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Implementation of a peer support intervention to promote the detection, reporting and management of adverse drug reactions in people living with HIV in Uganda: a protocol for a quasi-experimental study

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3 **Implementation of a peer support intervention to promote the detection,**
4 **reporting and management of adverse drug reactions in people living with HIV**
5 **in Uganda: a protocol for a quasi-experimental study**
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Abstract

Introduction: Patients have contributed <1% of all spontaneous adverse drug reaction (ADR) reports in Uganda's pharmacovigilance database. Peer support combined with mobile technologies could empower people living with HIV (PLHIV) to report ADRs and improve ADR management through linkage to care. We seek to test the feasibility and effect of a peer support intervention on ADR-reporting by PLHIV receiving dolutegravir (DTG)-based antiretroviral therapy (ART) and/or Isoniazid Preventive Therapy (IPT) in Uganda; identify barriers and facilitators to implementing this intervention; and characterise ADR-reporting and management.

Methods and analysis: A quasi-experimental study with both quantitative and qualitative methods will be implemented over 4-months at 12 intervention and 12 comparison ART-sites selected from four geographical regions of Uganda. From each region, two blocks each consisting of a tertiary care, secondary care and primary care ART-site will be selected by simple random sampling. In each of the four regions, one block of ART-sites will be enrolled into the intervention arm and the other block into the comparison arm.

The study units include ART-sites and PLHIV on DTG-based ART and/or IPT in both arms. The intervention arm will have peer supporters who will be expert clients from among PLHIV and/or recognized community health workers. PLHIV at intervention sites will be assigned to peer supporters to empower them to report ADRs directly to the National Pharmacovigilance Centre (NPC).

Direct patient-reporting of ADRs to NPC in both arms will leverage the Med Safety App and toll-free Unstructured Supplementary Service Data interface to augment traditional pharmacovigilance methods.

Ethics and dissemination: The study received ethical approval from the School of Health Sciences Research and Ethics Committee at Makerere University College of Health Sciences (MAKSHSREC-2020-64) and administrative clearance from Uganda National Council for Science and Technology (HS1206ES). The results will be shared with PLHIV, policy-makers, the public and academia. [299 words].

Trial registration: ISRCTN75989485

Strengths and limitations of the study

The study will blend a novel peer support intervention with mobile data transmission technologies to promote the detection and reporting of suspected adverse drug reactions (ADRs) by people living with HIV

People living with HIV who experience serious ADRs will be linked directly to health facilities for ADR management

An implementation research approach will be employed to identify the factors that could influence the uptake of peer support in patient-reporting of ADRs while documenting predefined outputs and outcomes relevant to the research objectives

The study will generate pilot data on effect sizes to aid the planning of future randomized controlled trials using peer support to promote patient-reporting of ADRs

For peer review only

Introduction

Adverse drug reactions (ADRs) are a leading cause of morbidity, mortality and increased healthcare costs[1-3]. The timely detection and reporting of ADRs promotes their appropriate management, more accurate prediction and prevention[4]. Pharmacovigilance systems worldwide have identified and led to withdrawal from the market of at least 462 harmful medicines, primarily through passive spontaneous ADR-reporting by healthcare professionals (HCPs)[5], thereby contributing to patient safety. The major drawback of the spontaneous pharmacovigilance system is its reliance on individual HCP motivation. It is estimated that only about 10% of ADRs are reported through the spontaneous pharmacovigilance system, which is a very low rate of ADR-reporting[6-8]. Several factors hinder ADR-reporting by HCPs including medical specialty, lower-level healthcare facility, older HCP age, heavy workloads, shortage of reporting tools, ignorance and fear of litigation[8, 9].

Patient-reporting of suspected ADRs is given little attention in developing countries. Yet, patients are a known complementary source of pharmacovigilance data[10-12]. Patients can make detailed ADR-reports and with similar quality as ADR-reports from HCPs. Patients can also report previously unknown ADRs[13]. Thus, patients are well-placed to participate in ADR-reporting because they have first-hand experience of their own state of health and treatment. Patient involvement in ADR-reporting aligns with the increasing global momentum towards patient-centred healthcare[14]. Yet, patient participation in pharmacovigilance is under-explored with little empirical data, especially in low- and middle-income countries (LMICs). In Uganda, patients' contribution to ADR-reporting is very low indeed and is estimated at less than 1% of the reports in the national pharmacovigilance database (Victoria Nambasa, Pharmacovigilance Manager at National Drug Authority (NDA); personal communication; 6 April 2020).

The quest for expanded avenues to increase the reporting of suspected ADRs has never been more apparent than in Uganda where dolutegravir (DTG) and Isoniazid Preventive Therapy (IPT) have been massively rolled-out since 2018 and 2019, respectively. Anecdotal evidence in Uganda shows that increased use of DTG and IPT has led to a higher incidence of associated ADRs[15, 16], necessitating a more robust pharmacovigilance system that leverages the reporting of ADRs by PLHIV on DTG-based regimens and IPT. Hyperglycaemia occurs in <7% of ART-naïve PLHIV after 96-weeks of follow-up and 14% at 48-weeks in ART-experienced PLHIV in Europe and North America[17]. Other DTG-related serious ADRs occur in 1.7% (33/1950) for neuropsychiatric effects and 0.1% (1/1073) for hepatotoxicity among Europeans[18, 19]. The incidence of IPT-related ADRs is 0.5% according to a South African trial of 24,221 PLHIV in which liver function tests were not routinely done; skin rash (0.25%), peripheral neuropathy (0.21%), clinical hepatotoxicity (0.07%) and convulsions (0.02%) were also observed[20]. This study proposes to test the feasibility and effect of a peer support intervention combined with mobile phone-based tools to promote the reporting of ADRs in PLHIV on DTG-based ART and/or IPT in Uganda. If successful, this study will contribute to the development of a more robust pharmacovigilance system to better document serious ADRs in the Ugandan setting.

Patient-centred peer support has shown promise in the management of chronic illnesses such as diabetes and mental health[21, 22]; and in improving retention in HIV care and adherence to ART[23, 24]. Thus, peer support could substantially promote the detection, reporting and management of ADRs by PLHIV. In the current study, peer support is based on the premise

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3 that PLHIV who have previously experienced ADRs linked to ART can – as peer supporters -
4 encourage, mentor and support other similarly affected but less experienced PLHIV to detect
5 and report ADRs[25]. Peer supporters could serve as positive role models to improve the self-
6 efficacy and confidence of other PLHIV whom they could guide to identify and report ADRs
7 using the available tools. Direct patient-reporting of ADRs could utilize the Med Safety mobile
8 application, a toll-free Unstructured Supplementary Service Data (USSD) interface and the
9 traditional pharmacovigilance methods of paper-form, online forms and voice call. The aim
10 remains to have all suspected ADR reports submitted to the National Pharmacovigilance
11 Centre (NPC) database for analysis and subsequent processing. However, those that require
12 clinical management should be brought to the attention of the HCP for appropriate
13 management and prevention[25-27]. From guiding less experienced PLHIV, expert clients
14 serving as peer supporters could equally be empowered to build their own self-esteem[28,
15 29].
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20 Our peer support intervention for strengthening the Ugandan pharmacovigilance system
21 through patient-reporting of ADRs is intended to leverage the available mobile technologies
22 e.g. the USSD platform available for both low-tech non-smartphones and high-tech
23 smartphones[30]; and the Med Safety mobile application for high-tech smartphones[31].
24 USSD is a real-time text-driven technology which allows users to interact directly from their
25 mobile phones by making a selection from a menu. It allows for faster two-way communication
26 of information and enables rapid exchange of data - up to seven times faster than SMS[32].
27 The USSD interface has been a key success factor in the extensive penetration of mobile
28 money banking in rural unbanked sub-Saharan Africa[33]. No Internet connection is needed.
29 This project's toll-free USSD code has been developed by a private Ugandan software
30 company[34]. Med Safety is a smartphone mobile application for ADR-reporting that was
31 recently adapted for LMICs from the prototype app funded by the European Union's Innovative
32 Medicines Initiative – the WEB-RADR project. Adaptation of the mobile app is led by UK's
33 Medicines and Healthcare products Regulatory Agency in collaboration with World Health
34 Organization (WHO) and the WHO Collaborating Centre for International Drug Monitoring, the
35 Uppsala Monitoring Centre (UMC)[35]. Med Safety was launched in Uganda in February 2020.
36 Using both USSD and Med Safety alongside existing pharmacovigilance methods could
37 strengthen peer support-enhanced patient-driven pharmacovigilance in Uganda.
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42 Lastly, the study will use an implementation science approach to evaluate the peer support
43 intervention among PLHIV. Implementation research is critical in identifying factors that could
44 influence uptake of the intervention while documenting predefined outputs and outcomes
45 relevant to the research objectives[36]. Our ultimate goal is to increase patient reporting of
46 ADRs in LMICs such as Uganda with weak pharmacovigilance systems. Hence, this study
47 aims to develop and assess the feasibility of a peer support intervention combined with mobile
48 phone-based tools to promote the detection and reporting of ADRs in PLHIV on DTG-based
49 ART and/or IPT in Uganda. It will identify the barriers and facilitators to implementing the
50 intervention, characterise ADR-reporting and management and estimate the effect of the
51 intervention on ADR-reporting among PLHIV.
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55 **Research hypotheses and objectives**

56 Research hypotheses:

57 We hypothesize that the patient-centred peer support intervention combined with existing
58 mobile data transmission technologies for promoting the detection, reporting and management
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3 of ADRs in PLHIV is feasible and acceptable. We also hypothesize that this peer support
4 intervention combined with mobile data transmission technologies will significantly increase
5 the number of ADR reports submitted to NPC by PLHIV who receive the intervention during
6 4-months of follow-up when compared to PLHIV who do not receive the intervention.
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9 Specific objectives:

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1. To develop a peer support intervention combined with mobile data transmission technologies to promote the detection, reporting and management of ADRs in PLHIV receiving DTG and/or IPT in Uganda
 2. To explore the barriers and facilitators to implementation of the peer support intervention combined with mobile data transmission technologies to promote ADR detection, reporting and management among PLHIV on DTG and/or IPT in Uganda
 3. To describe the patterns of ADR-reporting (number, rate, quality, time to reporting, seriousness etc.) by PLHIV receiving DTG and/or IPT in whom the peer support intervention combined with mobile data transmission technologies is implemented in Uganda
 4. To estimate the effect of the peer support intervention combined with mobile data transmission technologies on the rate of ADR-reporting by PLHIV receiving DTG and/or IPT in Uganda

Methods

Study setting

Uganda has a tiered healthcare system with different levels of healthcare from the National Referral Hospitals which provide tertiary and super-specialized healthcare, through Regional Referral Hospitals (RRHs), General Hospitals, level IV Health Centers (HC IV), level III Health Centers (HC III), to level II Health Centers (HC II) that progressively offer less scope and breadth of health services to out-patient services[37]. HIV treatment and care is provided from HC III and upwards giving a total of 1,832 accredited centers that provide ART services in Uganda. Uganda adopted the Differentiated Service Delivery Models (DSDM), where stable clients have less frequent clinical assessment visits. In 2019, about 80% (1,466/1,832) of the ART accredited sites and 78% (975,675/1,241,478) of PLHIV on ART had access to the DSDM model. An additional, 12% (114,363/975,675) of clients enrolled on DSDM received ART services from the community through Community Drug Distribution Points (CDDP) and Community Client-Led ART Distribution (CCLAD)[38].

Uganda has an estimated 1.46 million PLHIV, of whom prevalence among people aged 15 to 49 years is 5.8% with women having a higher prevalence (7.1%) than men (4.3%). Among the PLHIV, 93% are aged ≥ 15 years and 60% of the HIV-infected adults are women. In 2019, there were 53,413 new HIV infections of which 40,000 were among adults and 21,000 Ugandans died of AIDS-related illnesses[39]. Following the "Test and Treat" policy for HIV adopted in 2016 and scaled up in 2017, the ART coverage was at 89% in 2019. Approximately 96% of PLHIV on ART are taking first-line regimens and >443,000 PLHIV are on TLD. About 17% of PLHIV are ART-naïve at treatment initiation. In 2019, about 41% of TB patients were HIV-positive and 97% of HIV-positive TB patients were receiving ART[39, 40]. By the end of 2019, 477,190 of PLHIV were enrolled on IPT. Strategies to strengthen pharmacovigilance were instituted as part of DTG/IPT roll-out in the 2020 revised Consolidated Guidelines for Prevention and Treatment of HIV and AIDS in Uganda[16]. The guidelines support ADR identification, monitoring and reporting, particularly for DTG and IPT. Pharmacovigilance sentinel sites were established at 18 sentinel sites (RRHs and Centers of Excellence). These ART-sites received training and ADR-reporting tools. ADRs are reported to the NPC at NDA through a paper-based system, online system, toll-free phone line or through NDA's Med Safety App.

For the current study, the authors have divided the country into four geographical regions to establish a sampling framework that leads to selection of national level representation of health facilities and factors that influence provision of care to PLHIV and their pharmacovigilance-related needs. In each region, two blocks of health facilities with ART-sites will be selected of which one block will implement the intervention and the other will serve as the comparison block of health facilities. Each block will consist of an ART-site at a RRH (tertiary care), a HC IV (secondary care) and HC III (primary care), respectively. Therefore, 12 intervention ART-sites will be matched by level of care and region with 12 comparison ART-sites from the four regions of Uganda.

