injecting drugs); and
- health (e.g., time since HIV diagnosis, mental health, comorbid conditions, drug treatment history).

Interview participants will initially be recruited from NGOs, drug treatment programs, and HIV clinics through direct recruitment and participant referral. Facilitated by outreach workers affiliated with each agency, research assistants will identify seed participants to serve as initial contact for recruiting from the target population. We will identify a heterogeneous set of seeds at each site to enable us to reach relevant subgroups, including those who are and are not in HIV care and other services. Participants who have been successfully recruited will be given information cards about the study to refer acquaintances and members of their social networks who may meet inclusion criteria.[82] This chain referral approach has been successfully used elsewhere in the region to reach and recruit individuals who are not clients of an NGO.[83]

PLWH Interview content: These interviews will ask about:

- health status and mental health diagnoses, including histories with substance use and treatment;
- family and relationship status, housing stability, and sources of support (financial, social, emotional);
- knowledge of and experiences with organizations that assist PLWH and PWID;

- experiences with these agencies, including how they learned about them, motivation for seeking help, eligibility criteria, and application procedures;
- experiences of service denial, perceived or experienced stigma, and treatment by staff;
- ideas about what services are still needed [SEE APPENDIX B].

Data analysis Qualitative data management and analysis will be conducted with MAXQDA software. All interview recordings will be transcribed, translated, and uploaded to MAXQDA for coding and analysis. We will code all documents by document type (e.g., provider or PLWH interview), demographic information (city/region, years since HIV diagnosis, gender, socioeconomic status), role (director, frontline staff, policy maker). Then, we will create and apply text codes that reflect key dimensions of the DAP framework, including provider factors (prior experience with incorporating data in service provision, attitudes toward the D2C strategy, educational and training backgrounds); organizational factors (leadership buy-in, organizational climate, training and resource capacity); system factors (funding, contracts, policies); and client characteristics (comorbidities, prior experiences in care, level and type of need). In-depth interviews will be analyzed within the context of DAP to identify the system level, organizational, provider, and patient roles and characteristics that will inform the adaptation and implementation of the D2C strategy at each site and contextual factors that will need to be addressed for successful integration of a D2C strategy into the clinical setting. For example, data analysis may determine that HIV-positive PLWH need specific services that implementing organizations currently do not offer or that providers lack technical skills to retrieve and interpret acuity data. We will address these issues in the finalization of the D2C strategy, including identifying referral organizations, and through training, capacity-building, technical assistance strategies. We will also use findings from Aim 1 data analysis to match sites for paired randomization, as described below in Aim 2.

Finalize the d2c strategy The finalization activities will include: (1) refining data extraction protocols and developing a case management module within the MIS; (2) developing a report generation and dissemination protocol for each clinic and (3) specify clinic/implementation team structure, roles, and management plans based on findings from in-depth interviews.

Develop data extraction protocols and create case management module within MIS

The MIS is designed as an electronic medical record system, to be used by clinical providers for routine patient data management. It has centralized architecture, where all data are immediately uploaded to a national-level server. According to the feedback we received in our ART OPTI project, tracking and prioritization of out-of-care patients is one of the most requested features for the MIS. We will partner with the Public Health Center of the MoH, the government body responsible for HIV response and coordination of PEPFAR activities in Ukraine and owner of the MIS to create a module within the MIS that will: a) identify all HIV-positive PWID meeting the criteria of not-in-care [patients registered as HIV-positive who had no HIV medical visits in a calendar year]; b) provide a useful summary of all clinical information that will be needed for case managers [drug use, CD4, viral load, ART history, HIV care appointments made and kept, co-morbid diagnoses and medications, and MAT history]; and c) provide a portal for entry and export of case management data (referrals made, appointments kept, contact attempts, case management notes).

Specific Aim 2: To pilot a randomized clinical trial of a D2C strategy versus standard of care

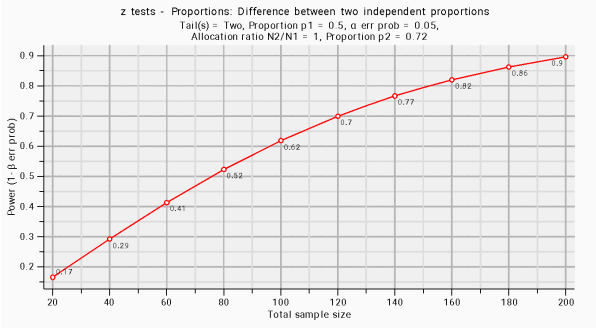
Study Design

This pilot study is designed to test the performance characteristics and capabilities of study design, measures, procedures, recruitment criteria, and operational strategies that are under consideration for use in a prospective RCT. We will also assess feasibility of the RCT by measuring the key parameters for sample size calculation, namely the effect size and coefficient of variation.

D2C is a structural intervention designed to sustainably change the HIV care providers' practices and facilitate information exchange at the facility level. To address the implementation science questions by measuring the provider-level outcomes and avoid contamination of the control condition due to unblinded allocation of intervention at the patient level, we propose a cluster-randomized trial design for this pilot study and the prospective RCT. We will select eligible HIV clinics (see "Study Sites," above) and randomly assign them 1:1 either to the intervention or the control arms. To achieve greater comparability between the arms, we will match pairs of eligible sites based on organizational context factors derived from Aim 1 data analysis, including facility size and type (e.g., NGO vs. public clinic), service delivery structure (e.g., social workers vs. nurses), and existing services for HIV-positive PWID (e.g. Steps Toward Health) and will randomize within the pairs. This will minimize the degree of between-cluster variation within the groups and increase power and precision. Randomization will be conducted by the data manager using a computer program.