Study design

The study will employ a quasi-experimental design with pre-post and there-there comparisons to measure the preliminary impact of the peer support intervention on ADR-reporting by PLHIV, **Figure 1**. The study will use both quantitative and qualitative methods to triangulate the research findings. The qualitative research methods aim to understand the barriers and

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3 facilitators to implementing the peer support intervention for promoting ADR detection,
4 reporting and management from the perspective of PLHIV and in the context of their interface
5 with Uganda's healthcare system[41] and thus they will be predominantly implemented in the
6 intervention arm. We will explore the experiences of PLHIV in the utilization of the peer support
7 intervention and elicit their preferences to further refine the intervention and implementation
8 strategy.
9

10 11 The intervention

12 The peer support intervention leverages mobile data transmission technologies (Med Safety,
13 USSD) in addition to traditional pharmacovigilance methods (paper, online, voice call). The
14 peer support mechanism has several layers of supervision from the mentored PLHIV, through
15 peer supporters, peer supervisors, study coordinator to study investigators at the top of the
16 hierarchy, see **Figure 2**.
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19 The PLHIV to be mentored in the intervention arm will be assigned to peer supporters to guide
20 their ART care for 4-months. The peer supporters will constitute a mixed group of lay people,
21 namely; i) expert clients who are PLHIV with more experience in the use of ART and, ii)
22 recognized community health workers (CHWs). Most CHWs in Uganda's HIV programs are
23 expert clients. Thus, it is possible to recruit CHWs all of whom are expert clients. Mentored
24 PLHIV in the intervention arm will identify with the peer supporters whom they will rely on to
25 improve their healthcare-seeking behaviour and to report ADRs to NPC; they should own
26 mobile phones.
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29 The PLHIV will be identified at the study sites and matched with the respective peer supporters
30 of similar age, gender and proximity of residence. The non-random allocation of participants
31 is intended to promote easier and faster bonding of the peer-relationships. Five (5) PLHIV will
32 be assigned to one (1) peer supporter from the same community. A weekly (minimum
33 fortnightly) face-to-face/phone call interaction will be held between a peer supporter and each
34 assigned PLHIV. Thus, a peer supporter will be expected to interact with one PLHIV per day
35 and five PLHIV in five days each week. Peer supporters will use one-on-one in-person support
36 blended with mobile phone-based interaction to guide each assigned PLHIV to recognize and
37 report suspected ADRs to NPC. The peer supporter will also administer a short weekly
38 questionnaire to each assigned PLHIV regarding ADR experience in the past 1-week.
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41 This peer support intervention adapts the "humanizing healthcare model" developed by *peers*
42 *for progress*, a group that demonstrates the value and best practices of peer support. The
43 model is based on four functions, namely; assistance in daily management, providing social
44 and emotional support, linking to clinical and community resources and ongoing support[42],
45 see **Figure 3**.
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48 Both the supported PLHIV and peer supporters will be trained on the following aspects: ART;
49 how to live positively with HIV; recognition of suspected ADRs and how to report them via Med
50 Safety, USSD or traditional methods (paper, online, voice call) to NPC; and about linkage or
51 referral to health facility care e.g. when a serious ADR occurs. The supported PLHIV and peer-
52 supporters will be trained to interact in a manner that ensures confidentiality. The data
53 generated from Med Safety and USSD will be safeguarded according to applicable laws on
54 data protection. The linkage to appropriate care of PLHIV by the peer supporter will aim to; i)
55 promote healthcare-seeking behaviour of the PLHIV, ii) improve the monitoring of HIV
56 treatment (management of serious ADRs, ART adherence, retention in care), iii) enhance
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3 timely refill of ART prescriptions and/or, iv) provide for any other special care that PLHIV might
4 require.
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6 Peer supporters will be separately trained and skilled in interpersonal interaction to be
7 responsive to PLHIV and encourage them to identify and report any suspected ADRs. The
8 training components for peer supporters will include care in chronic illness, ART, adherence
9 to ART, ADRs, ADR-reporting, care-seeking, counselling and facilitative supervision. Training
10 for the peer supporters will take up to three days. It will include a one-day didactic session
11 followed by two days of on-the-job, one-on-one training. In addition to being trained, peer
12 supporters will receive supplementary educational materials. Four follow-up
13 supervisory visits/phone calls at two-week intervals will be conducted by the trainers to
14 reinforce the knowledge, skills and attitudes gained by the peer supporters. Each supported
15 PLHIV will receive one-day's training during his/her clinic visit which will include a didactic
16 session and one-on-one discussion in a non-classroom environment. The trainers will be
17 qualified individuals carefully identified by the project team with the requisite knowledge to
18 offer the training and expertise in adult learning and counselling.
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23 The peer support mechanism will have two additional layers of supervision, see **Figure 2**. The
24 first level of additional oversight will be provided by four (4) peer supervisors identified from
25 among the peer supporters at each of the four selected RRHs. Peer supervisors will be
26 seconded by the study sites and collaborating patient safety groups involved in the recruitment
27 of peer supporters. Each peer supervisor will oversee 15 peer supporters in his/her region (10
28 from RRH, 3 from HC IV, 2 from HC III). The peer supervisor will call each peer supporter
29 twice a month. During these 'booster' sessions, the peer supervisor will review, emphasize
30 and re-educate peer supporters on expectations of the intervention e.g. setting and reviewing
31 goals with PLHIV. The second level of oversight will be provided by the project coordinator
32 who will oversee the four (4) peer supervisors whom he/she will meet/call every month. At
33 least one study investigator, mostly the principal investigator, will participate in these
34 meetings/calls. The project coordinator will have the requisite knowledge, skills and
35 competence to train PLHIV and peer supporters. The project coordinator will provide support
36 supervision and counselling to motivate the peer supervisors, peer supporters and PLHIV.
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41 The comparison group

42 PLHIV in the comparison group will be mobile phone owners who will be trained to recognize
43 suspected ADRs and report them to NPC via Med Safety, USSD or the traditional
44 pharmacovigilance methods (paper, online, toll-free voice call) to a peer-supporter, HCP or
45 NPC, see **Figure 4**. Smartphone owners will be guided to install Med Safety for ADR-reporting.
46 PLHIV with non-smartphones or smartphone owners who will not install Med Safety will report
47 ADRs by USSD or the traditional reporting methods. PLHIV in this group will not receive
48 dedicated peer support.
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51 Study units, participants and selection

52 Study units and participants:

53 This study has multiple study units and layers to assess the feasibility of implementation and
54 effect of the intervention on promoting the detection and reporting of suspected ADRs in
55 PLHIV on DTG-based ART and/or IPT in Uganda. From micro to macro-level, the study units
56 include PLHIV receiving DTG-regimens and/or IPT; the pair of PLHIV and peer supporter; the
57 peer supporter; the combination of the PLHIV with peer supporter and ART-site; peer
58 supervisor; the pair of peer supervisor and peer supporter; and the ART-site. At the study
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ART-site, HCPs and health facility managers will be included. Lastly, the reporting of suspected ADRs by PLHIV, peer supporters, HCPs and ART-sites to the NPC will also be examined.

Study participants will give written/thumb-printed informed consent if aged ≥ 18 years and [43]. About 17% of PLHIV are ART-naive, 95% are aged 15 years and older, and 89% receive first-line ART either as treatment-naive or treatment-experienced PLHIV[40].

Eligibility criteria:

Inclusion criteria: Selection of study units will occur at three levels: *First*, eligible PLHIV should i) be aged ≥ 15 years, ii) receive ART at the selected study sites, iii) own a mobile phone (smartphone, basic feature phone) and, iv) provide written/thumb-printed informed consent. Child consent can be given by emancipated minors aged 15 to 17 years in Uganda[43] *Second*, eligible peer supporters (expert clients, CHWs) will be those that are recognized and seconded by the study sites or collaborating patient safety groups. These peer supporters will be those that are attached to the study sites and have already received institutional training in their role as expert clients/CHWs; they should own mobile phones. Peer supporters will participate only in the intervention arm of the study. *Third*, study health facilities will be selected and enrolled as follows; in each of the four geographical regions, blocks of three health facilities each with an ART-site, including at least a RRH, HC IV and HC III will be created based on the catchment of each RRH. From the created blocks of three health facilities in each region, two blocks will be selected by simple random sampling to participate in the study as the intervention and comparison health facilities, respectively. This will give 24 ART-sites consisting of 12 intervention sites (4 RRHs, 4 HC IVs, 4 HC IIIs) matched by level of care and region with 12 comparison sites (4 RRHs, 4 HC IVs, 4 HC IIIs) selected from the four geographical regions of Uganda.

Exclusion criteria: Exclusion will apply only at the level of PLHIV as the study will need to retrospectively assess the occurrence of ADRs during the 4-month period preceding study enrolment. We shall exclude PLHIV on ART for < 6 -months and expert clients/ CHWs who will be unable to commit, from the outset, at least 5-hrs per week to the study for up to 4-months.

Sample Size and Sampling Considerations

Sample size computation is based on the possible effect of the peer support intervention on the rate of ADR-reporting by PLHIV, with adjustment for clustering. We assume a conservative intra-cluster correlation coefficient of 0.045 and a priori increase of 50% in the rate of ADR-reporting to NDA, from 6 ADR-reports per 100 person-years at baseline[44] to 9 ADR-reports per 100 person-years at end-line evaluation. We assume a standard deviation of 12 ADR-reports per 100 person-years computed from the monthly ADR-reports submitted to NPC for one-year (October 2018 to September 2019). The study is designed to have at least 80% power to estimate an effect size of 1.5. Thus, 126 PLHIV will be required in the intervention arm and 126 PLHIV in the control arm.

Since the caseload for each peer supporter will be 5 PLHIV in the intervention arm, 60 peer supporters (15 from each of the 4 regions) will be responsible for 300 PLHIV on DTG and/or IPT. Thus, the peer support arm will include 300 PLHIV and the control arm 300 PLHIV all of whom should own functional mobile phones (smartphone or non-smartphone or both). Thus, a total of 600 PLHIV will be enrolled; 400 from RRHs, 120 from HC IVs and 80 from HC IIIs.

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3 The PLHIV will be enrolled consecutively until the required sample size is attained.
4 Smartphone owners will be guided to install Med Safety for ADR-reporting. We assume that 7
5 in 10 PLHIV at the ART-sites will have mobile phones and only one in 10 will possess
6 smartphones[45]. Thus, only up to 10% (or 60) of PLHIV with smartphones will be helped (with
7 maximal support from peer supporters) to download Med Safety. The rest of the 540 PLHIV
8 without smartphones or smartphone owners who will not install Med Safety will report ADRs
9 by USSD or the traditional methods.
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12 Study variables

13 *Primary outcomes:* Feasibility of the peer support intervention - attrition rate recorded as the
14 number of study participants who remain in the study until the end of follow-up at 4 months;
15 Number of suspected ADR reports submitted to NPC by PLHIV as measured by questionnaire
16 and data abstracted from the national pharmacovigilance database at baseline and 4 months
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19 *Other process/output/outcome variables:*

- 20 1. Acceptability of the peer support intervention measured using a questionnaire and
21 qualitative interviews at 4 months post-intervention
- 22 2. Barriers/facilitators of the peer support intervention measured using a questionnaire
23 during the intervention and qualitative interviews at 4 months post-intervention
- 24 3. Fidelity to the peer support intervention measured using a questionnaire and
25 qualitative interviews at 4 months post-intervention
- 26 4. Rate of ADR-reporting to NPC by PLHIV as measured by questionnaire and data
27 abstraction from the national pharmacovigilance database at baseline and 4 months
- 28 5. Quality of ADR-reports by PLHIV measured by questionnaire and data abstraction
29 from the national pharmacovigilance database at baseline and 4 months
- 30 6. Time to ADR-reporting to NPC by PLHIV since enrolment measured by questionnaire
31 and data abstraction from the national pharmacovigilance database during 4 months
- 32 7. Time from ADR onset to registration in the national pharmacovigilance database
33 measured by questionnaire and data abstraction from the database during 4 months
- 34 8. Health-related quality of life measured by questionnaire at baseline and 4 months
- 35 9. Management of ADRs recorded using a questionnaire during the 4 months
- 36 10. Number of PLHIV linked to health facilities by peer supporters for ADR management
37 as measured by questionnaire during the 4-month intervention period
- 38 11. Health-seeking behaviour measured using a questionnaire at baseline and 4 months
- 39 12. Self-efficacy measured by questionnaire at baseline and 4 months
- 40 13. Self-reported ART adherence measured by questionnaire at baseline and 4 months
- 41 14. Mood (positive/ negative affect) measured by questionnaire at baseline and 4 months

42 **Patient and Public Involvement**

43 Direct involvement of PLHIV in the detection and reporting of suspected ADRs, and patient
44 safety groups in recruitment of PLHIV, will have value in improving the public's awareness of
45 ADRs and the available pharmacovigilance tools (Med Safety, USSD, toll-free voice call, etc.).
46 Together, these will be essential for ensuring that changes to clinical practice to promote
47 patient safety based on our work are acceptable to the public.

48 The study team will work with PLHIV to assess whether the available pharmacovigilance
49 tools meet their needs, to identify potential improvements and to understand facilitators and
50 barriers to using these pharmacovigilance tools. Wider public input into the refinement of the
51 tools and mechanisms to encourage uptake will add value to our work. This work will also be
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of value to the wider public as Med Safety can be used to report ADRs to any drug, and users can receive drug safety information directly from NPC.

Data management and statistical analysis

Quantitative data

Data collection and management: Baseline and end-line semi-structured questionnaires will be administered to the PLHIV and peer supporters (expert clients) in the intervention arm and PLHIV only in the comparison arm.

The baseline questionnaire will record socio-demographics (age, sex, monthly income, education level, residence) of all study participants. Clinical details (ART adherence; ADRs; ART-regimen; ART-status i.e. first-line, second-line, third-line; duration on ART; comorbidities) and healthcare-seeking behaviour of study PLHIV will be measured. Data will be transmitted to a password-protected online database via the Open Data Kit (ODK) suite of tools. Participating PLHIV will be asked at enrolment if they experienced suspected ADRs in the 4-months preceding the study; and their clinical charts will be reviewed for additional information regarding suspected ADRs. The clinical charts will be accessed by the health facility staff.

Additional data collection for the intervention group: On a weekly basis for up to 4-months, peer supporters will inquire from each assigned PLHIV (during a 1 hour face-to-face or phone call interaction) if one or more suspected ADR(s) was/were experienced and if the ADR had any impact on quality of life and/or ART adherence. Peer supporters will document if the ADR(s) was/were reported; and, if reported, by which means (Med Safety, USSD, voice call, other methods). Peer supporters will document all ADRs experienced by the PLHIV during the previous 1-week (using a tool designed to capture the medicines and ADRs); and will guide the PLHIV to report ADRs directly to NPC using the available pharmacovigilance methods. Active surveillance of ADRs linked to DTG and/or IPT will be prioritized but ADRs linked to other medicines will also be documented. We will document the management of serious and non-serious ADRs (number of serious and non-serious ADR cases referred for health facility management; actions taken by health facilities in the management of serious and non-serious ADRs e.g. stopping treatment, changing treatment, continuing treatment with adherence counselling, doing nothing, etc.).

The end-line questionnaire for PLHIV will measure their healthcare-seeking behaviour, linkage to care for ADR management and adherence to ART. The PLHIV will also be asked to report their experiences while receiving peer support to assess the intervention's feasibility and acceptability (e.g. user satisfaction). The study will also assess the participants' experiences when using the various pharmacovigilance methods (Med Safety, USSD, toll-free voice call, etc.). We shall assess the ease of use, language and costs of the available pharmacovigilance methods (Med Safety, USSD, toll-free voice call, etc) alongside peer support.

Med Safety App and USSD data collection: PLHIV will submit ADR-reports via Med Safety and/or USSD with initial assistance from peer supporters. Each app-based ADR-report will be automatically converted into the standard E2B (R2) format prior to its receipt in the Vigilance Hub[46]. The app is hosted by Uganda's NDA which manages the reported ADR data. For USSD reporting, PLHIV will dial the USSD code and answer a set of questions. The data will be stored in real-time on a dashboard accessible to the project staff.

Statistical analysis: All ADR-data in both the national and project databases and received from the study sites during the study period will be exported into Stata version 15.0 MP for

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3 descriptive analysis – frequencies, proportions and their 95% confidence intervals (StataCorp
4 LLC, College Station, Texas). Duplicate ADR-reports will be identified and analysed
5 accordingly. Summary estimates will be reported by pharmacovigilance method (Med Safety,
6 USSD, toll-free voice call, etc.).
7

8
9 To assess the feasibility to retain peer supporters and PLHIV, we shall compute the attrition
10 rate which is the proportion of study participants who remain in the study until the end of follow-
11 up at 4 months.
12

13 The number of suspected ADRs reported to NPC by the PLHIV overall and in each study arm
14 will be described by subgroup: serious ADR (yes/no); peer supporter guided (yes/no); DTG-
15 linked (yes/no); IPT-linked (yes/no); DTG/IPT-linked (yes/no); linked to other medicines
16 (yes/no); level of reporting (PLHIV, peer supporter, HCP, health facility) etc.
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19 The rate of ADR-reporting (m_a) by PLHIV (per site, overall) per completed-month (m_1) of follow-
20 up will be computed as follows: $m_a = [n_a \text{ reports}/(N_a \text{ completed-months of follow-up})]$, where
21 n_a is the number of reported ADRs and N_a the number of completed-months of follow-up.
22 Reporting rates of same-day ADR-onsets will be documented; and time from ADR-onset to
23 registration in the national database recorded for all other events[37]. Time to ADR-reporting
24 to NPC for a PLHIV will be the time from the day a PLHIV is enrolled into the peer support
25 intervention to the time he/she reports the first suspected ADR to NPC. Time-to-event data
26 will be analysed by survival analysis techniques.
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28

29 We will explore the influence of level of care on the uptake of the peer support intervention in
30 Uganda's healthcare system - such as whether rolling it out at primary care facilities or tertiary
31 hospitals influences uptake.
32

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34 The change in outcome measures (e.g.) between pre- and post-intervention in PLHIV will be
35 assessed using a linear mixed model with random effect for peer supporter. Random effect
36 will be included to account for clustering of PLHIV with peer supporters. The ICC will be
37 estimated from this model. Since supporters are a mixed population of expert clients and
38 CHWs, a stratified analysis will be conducted. To aid the planning of future randomized
39 controlled trials from this pilot's data, we shall report effect sizes.
40

41 Qualitative data

42 **Data collection:** Post-intervention, a combination of focus group discussions (FDGs), in-
43 depth interviews (IDIs) and Key Informant Interviews (KIIs) will be conducted with purposively
44 selected study participants. A lead qualitative researcher will be assisted by two well-trained
45 research assistants. Semi-structured interviews informed by the Consolidated Framework for
46 Implementation Research (CFIR)[47] will be used to elicit participants' perspectives on the
47 facilitators and barriers to implementing the peer support intervention at four purposively
48 selected health facilities.
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52 We will conduct six FGDs with three categories of PLHIV in the intervention arm; two with
53 those enrolled in Community Drug Distribution Points (CDDPs), two in Community Client-Led
54 ART Delivery (CCLAD) and two in facility-based ART delivery models.
55

56
57 A total of 12 IDIs will be conducted with peer supporters (expert clients, CHWs) attached to
58 each of the three ART delivery models; a) CDDP, b) CCLAD, c) Facility-Based, see **Figure 5**.
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3 Four KIIs will be conducted with HCPs/facility managers with insights in the implementation
4 experience of the peer support intervention at their respective host facilities from an
5 organizational-context.
6

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8 As a first step, participants will complete a written informed consent form. We will then capture
9 baseline characteristics: age, gender and educational level. A CFIR-informed semi-structured
10 guide will be used for the interviews. The semi-structured guide will explore participants'
11 experiences with the peer support intervention, their preferences and suggestions for
12 improvement of the intervention and the challenges encountered in using USSD and/or Med
13 Safety. On average, the duration of the FGDs and IDIs will be approximately 45-60 min. The
14 FGDs, IDIs and KIIs will be conducted until theoretical saturation is reached. Theoretical
15 saturation means that no new knowledge is generated and all aspects of a theory are covered.
16 All the data generated from the focus groups and interviews will be explored for themes and
17 sub-themes.
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21 **Guiding qualitative analytical framework:** The CFIR will be adopted as the overall guiding
22 analytical framework for this study. The CFIR is a comprehensive 'meta-theoretical'
23 implementation research framework compiled from more than 20 sources and is cross-cutting
24 in more than 13 scientific disciplines; it guides systematic assessment of multi-level
25 implementation settings to identify factors that influence intervention implementation and
26 effectiveness [48]. The CFIR informs the conceptualization of this study, will guide the
27 development of data collection tools and will serve as an overarching deductive thematic
28 framework in analysis of study findings and the overall synthesis and interpretation of results
29 for this study. The CFIR is widely-applied because of its multi-level, 'ecological' dimensions
30 on multi-faceted influences on healthcare intervention implementation outcomes[49]. The
31 CFIR has been applied across diverse interventions and varied content fields[48].
32
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34
35 More specifically, the CFIR-derived domains that will guide the study are the following:

36 *Intervention characteristics:* Implementation of the peer support intervention could potentially
37 be impacted by factors including its perceived effectiveness in ADR-reporting, relative
38 advantages over alternative reporting approaches, adaptability in varied resource-constrained
39 settings, trialability, complexity, design quality and presentation, and cost-effectiveness.
40

41 *Outer setting:* external influences on implementation of peer support may include external
42 policies and incentives, socio-cultural belief systems, peer pressure dynamics and socio-
43 economic context.
44

45
46 *Inner setting:* characteristics of the implementing organization (or host health facility) such as
47 organizational culture, the relative priority assigned to the peer support intervention (including
48 funding support), presence of intervention 'champions', availability of supportive administrative
49 or physical infrastructure, congruence with host organization's mission and vision, quality of
50 leadership support and implementation climate(s).
51

52
53 *Characteristics of individuals:* Patients' beliefs, knowledge, level of income, self-efficacy, and
54 personal attributes that may affect the implementation and uptake of the peer support
55 intervention.
56

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58 *Process of implementation:* Influences on implementation outcomes may derive from different
59 implementation phases involved in roll-out of the peer support strategy such as degree and
60 quality of involvement of primary beneficiaries in designing the intervention, planning,

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3 execution, degree of effectiveness of monitoring and evaluation strategies and presence of
4 key intervention stakeholders and influencers including opinion leaders, stakeholder
5 engagement, and intervention champions.
6

7 The CFIR will be used to identify barriers and facilitators of the peer support intervention for
8 promoting ADR-reporting by PLHIV.
9

10 **Data analysis:** Our qualitative data analysis will follow the procedures recommended by Miles
11 & Huberman (1994)[50]. Interviews and FGDs will be audio-recorded and transcribed verbatim
12 into text transcripts by three research assistants (and translated into English where
13 necessary). Data will be analysed, in an iterative process, involving four major steps:
14
15

16 a) *Data familiarization:* An experienced qualitative researcher and one other investigator will
17 read the interview transcripts multiple times for data familiarization.
18

19 b) *Developing a coding framework:* We shall adopt the five CFIR-derived domains
20 (*Intervention characteristics, outer setting, inner setting, characteristics of individuals, and*
21 *process of implementation*) as an overarching deductive thematic framework, combined with
22 an inductive approach based on the data[51].
23
24

25 c) *Data abstraction:* The coded data will be categorized into thematic categories.
26

27 d) *Overall interpretation and synthesis:* Our overall synthesis of study findings will adopt a
28 team-based process of peer-debriefing involving all investigators to resolve disagreements in
29 interpretation of study findings.
30
31

32 **Quality assurance**

33 To ensure uniform study procedures and high-quality data, all research assistants recruited
34 for the study will receive face-to-face training on the following: the informed consent process,
35 participant interviewing techniques, confidentiality issues, pharmacovigilance, use of the Med
36 Safety App, use of the USSD, ADRs, use of the Open Data Kit (ODK) software for data entry
37 into an online password-protected database; and qualitative and quantitative study designs,
38 among others.
39
40

41 The FGDs and KIs will be led by an expert in qualitative research. Research assistants with
42 prior training in qualitative research methods will also be hired for the qualitative study
43 component. All research assistants will receive face-to-face training in both qualitative and
44 quantitative research methods.
45

46 Questionnaire data will be transmitted through ODK to an online database by the research
47 assistants while still in the field. The study statistician will check the online data for integrity
48 and contact field staff as soon as possible while still in the field to correct any data entry errors.
49 Prior to entry into ODK, all research assistants shall be required to cross-check the data on
50 study questionnaires to eliminate errors and ensure data completeness.
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53 **Results uptake and use**

54 *Outcomes/Impact/Outreach:* The peer support intervention is expected to increase patient-
55 reporting of ADRs to NPC. It is anticipated that the patients will subsequently; i) find it easier
56 and faster to report ADRs (including DTG- and IPT-related reactions) anywhere and at any
57 time using their mobile phones and, ii) receive medication-safety alerts directly from NPC on
58 their phones. We expect this project to promote pharmacovigilance in Uganda by improving;
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3 i) the exchange of medication-safety information between patients, peer supporters, HCPs
4 and NPC, ii) the awareness of pharmacovigilance by patients and the public through the
5 mobile phone and other awareness campaigns and, iii) the rate of ADR-reporting by patients.
6

7
8 *Potential impact on policy or programs:* This project could foster the increased involvement of
9 patients in pharmacovigilance activities and improve the efficiency of pharmacovigilance
10 systems in Uganda with real-time monitoring of DTG and INH safety in PLHIV in the first
11 instance, thus, increasing the volume of analysable data for quick decision-making by both
12 clinicians and policy makers.
13

14 We expect to promote collaboration between consumers/public and the NPC, national AIDS
15 Control Program - Ministry of Health and the National TB and Leprosy Control Programme
16 (NTLP). The accumulation of relevant medication-safety data from spontaneous and active
17 ADR-reports permits robust detection of safety signals at the national and international levels.
18

19
20 *Scalability:* After this pilot project, we expect the peer support intervention to be tested in a
21 nationwide randomized controlled trial; and the USSD and Med Safety App to be modified
22 accordingly and implemented at all 1,832 ART-sites in Uganda to complement the existing
23 active and passive pharmacovigilance methods for ART and TB treatment. We hope to embed
24 peer support in routine pharmacovigilance practice to promote the detection and reporting of
25 ADRs by PLHIV in Uganda. The Med Safety App is available in English and will be
26 subsequently translated into other local languages according to need.
27

28
29 The USSD and Med Safety are potentially invaluable tools for the pharmacovigilance of drugs
30 used for other diseases e.g. non-communicable diseases like cancers, diabetes mellitus,
31 hypertension etc.
32

33
34 Peer support, USSD and Med Safety will be scaled-up to support spontaneous ADR-reporting
35 in both public and private health facilities at all levels of healthcare ranging from hospitals,
36 medical centres and clinics to pharmacies and drug shops, not least, the general public.
37

38
39 The Med Safety-generated pharmacovigilance data at NPC could be linked with the patients'
40 clinical data at ART-sites, stock consumption data from the Supply Management Chain
41 system; and the electronic Health Management Information System. Machine learning/artificial
42 intelligence analytical techniques could then be used on big data in the near future to foster
43 improved systems.
44