Sample size

We used methodology from Hayes et al[84] to determine the effect size that the intervention needs to demonstrate in a feasible matched-pair randomized trial. We assumed the cluster size of 75 patients (based on the optimal case manager workload) with 5 clusters per arm (potentially manageable number given the existing research infrastructure in Ukraine), coefficient of variation between clusters within matched pairs equal to 0.15 (empirically estimated based on the data from 56 clinics in the ART OPTI study, see Previous Studies), power of 80% and 0.05 significance level. Proportion of participants re-engaging into ART within 3 months after inclusion into the study was used as the key outcome. Under the assumptions, the relative difference between the study arms should be at least 22% (e.g. 50% vs 72%). The adjacent chart shows the power and sample size of a pilot trial needed to detect this difference with 0.05 significance level. To achieve 80% power, we will need to recruit 160 participants, or 80 per arm. We propose to divide the sample equally between 4 sites (2 per arm) to test the matching procedures. We do not adjust for loss-to-follow-up because for our main outcomes (ART initiation, viral suppression), loss to follow-up is equal to not achieving the outcome.



Intervention Overview

Clinics randomized to the intervention arm will implement the D2C strategy as described above, including Health Data Information, Active Surveillance, and Case Management with the addition of the data component. The D2C strategy will involve a 5-step process: (1) identify not-in-care PLWH using the MIS, (2) verify eligibility criteria, (3) contact patients and invite to visit the clinic, (4) determine care status and reengage into care, and (5) provide case management services and confirm engagement in care.[12]

Steps 1 and 2 will follow the same procedure at both intervention and control sites to ensure equal conditions of study enrollment. Step 3 will be conducted using Active Outreach at the intervention sites. Steps 4 and 5 will be achieved through use of an Acuity Tool and derived Acuity Score. The Acuity Tool will be used to identify barriers to HIV care engagement, including mental health and substance abuse, and to establish referrals to other services, as described above in Overview of Data to Care Strategies.

Procedures

Patient selection and verification of inclusion criteria

A Recruiter (clinical staff authorized to access MIS at each site) will use the D2C module in the MIS to access the "Tracking Journal" which includes patients who have a confirmed HIV diagnosis, started ART, and missed their clinical appointments (medication pick-up or other). Going through the list ('New cases' or 'In progress' or 'Not tracked' sections), Recruiter reviews the MIS data (including in other modules) and identify patients who meet the following criteria:

a) registered within the MIS as having received a positive HIV diagnosis at any time in the past
b) missed a clinical visit (ART pick-up or other) more than 7 days ago
c) registered with IDU as probable mode of HIV transmission, or history of IDU documented at any clinical visit
d) not been contacted by other clinical staff after the current missed visit
e) 18 years or older

For each patient meeting these criteria, Recruiter puts an "E" letter in the beginning of the Comment field in the Tracking Result section (before any other text in this field, separated by a space). This letter indicates that the patient is eligible for recruitment into the study and filters the Tracking Journal to display only these patients.

Patient outreach and verification of exclusion criteria

Next, using the contact information available in the MIS and paper documentation, Recruiter attempts to contact the patients in the E-list by phone using the procedure described in the "Tracking SOP" developed by the Public Health Center. If the contact is successful, Recruiter first has to make sure that he is talking to the intended patient, without revealing that he is calling regarding HIV treatment. Once the patient (or a trustee) identity is confirmed, Recruiter asks about the reasons of the missed visit, and assesses the following exclusion criteria and takes corresponding actions:

- Patient is already re-engaged in care and visited the clinic recently
  - In this case Recruiter verifies the MIS clinical records and updates if necessary
- Patient has sufficient supply of medications (available to him for any reason)
  - Recruiter asks about the amount, and records the date of the next visit accordingly
- Patient moved to another clinic, city, country, or penitentiary institution
  - Recruiter provides information about clinics where the patient may continue treatment and initiates the formal patient transfer procedure
- Patient died
  - Recruiter initiates the de-registration procedure

In these cases, Recruiter adds a "X" letter to the Comment field (to make "EX"). All phone contact details are recorded in the MIS.

If the contact is successful and exclusion criteria are not met, Recruiter explains why it is important to continue treatment without interruptions and informs the patient that he or she is eligible to enroll into a research study, using a standard script (Appendix 1, two versions for the study arms). Regardless of the interest in the study, Recruiter schedules patient's next visit at the earliest convenience, and records the date in the MIS. In these cases, Recruiter adds a "L" letter to the Comment field (to make "EL").

If the first contact is unsuccessful, Recruiter adds a "R" letter to the Comment field (to make "ER"). The following contact attempts are conducted according the "Tracking SOP" – minimum three additional attempts with 1-2 weeks apart and engaging social workers and other projects if available, with additional invitation to participate in the study using the script. If the patient is reached but refuses to come to the clinic during the first contact, the status is also updated to "ER". Additional three attempts to contact and convince the patient to come are made following the same procedure. The status of the patient remains as "ER" until he agrees to come to the clinic, or the final (fourth) attempt is unsuccessful. After four unsuccessful attempts (with or without contact with the patient) the status is changed to "ERZ".

At the Intervention sites, Recruiter exports the ER-list and gives it to a Case Manager (through Data Manager). The list includes, if available, Syrex and Case++ codes (alphanumeric unique IDs used by prevention and care and support NGOs) to enable outreach through NGOs. Case Manager at the Intervention sites undertakes additional efforts to reach and recruit the patients using all available methods (phone calls, home visits [following the procedures outlined in the "Tracking SOP"], community and social networks, harm reduction and HIV-service NGOs). Up to three contact attempts (bi-weekly) will be made for each participant. The dates and results of the attempts are recorded in the online Recruitment Log (developed based on the ER-list, Annex 2). In case of a successful contact, Case Manager assesses the exclusion criteria described above, invites to participate in the study, and schedules the next visit. Recruiter monitors the Case Manager's contact attempts in the Recruitment Log bi-weekly and transfer information to the MIS, including the updates to the E-status (from "ER" to "ERX" or "ERL"). After three unsuccessful attempts by Case Manager (four total including the initial attempt by Recruiter) the status is changed to "ERZ".

Additional contacts with the patients on the EL-list may be made by Recruiter and/or Case Manager on the day before the scheduled visit to confirm the appointment and ensure the patient remembers about the visit.