45
46 *Sustainability:* Peer support to promote the detection and reporting of ADRs by PLHIV can be
47 embedded in the HIV/AIDS program of Uganda just as community engagement programmes
48 have been successful in Maternal and Child Health programmes; and are being rolled out in
49 the COVID-19 Community Engagement Strategy and the Young people and Adolescent Peer
50 Support Model for improving HIV care and treatment outcomes for Adolescents and young
51 PLHIV of 2019 in Uganda[52, 53]. The USSD and Med Safety will be integrated into NPC's
52 routine pharmacovigilance functions to complement existing pharmacovigilance methods.
53 Regional pharmacovigilance centres have pharmacovigilance focal persons who will continue
54 to support the NPC. All ADR-reports received by NPC are reviewed and submitted into an
55 existing national medication-safety database. The equipped peer supporters are a valuable
56 resource for scaling up peer support in the ART-sites after the study is concluded.
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3 The USSD interface and Med Safety will be freely available. Med Safety can be downloaded
4 and installed from both Google Play and Apple iOS stores. NPC pays the salaries of its full-
5 time pharmacovigilance staff who receive and process the reported medication-safety data.
6

7
8 The research collaboration between Makerere University's Department of Pharmacology,
9 Department of Pharmacy, NPC, ACP, MHRA and other stakeholders will continue to source
10 for additional research grants to support the future scale-up of evidence-based digital
11 pharmacovigilance in Uganda. The findings could be helpful to other countries to inform their
12 own pharmacovigilance activities.
13

14 **Dissemination**

15
16 Med Safety users will immediately benefit from the app's two-way communication functionality
17 as they will receive medication-safety alerts from NPC in addition to their submission to NPC
18 of ADR-reports.
19

20 We plan to present the project's research findings at local stakeholders' workshops organized
21 to ensure the balanced representation of HCPs, administrators, policy makers, patient safety
22 groups, the public and other local and international partners. At least one policy brief will be
23 prepared from this work. We shall also disseminate the results at three or more local and
24 international conferences, engage the public through local and international television
25 channels, and through social media (Facebook, Twitter, WhatsApp, blogging etc.). We shall
26 publish at least two manuscripts in internationally-recognized peer-reviewed journals.
27
28

29 **Ethical and environmental considerations**

30 The study received ethical approval from the School of Health Sciences Research and Ethics
31 Committee at Makerere University College of Health Sciences (MAKSHSREC-2020-64); and
32 was registered with the Uganda National Council for Science and Technology (HS1206ES).
33 Administrative clearance will be obtained from participating ART-sites and written/thumb-
34 printed informed consent from participating PLHIV and expert clients/CHWs. We consider the
35 introduction of USSD and Med Safety for ADR-reporting to be a minimal risk intervention.
36 However, we shall remind participants to mind their own confidentiality which could be lost
37 due to phone sharing. On the contrary, participants in the intervention group could potentially
38 benefit from peer-support. We received a waiver of consent from the ethics committee to
39 access anonymized clinical and medication data of PLHIV at the health facilities. The data will
40 be extracted by staff of the respective health facilities. Applicable international laws on data
41 protection will be observed as well as the Data Protection and Privacy Act, 2019 of the
42 Republic of Uganda[54].
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47 **Risk management**

48 *Small number of patients ($\leq 10\%$) expected to own functional smartphones:* Our main goal is
49 to demonstrate that Med Safety can be downloaded and used by PLHIV, which we can
50 achieve without the requirement for strict sample size and power calculations. Also, we shall
51 use the USSD which can work on both basic low-tech mobile phones and high-tech
52 smartphones.
53

54 *Duplicate ADR-reports:* Duplicates will be identified by the NPC staff and study statistician.

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57 *Loss to follow-up of peer supporters and PLHIV:* A major goal is to demonstrate the feasibility
58 of peer support for PLHIV to get involved in ADR-reporting. The study will provide preliminary
59 data on the magnitude of loss to follow-up to be expected in future studies.
60

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3 *Compromise in data quality by the research assistants:* The research assistants will be trained
4 by the study team. Questionnaire data will be transmitted online immediately using ODK –
5 thus giving a chance to the centrally located statistician to verify data integrity.
6

7 *COVID-19:* We shall observe the SOPs of social distancing, washing hands and wearing
8 masks by study participants and investigators to minimise the risk of spreading COVID-19.
9 The pandemic could limit face-to-face contact but is also an opportunity to show how more
10 remote engagement can support pharmacovigilance in a developing country setting. Remote
11 engagement could be more cost-effective to support participants through phone calls and
12 other forms of online interaction.
13
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15 **Collaboration**

16 MHRA adapted Med Safety for Uganda with NDA's approval. The NPC staff at NDA, where
17 NPC is located, will participate in this project. Involvement of the ACP in this
18 pharmacovigilance project will promote the integration of peer support-driven
19 pharmacovigilance in the HIV care and treatment programme of Uganda. The Department of
20 Pharmacology & Therapeutics and Department of Pharmacy, Makerere University conceived
21 this project and will coordinate the study. The WHO contracted MHRA to adapt the app for
22 Uganda and will, together with UMC, provide technical support.
23
24

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27
28

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32

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38

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42

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44

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46

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48

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54 See: <http://creativecommons.org/licenses/by-nc/4.0/>.
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Figures

Figure 1. Before-after and there-there quasi-experimental study design for a peer support intervention to improve adverse drug reaction reporting by people living with HIV in Uganda

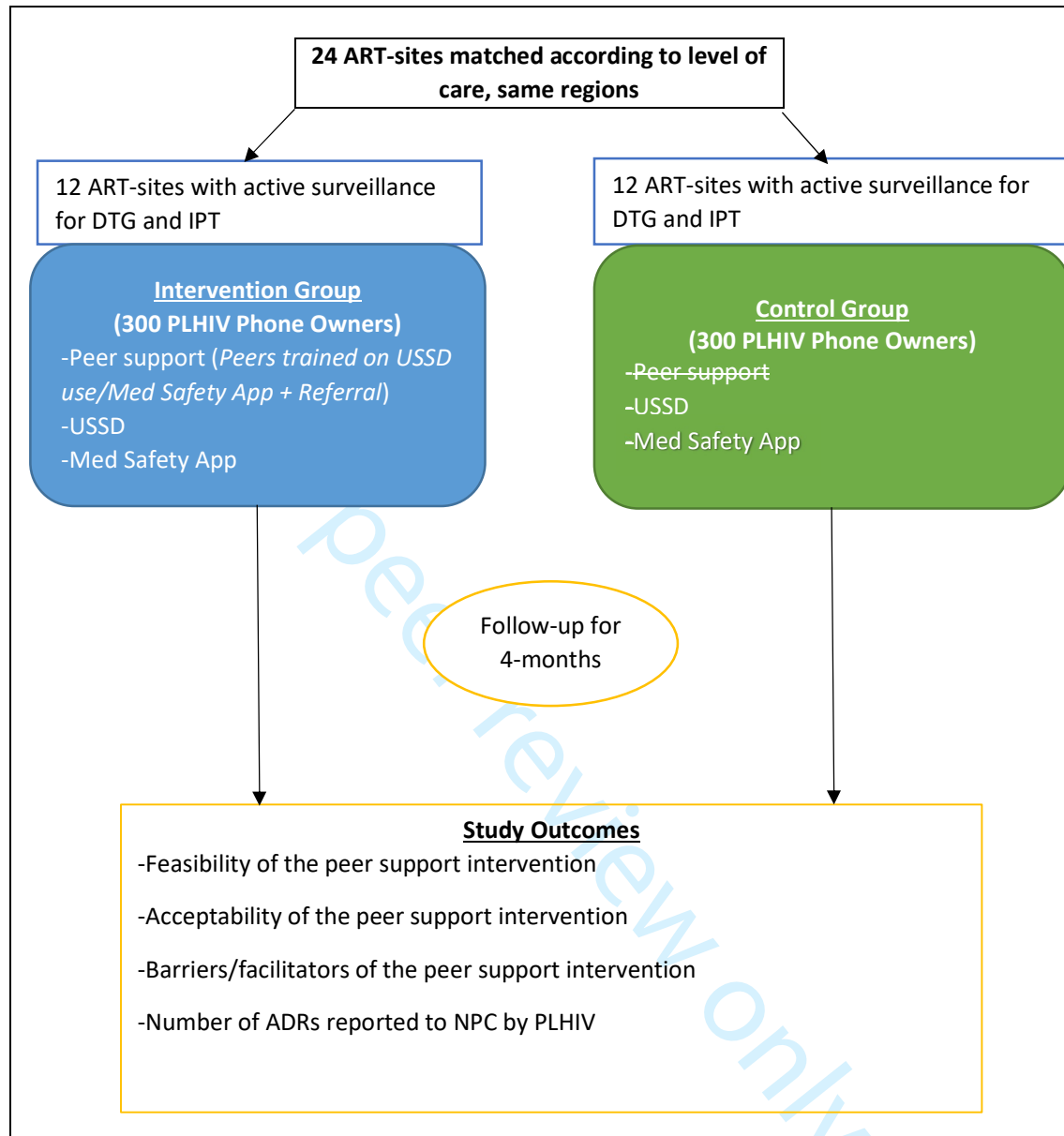
Figure 2: Layers of supervision in the peer support mechanism

Figure 3. Four key functions of the humanizing healthcare model for peer support as adapted from the framework by Peers for Progress

Figure 4. Intervention and comparison groups with two-way comparisons (before-after for each group (A&C, B&D), and between groups after intervention (C&D).

Figure 5. The five Differentiated Service Delivery models of HIV and TB care in Uganda, 2017.

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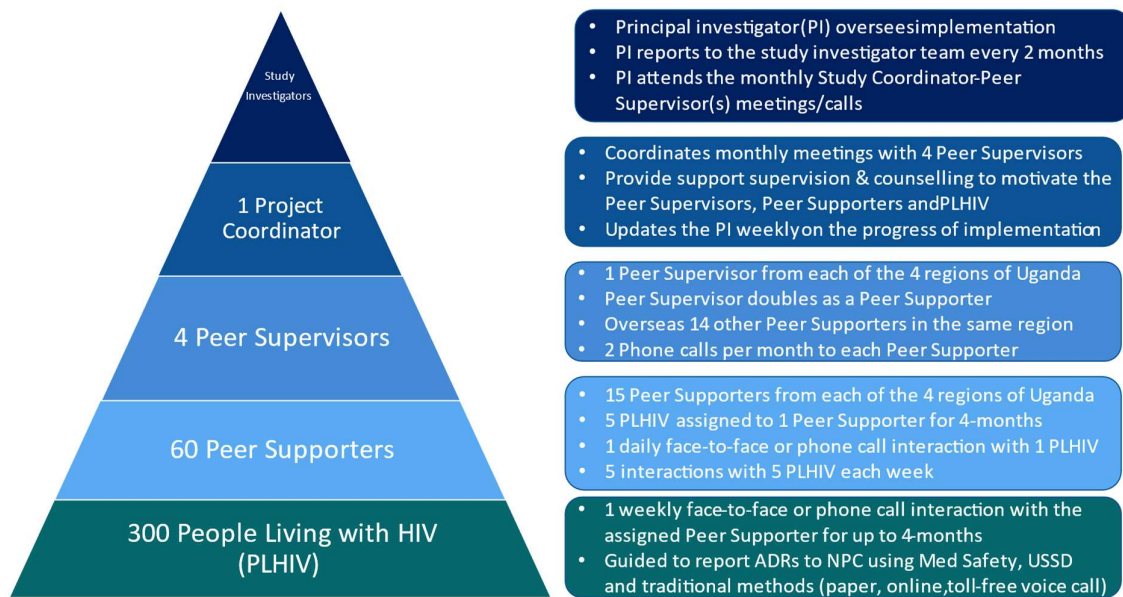


Figure 2. Layers of supervision in the peer support mechanism



23 *Source: Peers for Progress, Global Evidence for Peer Support; Humanizing Healthcare (September 2014)*

24 **Figure 3.** Four key functions of the humanizing healthcare model for peer support as adapted from
25 the framework by Peers for Progress
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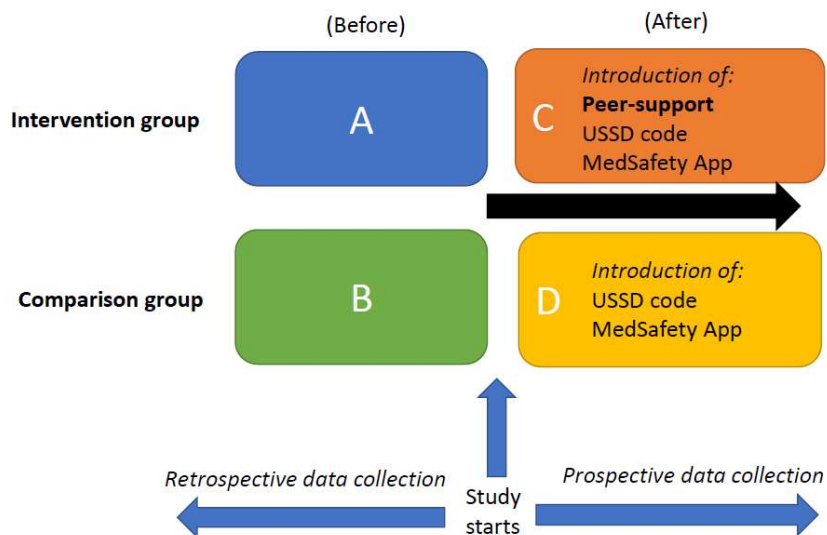
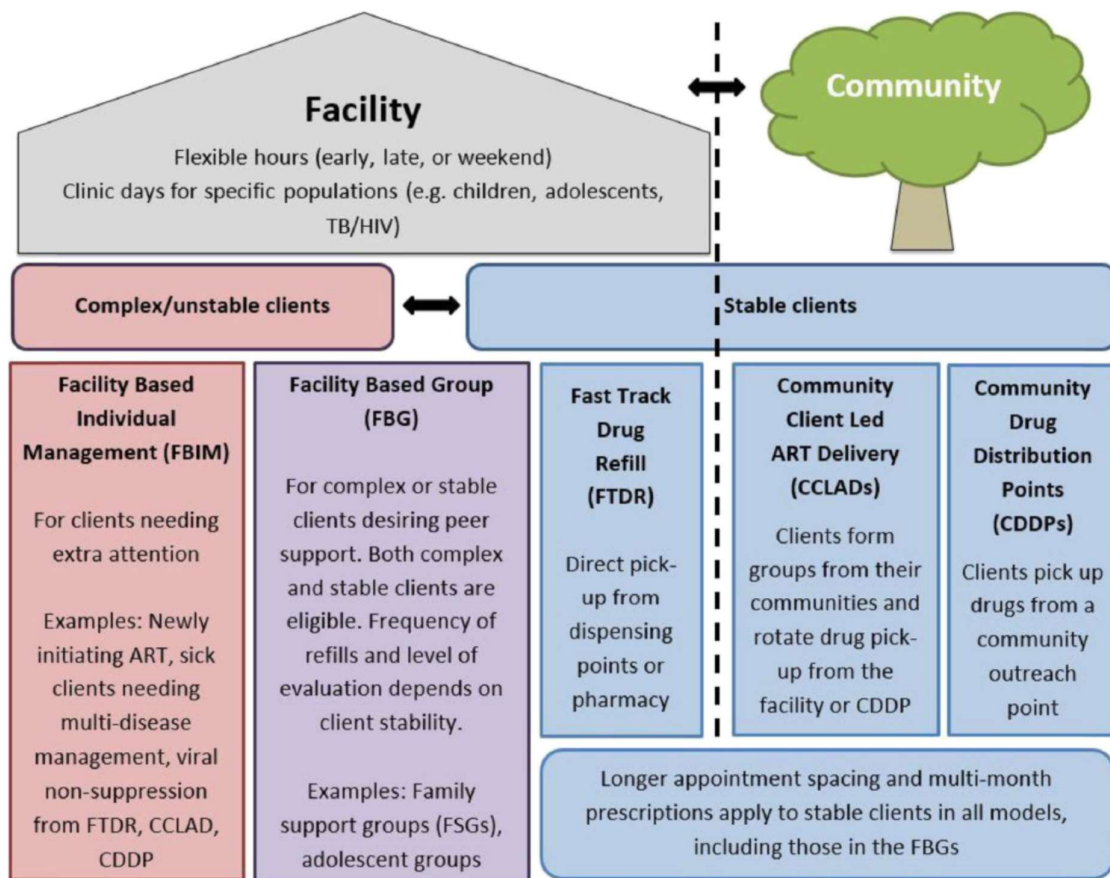


Figure 4. Intervention and comparison groups with two-way comparisons (before-after for each group (A&C, B&D), and between groups after intervention (C&D)).



Source: Ministry of Health, *Implementation Guide for Differentiated TB Services in Uganda* (June 2017).

Figure 5. The five Differentiated Service Delivery models of HIV and TB care in Uganda, 2017.

BMJ Open

Implementation of a peer support intervention to promote the detection, reporting and management of adverse drug reactions in people living with HIV in Uganda: a protocol for a quasi-experimental study

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3 **Implementation of a peer support intervention to promote the detection,**
4 **reporting and management of adverse drug reactions in people living with HIV**
5 **in Uganda: a protocol for a quasi-experimental study**
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Abstract

Introduction: Patients have contributed <1% of all spontaneous adverse drug reaction (ADR) reports in Uganda's pharmacovigilance database. Peer support combined with mobile technologies could empower people living with HIV (PLHIV) to report ADRs and improve ADR management through linkage to care. We seek to test the feasibility and effect of a peer support intervention on ADR-reporting by PLHIV receiving dolutegravir (DTG)-based antiretroviral therapy (ART) and/or Isoniazid Preventive Therapy (IPT) in Uganda; identify barriers and facilitators to implementing this intervention; and characterise ADR-reporting and management.

Methods and analysis: A quasi-experimental study with both quantitative and qualitative methods will be implemented over 4-months at 12 intervention and 12 comparison ART-sites selected from four geographical regions of Uganda. From each region, two blocks each consisting of a tertiary care, secondary care and primary care ART-site will be selected by simple random sampling. In each of the four regions, one block of ART-sites will be enrolled into the intervention arm and the other block into the comparison arm.

The study units include ART-sites and PLHIV on DTG-based ART and/or IPT in both arms. The intervention arm will have peer supporters who will be expert clients from among PLHIV and/or recognized community health workers. PLHIV at intervention sites will be assigned to peer supporters to empower them to report ADRs directly to the National Pharmacovigilance Centre (NPC).

Direct patient-reporting of ADRs to NPC in both arms will leverage the Med Safety App and toll-free Unstructured Supplementary Service Data interface to augment traditional pharmacovigilance methods.

Ethics and dissemination: The study received ethical approval from the School of Health Sciences Research and Ethics Committee at Makerere University College of Health Sciences (MAKSHSREC-2020-64) and administrative clearance from Uganda National Council for Science and Technology (HS1206ES). The results will be shared with PLHIV, policy-makers, the public and academia. [299 words].

Trial registration: ISRCTN75989485

Strengths and limitations of the study

The study will blend a novel peer support intervention with mobile data transmission technologies to promote the detection and reporting of suspected adverse drug reactions (ADRs) by people living with HIV

People living with HIV who experience serious ADRs will be linked directly to health facilities for ADR management

An implementation research approach will be employed to identify the factors that could influence the uptake of peer support in patient-reporting of ADRs while documenting predefined outputs and outcomes relevant to the research objectives

The study will generate pilot data on effect sizes to aid the planning of future randomized controlled trials using peer support to promote patient-reporting of ADRs

For peer review only

Introduction

Adverse drug reactions (ADRs) are a leading cause of morbidity, mortality and increased healthcare costs[1-3]. The timely detection and reporting of ADRs promotes their appropriate management, more accurate prediction and prevention[4]. Pharmacovigilance systems worldwide have identified and led to withdrawal from the market of at least 462 harmful medicines, primarily through passive spontaneous ADR-reporting by healthcare professionals (HCPs)[5], thereby contributing to patient safety. The major drawback of the spontaneous pharmacovigilance system is its reliance on individual HCP motivation. It is estimated that only about 10% of ADRs are reported through the spontaneous pharmacovigilance system, which is a very low rate of ADR-reporting[6-8]. Several factors hinder ADR-reporting by HCPs including medical specialty, lower-level healthcare facility, older HCP age, heavy workloads, shortage of reporting tools, ignorance and fear of litigation[8, 9].

Patient-reporting of suspected ADRs is given little attention in developing countries. Yet, patients are a known complementary source of pharmacovigilance data[10-12]. Patients can make detailed ADR-reports and with similar quality as ADR-reports from HCPs. Patients can also report previously unknown ADRs[13]. Thus, patients are well-placed to participate in ADR-reporting because they have first-hand experience of their own state of health and treatment. Patient involvement in ADR-reporting aligns with the increasing global momentum towards patient-centred healthcare[14]. Yet, patient participation in pharmacovigilance is under-explored with little empirical data, especially in low- and middle-income countries (LMICs). In Uganda, patients' contribution to ADR-reporting is very low indeed and is estimated at less than 1% of the reports in the national pharmacovigilance database (Victoria Nambasa, Pharmacovigilance Manager at National Drug Authority (NDA); personal communication; 6 April 2020).

The quest for expanded avenues to increase the reporting of suspected ADRs has never been more apparent than in Uganda where dolutegravir (DTG) and Isoniazid Preventive Therapy (IPT) have been massively rolled-out since 2018 and 2019, respectively. Anecdotal evidence in Uganda suggests that increased use of DTG and IPT has increased the burden of associated serious ADRs e.g. hyperglycaemia, hepatotoxicity and neuropsychiatric effects[15, 16]; necessitating a more robust pharmacovigilance system that leverages patient-reporting of suspected ADRs to DTG-regimens and/or IPT. This study proposes to test the feasibility and effect of a peer support intervention combined with mobile phone-based tools to promote the reporting of ADRs by people living with HIV (PLHIV) on DTG-based ART and/or IPT in Uganda. If successful, this study will contribute to the development of a more robust pharmacovigilance system to better document serious ADRs in Uganda.

Patient-centred peer support has shown promise in the management of chronic illnesses such as diabetes and mental health[17, 18]; and in improving retention in HIV care and adherence to ART[19, 20]. Thus, peer support could substantially promote the detection, reporting and management of ADRs amongst PLHIV. In the current study, peer support is based on the premise that PLHIV who have previously experienced ADRs linked to ART can – as peer supporters - encourage, mentor and support other similarly affected but less experienced PLHIV to detect and report ADRs[21]. Peer supporters could serve as positive role models to improve the self-efficacy of other PLHIV whom they could guide to identify and report ADRs using the available tools. Direct patient-reporting of ADRs could utilize the Med Safety mobile application, a toll-free Unstructured Supplementary Service Data (USSD) interface and the

1
2
3 traditional pharmacovigilance methods of paper-form, online forms and voice call. The aim
4 remains to have all suspected ADR reports submitted to the National Pharmacovigilance
5 Centre (NPC) database for analysis and subsequent processing. However, those that require
6 clinical management should be brought to the attention of the HCP for appropriate
7 management and prevention[21-23]. From guiding less experienced PLHIV, expert clients
8 serving as peer supporters could equally be empowered to build their own self-esteem[24,
9 25].
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12 Our peer support intervention for strengthening the Ugandan pharmacovigilance system
13 through patient-reporting of ADRs is intended to leverage the available mobile technologies
14 e.g. the USSD platform available for both low-tech non-smartphones and high-tech
15 smartphones[26]; and the Med Safety mobile application for high-tech smartphones[27].
16 USSD is a real-time text-driven technology which allows users to interact directly from their
17 mobile phones by making a selection from a menu. It allows for faster two-way communication
18 of information and enables rapid exchange of data - up to seven times faster than SMS[28].
19 The USSD interface has been a key success factor in the extensive penetration of mobile
20 money banking in rural unbanked sub-Saharan Africa[29]. No Internet connection is needed.
21 This project's toll-free USSD code has been developed by a private Ugandan software
22 company[30]. Med Safety is a smartphone mobile application for ADR-reporting that was
23 recently adapted for LMICs from the prototype app funded by the European Union's Innovative
24 Medicines Initiative – the WEB-RADR project. Adaptation of the mobile app is led by UK's
25 Medicines and Healthcare products Regulatory Agency in collaboration with World Health
26 Organization (WHO) and the WHO Collaborating Centre for International Drug Monitoring, the
27 Uppsala Monitoring Centre (UMC)[31]. Med Safety was launched in Uganda in February 2020.
28 Using both USSD and Med Safety alongside existing pharmacovigilance methods could
29 strengthen peer support-enhanced patient-driven pharmacovigilance in Uganda.
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35 Lastly, the study will use an implementation science approach to evaluate the peer support
36 intervention among PLHIV. Implementation research is critical in identifying factors that could
37 influence uptake of the intervention while documenting predefined outputs and outcomes
38 relevant to the research objectives[32]. Our ultimate goal is to increase patient reporting of
39 ADRs in LMICs such as Uganda with weak pharmacovigilance systems. Hence, this study
40 aims to develop and assess the feasibility of a peer support intervention combined with mobile
41 phone-based tools to promote the detection and reporting of ADRs in PLHIV on DTG-based
42 ART and/or IPT in Uganda. It will identify the barriers and facilitators to implementing the
43 intervention, characterise ADR-reporting and management and estimate the effect of the
44 intervention on ADR-reporting among PLHIV.
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48 **Research hypotheses and objectives**

49 Research hypotheses:

50 We hypothesize that the patient-centred peer support intervention combined with existing
51 mobile data transmission technologies for promoting the detection, reporting and management
52 of ADRs in PLHIV is feasible and acceptable. We also hypothesize that this peer support
53 intervention combined with mobile data transmission technologies will significantly increase
54 the number of ADR reports submitted to NPC by PLHIV who receive the intervention during
55 4-months of follow-up when compared with PLHIV who do not receive the intervention.
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58 Specific objectives:

1. To develop a peer support intervention combined with mobile data transmission technologies to promote the detection, reporting and management of ADRs in PLHIV receiving DTG and/or IPT in Uganda
2. To explore the barriers and facilitators to implementation of the peer support intervention combined with mobile data transmission technologies to promote ADR detection, reporting and management among PLHIV on DTG and/or IPT in Uganda
3. To describe the patterns of ADR-reporting (number, rate, quality, time to reporting, seriousness etc.) by PLHIV receiving DTG and/or IPT in whom the peer support intervention combined with mobile data transmission technologies is implemented in Uganda
4. To estimate the effect of the peer support intervention combined with mobile data transmission technologies on the rate of ADR-reporting by PLHIV receiving DTG and/or IPT in Uganda

Methods

Study setting

Uganda has a tiered healthcare system with different levels of healthcare from the National Referral Hospitals which provide tertiary and super-specialized healthcare, through Regional Referral Hospitals (RRHs), General Hospitals, level IV Health Centers (HC IV), level III Health Centers (HC III), to level II Health Centers (HC II) that progressively offer less scope and breadth of health services to out-patient services[33]. HIV treatment and care is provided from HC III and upwards giving a total of 1,832 accredited centers that provide ART services in Uganda. Uganda adopted the Differentiated Service Delivery Models (DSDM), where stable clients have less frequent clinical assessment visits. In 2019, about 80% (1,466/1,832) of the ART accredited sites and 78% (975,675/1,241,478) of PLHIV on ART had access to the DSDM model. An additional, 12% (114,363/975,675) of clients enrolled on DSDM received ART services from the community through Community Drug Distribution Points (CDDP) and Community Client-Led ART Distribution (CCLAD)[34].