First visit

The patients on the EL-list should be instructed to notify Recruiter and/or Case Manager before coming to the clinic, to expedite the visit procedures. If a patient from the EL-list comes to the clinic without notifying Recruiter or Case Manager, a receptionist should notify Recruiter and direct the patient to see them.

After meeting the patient, Recruiter conducts (or refers to) regular clinical visit procedures, refers the patient to Interviewer, and changes the E-status to "E(R)S". Interviewer conducts the Informed Consent procedure according to the study-specific SOP and using the consent form (Annex 3), and in case of consent performs baseline interview (see below). At the Control sites, Interviewers fill out the Contact Information Form (Annex 5) to enable tracking for follow-up interviews.

After the interview, the patient comes back to Recruiter, who makes referrals to available care and support services (Standard of Care sites) or introduces the patient to Case Manager (Intervention

sites). At the Intervention sites, Recruiter fills out the top section of the Case Management Checklist (Annex 4) and gives it to the Case Manager together with the patient.

Case Manager may conduct the first intervention session on the same day or schedule a meeting with the patient at the earliest convenience.

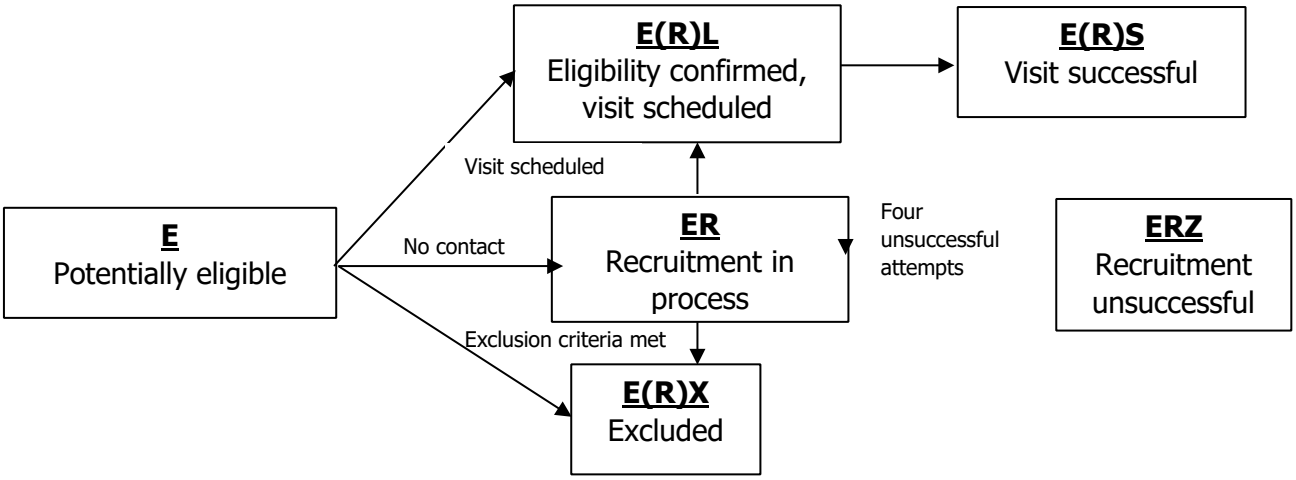


Figure. Patient status update workflow

Intervention Procedures

The case-management component will be implemented according to a Manual, developed by the study team. Briefly, the content and intensity of case management will be based on an overall Acuity Score across domains. Case Managers will assess clients every 3 months to determine the treatment plan and record this information in the Case Management forms to enable progress monitoring. Care teams of nurses, case managers, and outreach specialists will coordinate holistic wrap-around care to meet the social service and health needs of out-of-care patients, many of whom face substance abuse and mental health barriers to HIV care. Case managers will develop client-centered service plans based around "SMART" objectives (**S**pecific, **M**easurable, **A**chievable, **R**elevant, **T**ime-limited).

Case Managers will schedule new clients for intake appointments and work with clients to develop treatment plans. Specific duties include:

- use Acuity Tool to assess patient-identified financial, socioeconomic, and housing profiles and provide comprehensive internal or external referrals for supplemental or long-term resources;
- develop and implement personalized treatment plans for all clients based on the acuity assessments through existing case management programs;
- ensure accurate tracking and documentation of all interactions and activities with patients using the acuity tool and Tracking Module within the MIS;
- establish, develop, and maintain professional relationships with diverse treatment and service providers, including AIDS care, primary care, substance use, mental health, and social services;
- maintain current contact information using the Contact Information Form (Annex 0) and updates it at each visit.

Additionally, Case Managers assist Interviewers to schedule follow-up interviews (see below) in conjunction with the Intervention sessions (at 6 and 12 months).

Control Condition

Clinics randomized to the standard of care arm will continue to implement their client identification processes and case management as usual. One of the most common interventions with a focus on PWID is Steps Toward Health,[85] a case management program developed and tested through the PEPFAR-funded RESPOND project.[8,86] It is theory-driven and standardized in manuals that contain background information, logic models, client assessment worksheets, step-by-step instructions for each session, and monitoring and evaluation guidelines. This 5-session intervention includes modules on self-care, HIV transmission risk reduction, drug treatment, and ART adherence. It does not include active outreach, client tracking, or tailored treatment components. Other possible interventions include Community-based Retention Intervention, Patients' School, and others.

Provision of these interventions (the fact of enrollment) will be recorded in the MIS by Recruiter, but the actual process data will not be collected.

Data Collection

Data on **primary outcomes** will be obtained from clinical records in the MIS and absence of data will be equal to not achieving the outcome, therefore the effective sample size will be exactly 160 patients. Data from the MIS will be extracted monthly (Annex 6). The primary outcomes are defined as:

- Engagement in HIV care: at least 3 clinical visits over at least 6 months within 12 months after study enrollment.
- ART (re-)initiation: initiating or re-initiating ART within 3 months after study enrollment.
- ART adherence: the percentage of days in possession of medication (pharmacy refill gap method)[87]
- HIV Viral Suppression: having at least one VL test with <200cp/ml and none with >=200cp/ml within 12 months after study enrollment.