Uganda has an estimated 1.46 million PLHIV, of whom prevalence among people aged 15 to 49 years is 5.8% with women having a higher prevalence (7.1%) than men (4.3%). Among the PLHIV, 93% are aged ≥ 15 years and 60% of the HIV-infected adults are women. In 2019, there were 53,413 new HIV infections of which 40,000 were among adults and 21,000 Ugandans died of AIDS-related illnesses[35]. Following the "Test and Treat" policy for HIV adopted in 2016 and scaled up in 2017, the ART coverage was at 89% in 2019. Approximately 96% of PLHIV on ART are taking first-line regimens and >443,000 PLHIV are on TLD. About 17% of PLHIV are ART-naïve at treatment initiation. In 2019, about 41% of TB patients were HIV-positive and 97% of HIV-positive TB patients were receiving ART[35, 36]. By the end of 2019, 477,190 of PLHIV were enrolled on IPT. Strategies to strengthen pharmacovigilance were instituted as part of DTG/IPT roll-out in the 2020 revised Consolidated Guidelines for Prevention and Treatment of HIV and AIDS in Uganda[16]. The guidelines support ADR identification, monitoring and reporting, particularly for DTG and IPT. Pharmacovigilance sentinel sites were established at 18 sentinel sites (RRHs and Centers of Excellence). These ART-sites received training and ADR-reporting tools. ADRs are reported to the NPC at NDA through a paper-based system, online system, toll-free phone line or through NDA's Med Safety App.

For the current study, the authors have divided the country into four geographical regions to establish a sampling framework that leads to selection of national level representation of health facilities and factors that influence provision of care to PLHIV and their pharmacovigilance-related needs. In each region, two blocks of health facilities with ART-sites will be selected of which one block will implement the intervention and the other will serve as the comparison block of health facilities. Each block will consist of an ART-site at a RRH (tertiary care), a HC IV (secondary care) and HC III (primary care), respectively. Therefore, 12 intervention ART-sites will be matched by level of care and region with 12 comparison ART-sites from the four regions of Uganda.

Study design

The study will employ a quasi-experimental design with pre-post and there-there comparisons to measure the preliminary impact of the peer support intervention on ADR-reporting by PLHIV, **Figure 1**. The study will use both quantitative and qualitative methods to triangulate the research findings. The qualitative research methods aim to understand the barriers and

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3 facilitators to implementing the peer support intervention for promoting ADR detection,
4 reporting and management from the perspective of PLHIV and in the context of their interface
5 with Uganda's healthcare system[37] and thus they will be predominantly implemented in the
6 intervention arm. We will explore the experiences of PLHIV in the utilization of the peer support
7 intervention and elicit their preferences to further refine the intervention and implementation
8 strategy.
9

10 11 The intervention

12 The peer support intervention leverages mobile data transmission technologies (Med Safety,
13 USSD) in addition to traditional pharmacovigilance methods (paper, online, voice call). The
14 peer support mechanism has several layers of supervision from the mentored PLHIV, through
15 peer supporters, peer supervisors, study coordinator to study investigators at the top of the
16 hierarchy, see **Figure 2**.
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19 The PLHIV to be mentored in the intervention arm will be assigned to peer supporters to guide
20 their ART care for 4-months. The peer supporters will constitute a mixed group of lay people,
21 namely; i) expert clients who are PLHIV with more experience in the use of ART and, ii)
22 recognized community health workers (CHWs). Most CHWs in Uganda's HIV programs are
23 expert clients. Thus, it is possible to recruit CHWs all of whom are expert clients. Peer
24 supporters in the intervention arm will guide the mentored PLHIV to report ADRs to NPC and
25 improve the latter's healthcare-seeking behaviour. The PLHIV should own mobile phones.
26
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28 The PLHIV to be mentored will be identified by verbal communication/ written announcements
29 on noticeboards at the study sites and matched with the respective peer supporters of similar
30 age, gender and proximity of residence. The non-random matching of PLHIV to peer
31 supporters is intended to promote easier and faster bonding of the peer-relationships. Five (5)
32 PLHIV will be assigned to one (1) peer supporter from the same community. A weekly
33 (minimum fortnightly) face-to-face/phone call interaction will be held between a peer supporter
34 and each assigned PLHIV. Thus, a peer supporter will be expected to interact with one PLHIV
35 per day and five PLHIV in five days each week. Each PLHIV to be supported will be introduced
36 to an assigned PLHIV by the research team and focal health facility staff. The procedure for
37 the weekly interaction will be illustrated to the PLHIV-peer supporter pair. The mentored PLHIV
38 and peer supporter will be provided with the telephone contacts of the study coordinator/ focal
39 health facility staff whom they could notify at any time when they want to terminate
40 engagement.
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45 Peer supporters will use one-on-one in-person support blended with mobile phone-based
46 interaction to guide each assigned PLHIV to recognize and report suspected ADRs to NPC.
47 The peer supporter will also administer a short weekly questionnaire to each assigned PLHIV
48 regarding ADR experience in the past 1-week.
49

50 This peer support intervention adapts the "humanizing healthcare model" developed by *peers*
51 *for progress*, a group that demonstrates the value and best practices of peer support. The
52 model is based on four functions, namely; assistance in daily management, providing social
53 and emotional support, linking to clinical and community resources and ongoing support[38],
54 see **Figure 3**.
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57 Both the supported PLHIV and peer supporters will be trained on the following aspects: ART;
58 how to live positively with HIV; recognition of suspected ADRs and how to report them via Med
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3 Safety, USSD or traditional methods (paper, online, voice call) to NPC; and about linkage or
4 referral to health facility care e.g. when a serious ADR occurs. The supported PLHIV and peer-
5 supporters will be trained to interact in a manner that ensures confidentiality. The data
6 generated from Med Safety and USSD will be safeguarded according to applicable laws on
7 data protection. The linkage to appropriate care of PLHIV by the peer supporter will aim to; i)
8 promote healthcare-seeking behaviour of the PLHIV, ii) improve the monitoring of HIV
9 treatment (management of serious ADRs, ART adherence, retention in care), iii) enhance
10 timely refill of ART prescriptions and/or, iv) provide for any other special care that PLHIV might
11 require.
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14
15 Peer supporters will be separately trained and skilled in interpersonal interaction to be
16 responsive to PLHIV and encourage them to identify and report any suspected ADRs. The
17 training components for peer supporters will include care in chronic illness, ART, adherence
18 to ART, ADRs, ADR-reporting, care-seeking, counselling and facilitative supervision. Training
19 for the peer supporters will take up to three days. It will include a one-day didactic session
20 followed by two days of on-the-job, one-on-one training. In addition to being trained, peer
21 supporters will receive supplementary educational materials. Four follow-up
22 supervisory visits/phone calls at two-week intervals will be conducted by the trainers to
23 reinforce the knowledge, skills and attitudes gained by the peer supporters. Each supported
24 PLHIV will receive one-day's training during his/her clinic visit which will include a didactic
25 session and one-on-one discussion in a non-classroom environment. The trainers will be
26 qualified individuals carefully identified by the project team with the requisite knowledge to
27 offer the training and expertise in adult learning and counselling.
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31 The peer support mechanism will have two additional layers of supervision, see **Figure 2**. The
32 first level of additional oversight will be provided by four (4) peer supervisors identified from
33 among the peer supporters at each of the four selected RRHs. Peer supervisors will be
34 seconded by the study sites and collaborating patient safety groups involved in the recruitment
35 of peer supporters. Each peer supervisor will oversee 15 peer supporters in his/her region (10
36 from RRH, 3 from HC IV, 2 from HC III). The peer supervisor will call each peer supporter
37 twice a month. During these 'booster' sessions, the peer supervisor will review, emphasize
38 and re-educate peer supporters on expectations of the intervention e.g. setting and reviewing
39 goals with PLHIV. The second level of oversight will be provided by the project coordinator
40 who will oversee the four (4) peer supervisors whom he/she will meet/call every month. At
41 least one study investigator, mostly the principal investigator, will participate in these
42 meetings/calls. The project coordinator will have the requisite knowledge, skills and
43 competence to train PLHIV and peer supporters. The project coordinator will provide support
44 supervision and counselling to motivate the peer supervisors, peer supporters and PLHIV.
45
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49

50 The comparison group

51 PLHIV in the comparison group will be mobile phone owners who will be trained to recognize
52 suspected ADRs and report them to NPC via Med Safety, USSD or the traditional
53 pharmacovigilance methods (paper, online, toll-free voice call) to a peer-supporter, HCP or
54 NPC, see **Figure 4**. Smartphone owners will be guided to install Med Safety for ADR-reporting.
55 PLHIV with non-smartphones or smartphone owners who will not install Med Safety will report
56 ADRs by USSD or the traditional reporting methods. PLHIV in this group will not receive
57 dedicated peer support.
58
59

60 Study units, participants and selection

Study units and participants:

This study has multiple study units and layers to assess the feasibility of implementation and effect of the intervention on promoting the detection and reporting of suspected ADRs in PLHIV on DTG-based ART and/or IPT in Uganda. From micro to macro-level, the study units include PLHIV receiving DTG-regimens and/or IPT; the pair of PLHIV and peer supporter; the peer supporter; the combination of the PLHIV with peer supporter and ART-site; peer supervisor; the pair of peer supervisor and peer supporter; and the ART-site. At the study ART-site, HCPs and health facility managers will be included. Lastly, the reporting of suspected ADRs by PLHIV, peer supporters, HCPs and ART-sites to the NPC will also be examined.

About 17% of PLHIV are ART-naive, 95% are aged 15 years and older, and 89% receive first-line ART either as treatment-naive or treatment-experienced PLHIV[36].

Eligibility criteria:

Inclusion criteria: Selection of study units will occur at three levels: *First*, eligible PLHIV should i) be aged ≥ 15 years, ii) receive ART at the selected study sites, iii) own a mobile phone (smartphone, basic feature phone) and, iv) provide written/thumb-printed informed consent. Child consent can be given by emancipated minors aged 15 to 17 years in Uganda[39] *Second*, eligible peer supporters (expert clients, CHWs) will be those that are recognized and seconded by the study sites or collaborating patient safety groups. These peer supporters will be those that are attached to the study sites and have already received institutional training in their role as expert clients/CHWs; they should own mobile phones. A focal clinical staff assigned to the study by the health facility administration will approach and recruit the peer supporters. The recruited peer supporters will be screened by the research team to gauge their ability to be peer supporters e.g. the ability to use the Med Safety App/USSD, ability to read and write in English and good interpersonal skills. Satisfactory peer supporters will give written informed consent. Peer supporters will participate only in the intervention arm of the study. *Third*, study health facilities will be selected and enrolled as follows; in each of the four geographical regions, blocks of three health facilities each with an ART-site, including at least a RRH, HC IV and HC III will be created based on the catchment of each RRH. From the created blocks of three health facilities in each region, two blocks will be selected by simple random sampling to participate in the study as the intervention and comparison health facilities, respectively. This will give 24 ART-sites consisting of 12 intervention sites (4 RRHs, 4 HC IVs, 4 HC IIIs) matched by level of care and region with 12 comparison sites (4 RRHs, 4 HC IVs, 4 HC IIIs) selected from the four geographical regions of Uganda.

Exclusion criteria: Exclusion will apply only at the level of PLHIV and CHWs. We shall exclude PLHIV on ART for < 6-months and expert clients/ CHWs who will be unable to commit, from the outset, at least 5-hrs per week to the study for up to 4-months.

Many ADRs happen when starting ART although such PLHIV tend to be unstable on treatment. The priority of this pilot is to understand the dynamics (feasibility and acceptability) of the peer support intervention in a *stable group* of PLHIV on ART (for ≥ 6 months). If found to be feasible, the peer support intervention will be introduced, in future initiatives, to the *unstable group* of PLHIV on ART (for <6 months).