Data on **secondary outcomes** will be collected using the patient survey at baseline, 6 and 12 months after enrollment. The secondary outcomes will include items in the following domains:

- Substance Use: Substance use battery from the Ukrainian IBBS studies, AUDIT-C; DAST-10 scale for addiction severity.
- Trust in Physician Scale
- Substance Use & HIV Stigma Mechanism Scales
- Readiness for Drug Treatment Scale
- Mental Health: PHQ-9
- Risk behaviors: Risk Behavior Assessment (RBA), modified for the drug use patterns of PWID in Ukraine. The RBA assesses drug use and sex-related HIV risk behaviors.
- Quality of life: Short Form-12 (SF-12), a global measure of patient quality of life; HRQoL, HIV-related quality of life
- Medical co-morbidities and engagement in ancillary care: (OAT, TB, STI and Hepatitis treatment) by self-report.

- HIV Treatment Satisfaction Questionnaire
- Patient-side cost questionnaire
- Socio-demographic information, including age, housing status, sex/gender, family/marital status, income, education, employment status.

The surveys will be administered by an experienced Interviewer, hired at each site. The questionnaire will be programmed using REDCap platform installed on a UIPHP server.

Intervention implementation

At all intervention sites, we will document all implementation processes through quarterly implementation site meetings. Each quarter, the implementing teams at each intervention site (consisting of outreach specialists, clinic managers, case managers, and other service providers) will generate benchmark reports using the MIS and review the comprehensive clinic specific Health Information. The report will include both absolute numbers around key metrics (e.g., number clients linked to care from those identified as out of care, client distribution by acuity level, missed appoints) and areas of strength and in need of improvement (e.g., increasing efforts to locate not-in-care patients, continuing referrals to mental health services). In consultation with the investigators, the implementing teams at each site will review the report, analyze gaps in service delivery, and identify specific strategies for quality improvement. Implementing teams will be tasked with making concrete plans to improve or modify practices and assessing and re-assessing their goals and progress toward these goals.[96,97] Following presentation of the report, the team will discuss: the areas the agency wants to prioritize for improvement over the next quarter; strategies for strengthening or developing new workplans; identifying the key people to involve in order to implement the change; and developing an action plan. These consultations will be recorded on a standardized consultation form, which will be analyzed as part of the feasibility and acceptability evaluation within the CFIR-CS framework. These meetings also correspond to DAP phases 3 (Implementation) and 4 (Sustainment) in order to incorporate feedback processes into implementation of the D2C intervention.[13]

Statistical Analysis and Feasibility Assessment

We have powered this pilot study to evaluate feasibility of a prospective cluster RCT. The RCT will be considered feasible if the difference in the proportion of patients achieving the primary outcome (engagement in HIV care) will reach 22% between the study arms. We will estimate the impact of the intervention on the HIV care continuum using mixed effects models. For all outcomes, the data will have the same structure, with observations (t) nested within participants (i) nested within sites (j) nested within matched pairs (k). The correlations among observations will be addressed by using fixed-effects indicators for matched pair and normally distributed random intercepts for sites and for participants. Our mixed-effects models will include indicators for each of the two follow-up assessments, an indicator for site group assignment, and two group-assignment-by-follow-up interaction terms. We will also include sex/gender, age, and baseline covariates that have been identified in preliminary analyses as varying significantly across sites. A logit link function will be used for the primary outcome of ART (re-)initiation (defined above), and the coefficients for the two group-assignment-by-follow-up interaction terms will provide the estimates of the subject-specific intervention effects at 6 and 12 months post-baseline. We will examine the effects of sex/gender, age, substance use severity, ART history at baseline and other covariates in the multivariable models.

We will characterize patterns of behavior that impact HIV transmission (episodes of syringe sharing and episodes of unprotected intercourse in the prior 30 days without viral suppression) and we will use the same mixed-effects approach described above but with a log link function and negative

binomial distribution. These analyses will provide parameters for estimating the rate of onward HIV transmission for the cost-threshold analysis. All analyses will include the use of the mixed effects "meqrlogit," "meologit," and "menbreg" procedures using Huber/White robust variance-covariance estimators. We will examine whether missingness is associated with observed data using standard methods.[98–100] We will conduct a second set of outcome analyses using multiple imputation to evaluate the robustness of the primary outcome analyses to missingness and report estimates based on multiple imputation that would be valid based on the assumption that the data are missing at random (MAR). We will produce imputed datasets (m > 10) using chained equations,[101] run outcome analyses on all sets, and derive point and standard error estimates for treatment effects and other parameters from the distribution of estimates from the outcome analyses with imputed datasets.

We will also evaluate the use of mixed proportional odds regression[102,103] for determining whether intervention exposure is associated with an individual's location on five distinct stages of HIV care continuum: (1) not engaged in HIV care in the prior six months; (2) engaged in HIV care in the prior six months but no ART use in the prior 30 days; (3) ART use in the prior 30 days but no evidence of viral suppression in the prior 6 months; and (4) ART use in the prior 30 days with evidence of viral suppression in the prior 6 months. The HIV care continuum can be viewed as an ordinal categorical variable, and ordinal logistic regression will be used to evaluate if group assignment is associated with the location along the HIV care continuum. We will use the Score test to evaluate whether the proportional odds assumption of ordinal logistic regression.[104]

These analyses will be essential for planning a full study. The findings will be used for sample size estimates, and data on HIV transmission risk will be used to determine whether the intervention could reasonably be cost-saving or cost-effective. This pilot analysis will provide important information on the feasibility of using ordinal logistic regression in a larger trial or in other analyses of the HIV care continuum.