Sample Size and Sampling Considerations

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2
3 Sample size computation is based on the possible effect of the peer support intervention on
4 the rate of ADR-reporting by PLHIV, with adjustment for clustering. We assume a conservative
5 intra-cluster correlation coefficient of 0.045 and a priori increase of 50% in the rate of ADR-
6 reporting to NDA, from 6 ADR-reports per 100 person-years at baseline[40] to 9 ADR-reports
7 per 100 person-years at end-line evaluation. We assume a standard deviation of 12 ADR-
8 reports per 100 person-years computed from the monthly ADR-reports submitted to NPC for
9 one-year (October 2018 to September 2019). The study is designed to have at least 80%
10 power to estimate an effect size of 1.5. Thus, 126 PLHIV will be required in the intervention
11 arm and 126 PLHIV in the control arm.
12
13

14
15 Since the caseload for each peer supporter will be 5 PLHIV in the intervention arm, 60 peer
16 supporters (15 from each of the 4 regions) will be responsible for 300 PLHIV on DTG and/or
17 IPT. Thus, the peer support arm will include 300 PLHIV and the control arm 300 PLHIV all of
18 whom should own functional mobile phones (smartphone or non-smartphone or both). Thus,
19 a total of 600 PLHIV will be enrolled; 400 from RRHs, 120 from HC IVs and 80 from HC IIIs.
20

21
22 The PLHIV will be enrolled consecutively until the required sample size is attained.
23 Smartphone owners will be guided to install Med Safety for ADR-reporting. We assume that 7
24 in 10 PLHIV at the ART-sites will have mobile phones and only one in 10 will possess
25 smartphones[41]. Thus, only up to 10% (or 60) of PLHIV with smartphones will be helped (with
26 maximal support from peer supporters) to download Med Safety. The rest of the 540 PLHIV
27 without smartphones or smartphone owners who will not install Med Safety will report ADRs
28 by USSD or the traditional methods.
29
30

31 Study variables

32 *Primary outcomes:* Feasibility of the peer support intervention - attrition rate recorded as the
33 number of study participants who remain in the study until the end of follow-up at 4 months;
34 Number of suspected ADR reports submitted to NPC by PLHIV as measured by questionnaire
35 and data abstracted from the national pharmacovigilance database at baseline and 4 months
36
37

38 *Other process/output/outcome variables:*

- 39 1. Acceptability of the peer support intervention measured using a questionnaire and
40 qualitative interviews at 4 months post-intervention
- 41 2. Barriers/facilitators of the peer support intervention measured using a questionnaire
42 during the intervention and qualitative interviews at 4 months post-intervention
- 43 3. Fidelity to the peer support intervention measured using a questionnaire and
44 qualitative interviews at 4 months post-intervention
- 45 4. Rate of ADR-reporting to NPC by PLHIV as measured by questionnaire and data
46 abstraction from the national pharmacovigilance database at baseline and 4 months
- 47 5. Quality of ADR-reports by PLHIV measured by questionnaire and data abstraction
48 from the national pharmacovigilance database at baseline and 4 months
- 49 6. Time to ADR-reporting to NPC by PLHIV since enrolment measured by questionnaire
50 and data abstraction from the national pharmacovigilance database during 4 months
- 51 7. Time from ADR onset to registration in the national pharmacovigilance database
52 measured by questionnaire and data abstraction from the database during 4 months
- 53 8. Health-related quality of life measured by questionnaire at baseline and 4 months
- 54 9. Management of ADRs recorded using a questionnaire during the 4 months
- 55 10. Number of PLHIV linked to health facilities by peer supporters for ADR management
56 as measured by questionnaire during the 4-month intervention period
- 57 11. Health-seeking behaviour measured using a questionnaire at baseline and 4 months
58
59
60

12. Self-efficacy to report ADRs measured by questionnaire at baseline and 4 months
13. Self-reported ART adherence measured by questionnaire at baseline and 4 months
14. Mood (positive/ negative affect) measured by questionnaire at baseline and 4 months

Patient and Public Involvement

Direct involvement of PLHIV in the detection and reporting of suspected ADRs, and patient safety groups in recruitment of PLHIV, will have value in improving the public's awareness of ADRs and the available pharmacovigilance tools (Med Safety, USSD, toll-free voice call, etc.). Together, these will be essential for ensuring that changes to clinical practice to promote patient safety based on our work are acceptable to the public.

The study team will work with PLHIV to assess whether the available pharmacovigilance tools meet their needs, to identify potential improvements and to understand facilitators and barriers to using these pharmacovigilance tools. Wider public input into the refinement of the tools and mechanisms to encourage uptake will add value to our work. This work will also be of value to the wider public as Med Safety can be used to report ADRs to any drug, and users can receive drug safety information directly from NPC.

Data management and statistical analysis

Quantitative data

Data collection and management: Baseline and end-line semi-structured questionnaires will be administered to the PLHIV and peer supporters (expert clients) in the intervention arm and PLHIV only in the comparison arm.

The baseline questionnaire will record socio-demographics (age, sex, monthly income, education level, residence) of all study participants. Clinical details (ART adherence; ADRs; ART-regimen; ART-status i.e. first-line, second-line, third-line; duration on ART; comorbidities) and healthcare-seeking behaviour of study PLHIV will be measured. Data will be transmitted to a password-protected online database via the Open Data Kit (ODK) suite of tools. Participating PLHIV will be asked at enrolment if they experienced suspected ADRs in the 4-months preceding the study. The self-reported suspected ADRs will be corroborated with additional information on documented suspected ADRs from retrospective clinical chart review of the 4-month period prior to study enrolment. The clinical charts will be accessed by the health facility staff.

Additional data collection for the intervention group: On a weekly basis for up to 4-months, peer supporters will inquire from each assigned PLHIV (during a 1 hour face-to-face or phone call interaction) if he/she experienced one or more suspected ADR(s) and if the ADR had any impact on quality of life and/or ART adherence. Peer supporters will document if the ADR(s) was/were reported; and, if reported, by which means (Med Safety, USSD, voice call, other methods). Peer supporters will document all ADRs experienced by the PLHIV during the previous 1-week (using a tool designed to capture the medicines and ADRs); and will guide the PLHIV to report ADRs directly to NPC using the available pharmacovigilance methods. Active surveillance of ADRs linked to DTG and/or IPT will be prioritized but ADRs linked to other medicines will also be documented. PLHIV who experience serious ADRs will be linked directly to the health facilities where they receive ART for ADR management. Peer supporters will refer serious ADR cases to peer supervisors who will, in turn, refer these cases to focal clinical staff assigned to the study by the health facility administration; usually stationed at triage to connect the cases to clinicians. We will document the management of serious and

1
2
3 non-serious ADRs (number of serious and non-serious ADR cases referred for health facility
4 management; actions taken by health facilities in the management of serious and non-serious
5 ADRs e.g. stopping treatment, changing treatment, continuing treatment with adherence
6 counselling, doing nothing, etc.).

7
8 The end-line questionnaire for PLHIV will measure their healthcare-seeking behaviour, linkage
9 to care for ADR management and adherence to ART. The PLHIV will also be asked to report
10 their experiences while receiving peer support to assess the intervention's feasibility and
11 acceptability (e.g. user satisfaction). The study will also assess the participants' experiences
12 when using the various pharmacovigilance methods (Med Safety, USSD, toll-free voice call,
13 etc.). We shall assess the ease of use, language and costs of the available pharmacovigilance
14 methods (Med Safety, USSD, toll-free voice call, etc) alongside peer support.
15
16

17 **Med Safety App and USSD data collection:** PLHIV will submit ADR-reports via Med Safety
18 and/or USSD with initial assistance from peer supporters. Each app-based ADR-report will be
19 automatically converted into the standard E2B (R2) format prior to its receipt in the Vigilance
20 Hub[42]. The app is hosted by Uganda's NDA which manages the reported ADR data. For
21 USSD reporting, PLHIV will dial the USSD code and answer a set of questions. The data will
22 be stored in real-time on a dashboard accessible to the project staff.
23
24

25 **Statistical analysis:** All ADR-data in both the national and project databases and received
26 from the study sites during the study period will be exported into Stata version 15.0 MP for
27 descriptive analysis – frequencies, proportions and their 95% confidence intervals (StataCorp
28 LLC, College Station, Texas). Duplicate ADR-reports will be identified and analysed
29 accordingly. Summary estimates will be reported by pharmacovigilance method (Med Safety,
30 USSD, toll-free voice call, etc.).
31
32

33 To assess the feasibility to retain peer supporters and PLHIV, we shall compute the attrition
34 rate which is the proportion of study participants who remain in the study until the end of follow-
35 up at 4 months.
36
37

38 The number of suspected ADRs reported to NPC by the PLHIV overall and in each study arm
39 will be described by subgroup: serious ADR (yes/no); peer supporter guided (yes/no); DTG-
40 linked (yes/no); IPT-linked (yes/no); DTG/IPT-linked (yes/no); linked to other medicines
41 (yes/no); level of reporting (PLHIV, peer supporter, HCP, health facility) etc.
42
43

44 The rate of ADR-reporting (m_a) by PLHIV (per site, overall) per completed-month (m_1) of follow-
45 up will be computed as follows: $m_a = [n_a \text{ reports}/(N_a \text{ completed-months of follow-up})]$, where
46 n_a is the number of reported ADRs and N_a the number of completed-months of follow-up.
47 Reporting rates of same-day ADR-onsets will be documented; and time from ADR-onset to
48 registration in the national database recorded for all other events[33]. Time to ADR-reporting
49 to NPC for a PLHIV will be the time from the day a PLHIV is enrolled into the peer support
50 intervention to the time he/she reports the first suspected ADR to NPC. Time-to-event data
51 will be analysed by survival analysis techniques.
52
53

54 We will explore the influence of level of care on the uptake of the peer support intervention in
55 Uganda's healthcare system - such as whether rolling it out at primary care facilities or tertiary
56 hospitals influences uptake.
57
58

59 The change in outcome measures (e.g.) between pre- and post-intervention in PLHIV will be
60 assessed using a linear mixed model with random effect for peer supporter. Random effect

1
2
3 will be included to account for clustering of PLHIV with peer supporters. The ICC will be
4 estimated from this model. Since supporters are a mixed population of expert clients and
5 CHWs, a stratified analysis will be conducted. To aid the planning of future randomized
6 controlled trials from this pilot's data, we shall report effect sizes.
7

8 9 Qualitative data

10 **Data collection:** Post-intervention, a combination of focus group discussions (FDGs), in-
11 depth interviews (IDIs) and Key Informant Interviews (KIIs) will be conducted with purposively
12 selected study participants. A lead qualitative researcher will be assisted by two well-trained
13 research assistants. Semi-structured interviews informed by the Consolidated Framework for
14 Implementation Research (CFIR)[43] will be used to elicit participants' perspectives on the
15 facilitators and barriers to implementing the peer support intervention at four purposively
16 selected health facilities.
17

18
19 We will conduct six FGDs with three categories of PLHIV in the intervention arm; two with
20 those enrolled in Community Drug Distribution Points (CDDPs), two in Community Client-Led
21 ART Delivery (CCLAD) and two in facility-based ART delivery models.
22

23
24 A total of 12 IDIs will be conducted with peer supporters (expert clients, CHWs) attached to
25 each of the three ART delivery models; a) CDDP, b) CCLAD, c) Facility-Based, see **Figure 5**.
26

27
28 Four KIIs will be conducted with HCPs/facility managers with insights in the implementation
29 experience of the peer support intervention at their respective host facilities from an
30 organizational-context.
31

32
33 As a first step, participants will complete a written informed consent form. We will then capture
34 baseline characteristics: age, gender and educational level. A CFIR-informed semi-structured
35 guide will be used for the interviews. The semi-structured guide will explore participants'
36 experiences with the peer support intervention, their preferences and suggestions for
37 improvement of the intervention and the challenges encountered in using USSD and/or Med
38 Safety. On average, the duration of the FGDs and IDIs will be approximately 45-60 min. The
39 FGDs, IDIs and KIIs will be conducted until theoretical saturation is reached. Theoretical
40 saturation means that no new knowledge is generated and all aspects of a theory are covered.
41 All the data generated from the focus groups and interviews will be explored for themes and
42 sub-themes.
43

44
45 **Guiding qualitative analytical framework:** The CFIR will be adopted as the overall guiding
46 analytical framework for this study. The CFIR is a comprehensive 'meta-theoretical'
47 implementation research framework compiled from more than 20 sources and is cross-cutting
48 in more than 13 scientific disciplines; it guides systematic assessment of multi-level
49 implementation settings to identify factors that influence intervention implementation and
50 effectiveness [44]. The CFIR informs the conceptualization of this study, will guide the
51 development of data collection tools and will serve as an overarching deductive thematic
52 framework in analysis of study findings and the overall synthesis and interpretation of results
53 for this study. The CFIR is widely-applied because of its multi-level, 'ecological' dimensions
54 on multi-faceted influences on healthcare intervention implementation outcomes[45]. The
55 CFIR has been applied across diverse interventions and varied content fields[44].
56
57

58
59 More specifically, the CFIR-derived domains that will guide the study are the following:
60

1
2
3 *Intervention characteristics:* Implementation of the peer support intervention could potentially
4 be impacted by factors including its perceived effectiveness in ADR-reporting, relative
5 advantages over alternative reporting approaches, adaptability in varied resource-constrained
6 settings, trialability, complexity, design quality and presentation, and cost-effectiveness.
7

8
9 *Outer setting:* external influences on implementation of peer support may include external
10 policies and incentives, socio-cultural belief systems, peer pressure dynamics and socio-
11 economic context.
12

13 *Inner setting:* characteristics of the implementing organization (or host health facility) such as
14 organizational culture, the relative priority assigned to the peer support intervention (including
15 funding support), presence of intervention 'champions', availability of supportive administrative
16 or physical infrastructure, congruence with host organization's mission and vision, quality of
17 leadership support and implementation climate(s).
18

19
20 *Characteristics of individuals:* Patients' beliefs, knowledge, level of income, self-efficacy, and
21 personal attributes that may affect the implementation and uptake of the peer support
22 intervention.
23

24
25 *Process of implementation:* Influences on implementation outcomes may derive from different
26 implementation phases involved in roll-out of the peer support strategy such as degree and
27 quality of involvement of primary beneficiaries in designing the intervention, planning,
28 execution, degree of effectiveness of monitoring and evaluation strategies and presence of
29 key intervention stakeholders and influencers including opinion leaders, stakeholder
30 engagement, and intervention champions.
31

32
33 The CFIR will be used to identify barriers and facilitators of the peer support intervention for
34 promoting ADR-reporting by PLHIV.
35

36 **Data analysis:** Our qualitative data analysis will follow the procedures recommended by Miles
37 & Huberman (1994)[46]. Interviews and FGDs will be audio-recorded and transcribed verbatim
38 into text transcripts by three research assistants (and translated into English where
39 necessary). Data will be analysed, in an iterative process, involving four major steps:
40