Specific Aim 3a: To assess the feasibility, acceptability, and implementation-related processes and outcomes of the D2C strategy

We will use the **Consolidated Framework for Implementation Science adapted for complex systems (CFIR-CS)** to guide implementation evaluation of the D2C strategy.[15,105,106] Key aspects of the D2C intervention are that it covers multiple settings (i.e., patients must access and interact with providers in many different health care sectors), its success depends on interactions and communication between organizations (e.g., between case managers, addiction treatment specialists, and HIV treatment providers); and it uses multiple types and sources of data to identify patterns in services and outcomes that will be used to improve or modify practices. The CFIR-CS organizes implementation factors into 5 domains: **intervention characteristics** (accuracy of data, timeliness of data sharing with partner agencies, development of practice change action plans based on data), **organizational characteristics** (integrating D2C strategy into existing protocols, agency-wide buy-in, commitment to D2C strategy), **providers' roles and characteristics** (case managers' previous experiences, attitude toward the use of data in care provision, relationships with other medical and social service providers, time and resources devoted to providing case management for PLWH), **patients' roles and characteristics** (type of medical and social needs, level of need), and **implementation processes** (participating in the monitoring and practice improvement process, using MIS data to inform practice change). The implementation of the D2C strategy is affected by the **external context** in which these organizations and their staff operate (economic, social, and political factors that may affect implementation process such as MAT "slot" and psychosocial support service).

Measures of implementation are the intermediary outcomes[107] that describe how well the implementation was carried out and include use of the acuity tool with new and returning clients, and use of data generated from acuity tool and MIS to modify practices, documentation of patient visits and contacts. Implementation influences **outcomes**, which include patient outcomes (viral load, appointment kept); provider outcomes (uptake, consistent use, patient contact, outreach efforts, time spent with patients); and processes of care (recruitment rate, extent to which intervention tracks patients and follows up on and coordinates tests, referrals, and care across organizations, settings, and acuity tool domains).

Acceptability is defined as the perception among implementers that the D2C strategy is agreeable and satisfactory.[108] Feasibility is defined as the extent to which the D2C strategy can be successfully carried out in a given context.[108] Information to assess the feasibility, acceptability, and processes of D2C implementation will come from 3 sources: D2C usage data (quantitative), implementation meetings (qualitative), and practice improvement strategies at intervention sites (qualitative), and in-depth follow-up interviews (qualitative) with providers, other stakeholders, and PLHW.

Data-to-Care Usage Quantitative and qualitative process outcomes measures include but are not limited to:

MIS Usage: Measures of implementation and intervention uptake will include frequency of accessing MIS data, frequency of contact attempts, and efficiency of the contact (i.e., how many contact attempts were necessary before a participant meets with the case manager). Case managers will record this information in a "Sessions Notes" section of the case management module within the MIS.

Outreach: As part of their responsibilities, case managers will take notes that summarize each session with clients, including techniques employed to contact and track participants, link participants to services, and retain participants in case management. These data will be included in the "Session Notes" section.

Meeting notes and benchmark reports: Intervention site meeting notes ("Intervention Implementation," above, will provide information about clinic-level barriers and solutions to implementing the D2C strategy.

In-depth Interviews In-depth interviews will be conducted approximately 6 months after participants are contacted for case management, and within 1 month of the intervention conclusion for providers.

In-depth interviews with D2C implementers Follow-up interviews with directors and case managers across study sites will explore the overall effectiveness of the D2C intervention in connecting not-in-care clients to necessary services, incorporation of the D2C program into workflows; experiences with the D2C program and how the program has changed the service delivery context, including how case managers liaise between providers and facilitate enrollment processes; perceived feasibility of the D2C program, including ease of implementation, practicality, and viability;[108] and training and leadership required for successful implementation.[109] Specific questions will be asked about usability and user satisfaction with data entry systems, including perceived complexity, ease of use, confidence using the system, added value to case management activities, and training and support required to use the system efficiently.[110]

In-depth interviews with D2C participants We will interview up to 20 participants recruited through a purposive sampling strategy to obtain a maximum variation sample by strategy arm, linkage-to-care status, age group, and gender. We will attempt to interview participants who did not

re-engage or re-engaged and dropped out, using recruitment strategies described under Aim 2. Interviews will explore: experiences of the care strategy they were assigned to, interactions with case managers and other service providers, family and relationship status, housing stability, and sources of support (financial, social, emotional), experiences with HIV and other medical and social service providers, ideas about how to improve the programs.

Data Analysis Qualitative and quantitative process and outcomes data will be analyzed according to domains within the CFIR-CS to identify the case manager, organizational, and other contextual factors for successful implementation of the D2C strategy. Quantitative assessment of feasibility will explore MIS usage and results based on the 7 D2C steps (describe above, "Intervention Condition"), including use of the MIS to contact participants, extent to which case notes are recorded and updated with the MIS, and whether linkage/engagement status is entered into the surveillance system. Review of case manager use of the session notes tool within the MIS will assess the extent to which case managers record required information (e.g., outreach efforts). Errors (such as missing or incomplete data) will be used to inform future training efforts or changes to the module to improve usability (e.g., incorporation of task reminders or completion checklists). Qualitative assessment of feasibility and acceptability will take place through systematic analysis of implementing sites experiences with the intervention, including their benchmark reports. We will create and apply text codes that reflect key analytic concepts drawn from the CFIR-CS, including organizational climate, attitudes toward the use of data, time and resources devoted to providing case management, and engagement in and commitment to the PDSA process. We will create document codes that reflect each agency's overall success with the intervention (based on primary and secondary patient outcomes) to facilitate cross-site comparison and identification of barriers, facilitators, and processes that lead to intervention uptake and implementation. Qualitative analysis will focus on how case managers incorporated data into their overall workflows, the extent to which using the Acuity Tool facilitated identification of areas of need among clients and linkage to the appropriate services, barriers to entering data into the MIS portal and using this data, and systems of collaboration and referral between case managers and provider types. Analysis will also explore case managers' experiences working with new clients identified through the active surveillance system and how this intervention transformed their practice, including how different clinics organized implementation teams, role differentiation, communication strategies, and workload. Findings will inform how the D2C strategy can be adapted for broader implementation in different clinical and organizational contexts (e.g., Regional AIDS Center, NGOs that provide case management and other services for PLWH) and what organizational, policy, and capacity structures and processes are necessary for implementation.

Specific Aim 3b: Economic Analyses To assess the costs and cost-threshold of the D2C strategy

In accordance with the recommendations of the 2nd U.S. Panel on Cost-Effectiveness in Heath and Medicine,[111,112] we will: inventory and value the resources consumed in the intervention; estimate intervention effectiveness in regards to HIV infections averted; estimate treatment costs averted and QALYs saved; and evaluate conditions under which the intervention would be cost-saving or cost-effective.

Cost analysis: We will estimate the cost of delivering the program locally from a societal perspective that incorporates broader costs, including non-medical costs to participants and costs reflected in the recently recommended impact inventory.[112] We will use micro-costing[113,114] to directly enumerate every input used in the intervention such as staff time spent on each intervention activity, equipment, and materials. Any in-kind contributions will also be enumerated and costed. We will use both top-

down and bottom-up approaches,[115] and sources of data will include project records, salaries, cost worksheets, project manager interviews, and a project manager survey. The program manager will complete a survey to quantify per unit costs for program resources, including procedure-specific resources, general resources, fixed resources, and variable resources. Participant time, travel, and any child or elder care will be measured and costed based on prevailing local wage. Cost data for each type of resource will include "best estimates" for cost and units consumed, and credible ranges to be used in sensitivity analyses will be established by asking program staff to provide upper and lower bounds for any uncertain cost estimates.

Effectiveness, medical costs, and QALYs: Few HIV prevention studies are sufficiently powered to directly measure reductions in infections, and we will estimate HIV incidence among sexual and injection-drug-using partners under the standard of care scenario and under the intervention scenario using Bernoulli process models[116] of injection drug use and sexual intercourse with behavioral patterns based on participant assessments and HIV transmission probabilities based on an updated review of the literature. The model will be based on participant data with a one-year timeframe for intervention costs and HIV transmission, and we will incorporate literature-based estimates of lifetime treatment costs and QALYs associated with new HIV infections in Ukraine, discounted at 3% per annum.[111,117] Differences between the scenarios in estimated HIV transmission are expected to be driven primarily by ART use, but we will also incorporate observed data on intercourse, condom use, injection drug use, syringe sharing, and partner characteristics. The primary model will be based on the point estimates of parameters, but we will also conduct sensitivity analyses where input parameters are sampled from distributions that capture the uncertainty in our estimates. Many modeling approaches are available for modeling the incremental cost-effectiveness of D2C; given the exploratory nature of the proposed research, we believe a Bernoulli process model is appropriate.

Incremental cost-effectiveness and threshold analyses*:* The cost-utility ratio will be computed based on the estimation of net incremental cost (i.e., difference between the incremental intervention costs and the incremental HIV treatment costs averted) divided by the QALYs averted. For a given model run, intervention will be considered: cost-saving if the incremental intervention cost is less than the incremental treatment cost averted; cost-effective if the net incremental cost per QALY saved is less than society's willingness to pay to save one QALY; and not cost-effective if net incremental cost per QALY is greater than society's willingness to pay.[111] The proportion of model runs that are cost-effective or cost-saving will be used to characterize the probability that the intervention meets these thresholds. We will also use one-way sensitivity analyses to identify conditions under which the intervention would be 90% likely to be cost-effective or cost-saving, such as specific intervention cost thresholds and intervention effectiveness thresholds.

Adverse events (including suicide risk)

The question 9 in PHQ-9 instrument may indicate suicidal thoughts among participants ("Thoughts that you would be better off dead or of hurting yourself in some way"). In case the participant responds anything except "not at all", Interviewer asks an additional question: "In the last two weeks, have you had any thoughts of hurting yourself in some way?" (not at all, several days, more than half the days, nearly every day). If patient responds "not at all" to this question, the patient denies active suicidal thoughts. He or she is considered "very low or no risk" and no action is triggered at this point. If any other response is received, Interviewer will escort the patient to a clinician in the clinic for a formal assessment of suicide risk according to the national clinical standards (includes an assessment using the Columbia Suicide Severity Rating Scale). For those with a plan, the guidance stipulates that

patients will be transport emergently offsite to a psychiatric inpatient hospital for further evaluation and may be detained against their will for up to 72 hours.

Data management

All paper-based forms collected as part of study (informed consent, contact information forms, case management forms) will be stored at the local study sites in locked cabinets. After completion of data collection, all paper forms will be shipped to UIPHP and stored for three years, after which they will be destroyed.

The questionnaire will be completed on laptops/tablets provided to the participant by the Interviewer. The questionnaire will be programmed on REDCap online platform, which has sufficient functionality for data quality assurance, monitoring, and protection. The REDCap employs various methods to protect against malicious users who may attempt to identify and exploit any security vulnerabilities in the system. REDCap users have access only to data and information that they are supposed to have within the application by identifying user privileges. Each user has their own account, and the user account will only have access to REDCap projects that they created themselves or to projects which other users have granted them access. REDCap contains an auto-logout setting, which is customizable (default auto-logout time is 30 minutes), and will automatically log a user out of the system if they have not had any activity (e.g. typing, moving the pointer) on their current web page for the set amount of time. This prevents someone else from accessing their account and project data if they leave a workstation without properly logging out or closing their browser window. REDCap maintains a built-in audit trail that logs all user activity and pages viewed by every user, including contextual information (e.g., the project or record being accessed). Therefore, the Data Manager will be able to monitor any activity in the project, e.g. entering data, exporting data, modifying a field, running a report, or add/modifying a user.

All electronic information will be stored in password-protected computers with double-password protection for opening specified files, as compliant with the US Health Insurance Portability and Accountability Act (HIPAA). All study logs will be recorded with participants' codes as electronic records only and maintained in corporate cloud services (Google Drive for Business). Programs and software for data collection will only be available to be opened by the investigators. Electronic databases and analytic tools will be maintained through password-protected computers and files and maintained by the UIPHP IT support. Access permissions for storage locations will be provided to authorized personnel only. The research data will be stored for three years after completion of the study.

Human subjects

Ethical Review

All investigators will have research ethics training certification. The study protocol will be submitted for ethical review to the Institutional Review Board (IRB) at the Ukrainian Institute on Public Health Policy (Kyiv, Ukraine).

The Investigator will make safety and progress reports to the IRB within three months of study termination or completion. These reports may include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others.

Qualitative data collection

Informed Consent

For each IDI, potential participant informed consent forms will be provided by the Interviewer and written informed consent will be obtained. All questions that candidate may have will be adequately clarified and explained to them. Potential participants will be informed that their participation in the study is completely voluntary and that they have a right to withdraw their consents and stop their participation in the study at any time. Refusal or withdrawal from the study at any time will have no effect on the participant's employment or access to health facilities. Participants will be informed that any information that they disclose during the course of the study will be considered confidential (i.e., no personal identifiers will be used and only aggregated information across all participants will be reported). Participants will have the potential risks and benefits of the study explained to them as well. For all candidates, understanding of the essential parts of the document will be assured by asking questions to verify their knowledge of the study procedures.

Benefits

There is no immediate benefit to study subjects. However, knowledge obtained in this study can help improve programmatic objectives and benefit the community by helping to improve HIV services provision.

Compensation

IDI participants will receive compensation for their time in the amount of 300 Ukrainian Hryvnas (UAH).

Risks Associated with Loss of Confidentiality

As with all research, there are risks. As there are no treatment procedures or interventions in this protocol, the only risk is a potential breach of confidentiality. The participation in IDIs is considered a study procedure that is associated with minimal risk for participants, the only risk is of potential breach of confidentiality. The potential sites for breaches of confidentiality include the recruitment process, interview itself and/or at data management systems. While the questions in the IDI guides do not explicitly raise the specter of risk, Key informants may respond with potentially sensitive information and/or emerge as topics of the discussion during the IDIs, about various aspects of patient management practices, stigma and discrimination in medical care, or other sensitive topics.

Protection Against Loss of Confidentiality

Extensive measures will be taken to ensure confidentiality. After Informed Consent is obtained, IDI participants will be assigned a study code which is the only identifier in the study database. Key informants will be assigned Study Participant Code containing no identifiable information and consisting of geographical area abbreviation, professional degree and research serial number.

If during IDIs sensitive topics emerge and there is further inquiry through targeted probes during the IDIs, every effort will be made to ensure that the level of risk to participants does not exceed minimal risk. We seek to reduce risk using several strategies often used in such settings – these include: a) asking participants never to use personal identifiers (e.g., someone's name); b) to discuss observations that they "deem" sensitive or potentially risky for them in a general way, in the third person, in terms of their "observation of others" or "stories they have heard", and refrain from providing any names or any other identifying information. We will clearly stipulate this as part of the Informed Consent, pre-amble to the IDI guide and will reinforce it during the IDI conduct. In general, the risk for Key informants is minimal. We will take measures to reduce this risk and will carefully and frequently monitor this.

Prior to the start of each IDI the interviewer will also explain that the information that is discussed will remain anonymous and that all the information and views shared by the participant will be kept confidential. The participants will be instructed that they may choose to withdraw from the study at any point and decide not to complete the IDI activities if they feel participation causes them any distress. All participants will be able to choose a pseudonym they would like to be called throughout the study and assigned an anonymous identification code.

Quantitative data collection

Informed Consent

Written informed consent will be obtained from each study participant. One informed consent form (ICF) version will be used for both study arms.

The ICF will be read aloud to each eligible participant by the Interviewer. All questions that respondents may have will be adequately clarified and explained to them. Potential participants will be informed that their participation in the intervention is completely voluntary and that they have a right to withdraw their consent forms and stop their participation in the study at any time. Refusal or withdrawal from the study at any time will have no effect on the participant's access to health facilities or HIV-related care and treatment. Participants will be informed that any information that they disclose during the course of the study will be considered confidential (i.e., no personal identifiers will be used and only aggregated information across all participants will be reported). Participants will have the potential risks and benefits of the study explained to them as well. For all candidates, understanding of the essential parts of the document will be assured by asking questions to verify their knowledge of the study procedures. If a candidate agrees to participate in the study, the candidate, or a witness if a candidate is illiterate, will document provision of informed consent by signing on the consent form. Unsigned copy of consent forms will be offered to the participants.

Potential risks

Participation in HIV care and treatment in Ukraine is not associated with any punitive or social risks with the exception of common stigma. This study does not increase the risk of stigma associated with drug use or HIV for participants.

Protection Against Risks

Participation in the study is completely voluntary and confidential. The unique identifier code, linking all study records is based on information provided by participants verbally, and no documents are requested. It is not possible to identify a person using this code. Contact information will be requested to allow invitation for follow-up assessments, and this information will be kept strictly confidential (see below). Mobile phone numbers in Ukraine in most cases are not personally identifiable information, because prepaid numbers are not linked to any contract or personal registration data.

The study personnel will explain to participants that the information collected in the study may be accessed by the law enforcement entities only in case of an individualized request with regard to an open criminal case.

As part of the informed consent procedure, all potential participants will be instructed that they do not have to disclose personal information which they are uncomfortable sharing and that they can withdraw from the study at any time.

Participants will receive names and contact information of the organizations conducting the study, as well as other study team members, on their copy of the ICF. It will be explained to the participant that they may contact anyone on the list if they have any questions or comments regarding the study, if

they suffered in any way due to their participation/failure to participate in the study. The participants will be informed that they may refuse to answer any questions that make them feel uncomfortable and that participation in the intervention is voluntary. Absolutely no information on any participants of the study will be given to other participants.

To minimize psychological risk, the recruitment into the study will be done by a trained social worker, and interview will be conducted by a trained interviewer. The interviews will be carried out face-to-face and there will be no additional persons in the room during the interview except the interviewer and respondent. Study staff will also be equipped to refer participants who need additional counseling and assistance to community resources, including referrals for HIV care and treatment.

Compensation

Participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. The compensation will be 400 UAH for each fully completed questionnaire (at baseline, 6 and 12 months), which will make 1200 UAH total if all three are completed. The compensation will be provided after each interview. This information is also specified in the ICF.

Confidentiality

All study-related information will be stored securely at the study sites and in the main office. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, and study data-collection, process and administrative forms will be identified by a coded number to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored with restricted access according to local SOP. All local databases will be secured with password-protected access systems.

Participant study information will not be released without the written permission of the participant, except as necessary for monitoring by the Sponsor, government and regulatory authorities, and/or site IRBs.

Protocol Deviations

All protocol deviations, new/unexpected findings and changes to the study environment will be documented and immediately reported to the in-country study team who will then notify the Sponsor. If necessary, a formal report will be sent to the appropriate IRBs. Reporting of such incidents will be the responsibility of the Principal Investigators of this study. Any discussions, issues, and complaints related to the study will be reviewed promptly to ensure close monitoring of the impact of the study on participants. Appropriate action will be taken to resolve or deal with all issues accordingly.

Dissemination, notification and reporting of results

Notifying Participants of Study Findings

Written material summarizing the findings from this study will be made available to participants and study staff upon completion of the study.

Dissemination of Study Findings

In-country data and country-specific information will be made available to national policymakers, organizations, and implementing partners as soon as possible. Study staff will be notified of the findings upon their presentation or publication.

The study findings will be disseminated through presentations and publications in peer reviewed journals and other publications. Reports will be disseminated to international audiences, as well as to national and local stakeholders to assist in HIV treatment program planning. Any formal presentations at conferences or scientific publications will follow JHU and UIPHP procedures for publications and presentations.

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Appendix 1: Recruitment Scripts

Client Recruitment Script – Control Sites

Introduction

My name is [STATE NAME], and I am a staff member here at [NAME OF AGENCY]. I would like to invite you to participate in a research study we are part of that is being conducted by Jill Owczarzak at Johns Hopkins University and Kostya Dumchev at the Ukrainian Institute on Public Health Policy. This study is trying to learn if a new program is effective in helping people remain in HIV care. The new program involves case managers, also known as social workers, who identify and address medical and social needs. Some clinics have been selected to implement the new program, whereas other clinics will continue their standard operations. This will allow our study team to determine the effectiveness of the new program.

Statement of why he/she selected

Your clinic, [NAME OF CLINIC], has been selected as one of the standard-of-care locations. You are being invited to join this research study because you are registered as a patient at [NAME OF CLINIC] and might be eligible to be part of this study. Your participation in this research will help us understand the impact of a new program to support people living with HIV. We are enrolling people living with HIV and have histories of substance use to understand how services can be adapted to meet their needs.

Description of Procedures and Payment

If you decide to join the study, you will receive the standard of care at [NAME OF CLINIC].
You will also complete three surveys: one at the beginning, one after 6 months, and one at the final 12-month visit. Each survey will last about 1 hour and will ask you about your HIV, mental health, and substance use experiences.
If you agree to participate, you will receive 400 hryvnia for completing each of the three surveys.

Assessment of Interest in Participation

Are you interested in hearing more details about the research study?

- If not interested, thank the individual for his/her time.
- If interested, then move to the consent form.

Client Recruitment Script – Intervention Sites

Introduction

My name is [STATE NAME], and I am a staff member here at [NAME OF AGENCY]. I would like to invite you to participate in a research study we are part of that is being conducted by Jill Owczarzak at Johns Hopkins University and Kostya Dumchev at the Ukrainian Institute on Public Health Policy. This study is trying to learn if a new program is effective in helping people remain in HIV care. The new program involves case managers, also known as social workers, who identify and address medical and social needs.

Statement of why he/she selected

You are being invited to join this research study because you are registered as a patient at [NAME OF CLINIC] and might be eligible to be part of this study. Your participation in this research will help us understand the impact of a new program to support people living with HIV. We are enrolling people living with HIV and have histories of substance use to understand how services can be adapted to meet their needs.

Description of Procedures and Payment

If you decide to join the study, you will work with a case manager at the [NAME OF CLINIC] who will ask you questions about your health history, living situation, social support, and other basic needs. Based on your responses, the case manager will support you in staying connected to HIV care and treatment by working with you to address issues that may make it difficult to attend HIV care appointments. The frequency of meetings and check-in phone calls with the case manager will vary depending on your needs and preferences. The case manager will re-evaluate your situation every 3 months. These evaluations and planning sessions with the case manager will last approximately 45-60 minutes each. There will be a total of 5 such sessions during the study.

You will also complete three surveys: one at the beginning, one after 6 months, and one at the final 12-month visit. Each survey will last about 1 hour and will ask you about your HIV, mental health, and substance use experiences.

If you agree to participate, you will receive 400 hryvnia for completing each of the three surveys.

Assessment of Interest in Participation

Are you interested in hearing more details about the research study?

- If not interested, thank the individual for his/her time.
- If interested, then move to the consent form.

Appendix 2: Recruitment Log (structure)

Study Site ___
Responsible staff ___

Filled by the Data Manager:

MIS ID	Study ID	Diagnosis date

Filled by the Case Manager:

Contact attempt 1:

Date	Mode	Result	Comment
	Phone; Clinic visit; Outreach; Other	Visit scheduled; no contact; contact info incorrect; refusal; contact later other	

Contact attempt 2:

Date	Mode	Result	Comment

Contact attempt 3:

Date	Mode	Result	Comment

Contact result:

Refusal reason	Scheduled visit date	Scheduled visit time
No interest; No time; Cannot come; Other		

Filled by the Interviewer:

Visit date	Visit result
	Completed; Incomplete; No show; No consent