41 a) *Data familiarization:* An experienced qualitative researcher and one other investigator will
42 read the interview transcripts multiple times for data familiarization.
43

44
45 b) *Developing a coding framework:* We shall adopt the five CFIR-derived domains
46 (*Intervention characteristics, outer setting, inner setting, characteristics of individuals, and*
47 *process of implementation*) as an overarching deductive thematic framework, combined with
48 an inductive approach based on the data[47].
49

50 c) *Data abstraction:* The coded data will be categorized into thematic categories.
51

52
53 d) *Overall interpretation and synthesis:* Our overall synthesis of study findings will adopt a
54 team-based process of peer-debriefing involving all investigators to resolve disagreements in
55 interpretation of study findings.
56

57 **Quality assurance**

58 To ensure uniform study procedures and high-quality data, all research assistants recruited
59 for the study will receive face-to-face training on the following: the informed consent process,
60

1
2
3 participant interviewing techniques, confidentiality issues, pharmacovigilance, use of the Med
4 Safety App, use of the USSD, ADRs, use of the Open Data Kit (ODK) software for data entry
5 into an online password-protected database; and qualitative and quantitative study designs,
6 among others.
7

8 The FGDs and KIs will be led by an expert in qualitative research. Research assistants with
9 prior training in qualitative research methods will also be hired for the qualitative study
10 component. All research assistants will receive face-to-face training in both qualitative and
11 quantitative research methods.
12

13
14 Questionnaire data will be transmitted through ODK to an online database by the research
15 assistants while still in the field. The study statistician will check the online data for integrity
16 and contact field staff as soon as possible while still in the field to correct any data entry errors.
17 Prior to entry into ODK, all research assistants shall be required to cross-check the data on
18 study questionnaires to eliminate errors and ensure data completeness.
19

20 21 **Results uptake and use**

22 *Outcomes/Impact/Outreach:* The peer support intervention is expected to increase patient-
23 reporting of ADRs to NPC. It is anticipated that the patients will subsequently; i) find it easier
24 and faster to report ADRs (including DTG- and IPT-related reactions) anywhere and at any
25 time using their mobile phones and, ii) receive medication-safety alerts directly from NPC to
26 their phones. We expect this project to promote pharmacovigilance in Uganda by improving;
27 i) the exchange of medication-safety information between patients, peer supporters, HCPs
28 and NPC, ii) the awareness of pharmacovigilance by patients and the public through the
29 mobile phone and other awareness campaigns and, iii) the rate of ADR-reporting by patients.
30
31

32 *Potential impact on policy or programs:* This project could foster the increased involvement of
33 patients in pharmacovigilance activities and improve the efficiency of pharmacovigilance
34 systems in Uganda with real-time monitoring of DTG and INH safety in PLHIV in the first
35 instance, thus, increasing the volume of analysable data for quick decision-making by both
36 clinicians and policy makers.
37
38

39 We expect to promote collaboration between consumers/public and the NPC, national AIDS
40 Control Program - Ministry of Health and the National TB and Leprosy Control Programme
41 (NTLP). The accumulation of relevant medication-safety data from spontaneous and active
42 ADR-reports permits robust detection of safety signals at the national and international levels.
43
44

45 *Scalability:* After this pilot project, we expect the peer support intervention to be tested in a
46 nationwide randomized controlled trial; and the USSD and Med Safety App to be modified
47 accordingly and implemented at all 1,832 ART-sites in Uganda to complement the existing
48 active and passive pharmacovigilance methods for ART and TB treatment. We hope to embed
49 peer support in routine pharmacovigilance practice to promote the detection and reporting of
50 ADRs by PLHIV in Uganda. The Med Safety App is available in English and will be
51 subsequently translated into other local languages according to need.
52
53

54 The USSD and Med Safety are potentially invaluable tools for the pharmacovigilance of drugs
55 used for other diseases e.g. non-communicable diseases like cancers, diabetes mellitus,
56 hypertension etc.
57
58
59
60

Peer support, USSD and Med Safety will be scaled-up to support spontaneous ADR-reporting in both public and private health facilities at all levels of healthcare ranging from hospitals, medical centres and clinics to pharmacies and drug shops, not least, the general public.

The pharmacovigilance data at NPC could be linked with the patients' clinical data at ART-sites, stock consumption data from the Supply Management Chain system; and the electronic Health Management Information System. Machine learning/artificial intelligence analytical techniques could then be used on big data in the near future to foster improved systems.

Sustainability: Peer support to promote the detection and reporting of ADRs by PLHIV can be embedded in the HIV/AIDS program of Uganda just as community engagement programmes have been successful in Maternal and Child Health programmes; and are being rolled out in the COVID-19 Community Engagement Strategy and the Young people and Adolescent Peer Support Model for improving HIV care and treatment outcomes for Adolescents and young PLHIV of 2019 in Uganda[48, 49]. The USSD and Med Safety will be integrated into NPC's routine pharmacovigilance functions to complement existing pharmacovigilance methods. Regional pharmacovigilance centres have pharmacovigilance focal persons who will continue to support the NPC. All ADR-reports received by NPC are reviewed and submitted into an existing national medication-safety database. The equipped peer supporters are a valuable resource for scaling up peer support in the ART-sites after the study is concluded.

The USSD interface and Med Safety will be freely available. Med Safety can be downloaded and installed from both Google Play and Apple iOS stores. NPC pays the salaries of its full-time pharmacovigilance staff who receive and process the reported medication-safety data.

The research collaboration between Makerere University's Department of Pharmacology, Department of Pharmacy, NPC, ACP, MHRA and other stakeholders will continue to source for additional research grants to support the future scale-up of evidence-based digital pharmacovigilance in Uganda. The findings could be helpful to other countries to inform their own pharmacovigilance activities.

Dissemination

Med Safety users will immediately benefit from the app's two-way communication functionality as they will receive medication-safety alerts from NPC in addition to their submission to NPC of ADR-reports.

We plan to present the project's research findings at local stakeholders' workshops organized to ensure the balanced representation of HCPs, administrators, policy makers, patient safety groups, the public and other local and international partners. At least one policy brief will be prepared from this work. We shall also disseminate the results at three or more local and international conferences, engage the public through local and international television channels, and through social media (Facebook, Twitter, WhatsApp, blogging etc.). We shall publish at least two manuscripts in internationally-recognized peer-reviewed journals.

Ethical and environmental considerations

The study received ethical approval from the School of Health Sciences Research and Ethics Committee at Makerere University College of Health Sciences (MAKSHSREC-2020-64); and was registered with the Uganda National Council for Science and Technology (HS1206ES). Administrative clearance will be obtained from participating ART-sites and written/thumb-printed informed consent from participating PLHIV and expert clients/CHWs. We consider the

1
2
3 introduction of USSD and Med Safety for ADR-reporting to be a minimal risk intervention.
4 However, we shall remind participants to mind their own confidentiality which could be lost
5 due to phone sharing. On the contrary, participants in the intervention group could potentially
6 benefit from peer-support. We received a waiver of consent from the ethics committee to
7 access anonymized clinical and medication data of PLHIV at the health facilities. The data will
8 be extracted by staff of the respective health facilities. Applicable international laws on data
9 protection will be observed as well as the Data Protection and Privacy Act, 2019 of the
10 Republic of Uganda[50].
11
12

13 **Risk management**

14 *Small number of patients ($\leq 10\%$) expected to own functional smartphones:* Our main goal is
15 to demonstrate that Med Safety can be downloaded and used by PLHIV, which we can
16 achieve without the requirement for strict sample size and power calculations. Also, we shall
17 use the USSD which can work on both basic low-tech mobile phones and high-tech
18 smartphones.
19

20 *Duplicate ADR-reports:* Duplicates will be identified by the NPC staff and study statistician.
21

22 *Loss to follow-up of peer supporters and PLHIV:* A major goal is to demonstrate the feasibility
23 of peer support for PLHIV to get involved in ADR-reporting. The study will provide preliminary
24 data on the magnitude of loss to follow-up to be expected in future studies.
25

26 *Compromise in data quality by the research assistants:* The research assistants will be trained
27 by the study team. Questionnaire data will be transmitted online immediately using ODK –
28 thus giving a chance to the centrally located statistician to verify data integrity.
29

30 *COVID-19:* We shall observe the SOPs of social distancing, washing hands and wearing
31 masks by study participants and investigators to minimise the risk of spreading COVID-19.
32 The pandemic could limit face-to-face contact but is also an opportunity to show how more
33 remote engagement can support pharmacovigilance in a developing country setting. Remote
34 engagement could be more cost-effective to support participants through phone calls and
35 other forms of online interaction.
36
37
38
39

40 **Collaboration**

41 MHRA adapted Med Safety for Uganda with NDA's approval. The NPC staff at NDA, where
42 NPC is located, will participate in this project. Involvement of the ACP in this
43 pharmacovigilance project will promote the integration of peer support-driven
44 pharmacovigilance in the HIV care and treatment programme of Uganda. The Department of
45 Pharmacology & Therapeutics and Department of Pharmacy, Makerere University conceived
46 this project and will coordinate the study. The WHO contracted MHRA to adapt the app for
47 Uganda and will, together with UMC, provide technical support.
48
49

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52

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56

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60

1
2
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5

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9

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11

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13

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15

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Figures

Figure 1. Before-after and there-there quasi-experimental study design for a peer support intervention to improve adverse drug reaction reporting by people living with HIV in Uganda

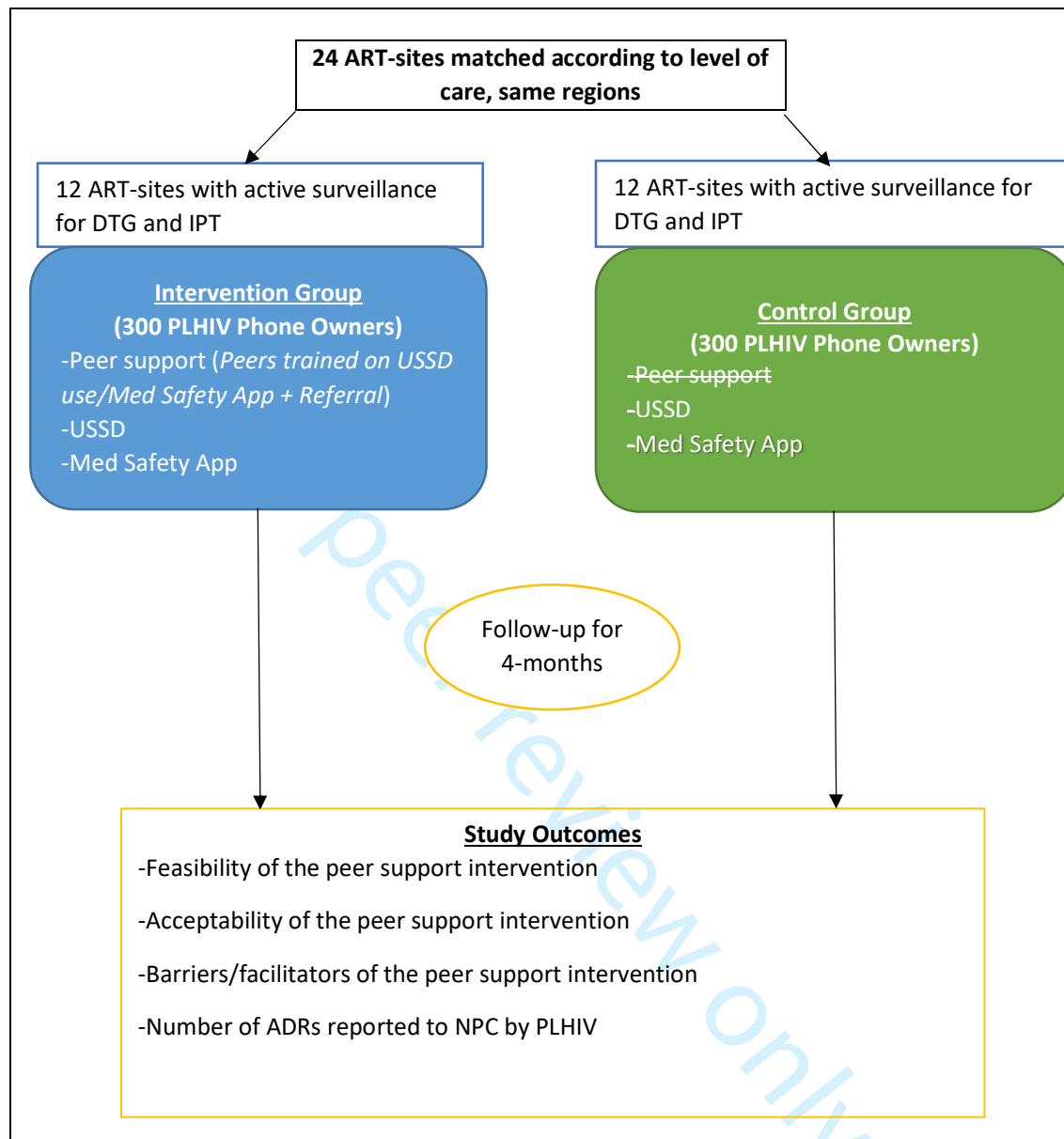
Figure 2: Layers of supervision in the peer support mechanism

Figure 3. Four key functions of the humanizing healthcare model for peer support as adapted from the framework by Peers for Progress

Figure 4. Intervention and comparison groups with two-way comparisons (before-after for each group (A&C, B&D), and between groups after intervention (C&D).

Figure 5. The five Differentiated Service Delivery models of HIV and TB care in Uganda, 2017.

For peer review only



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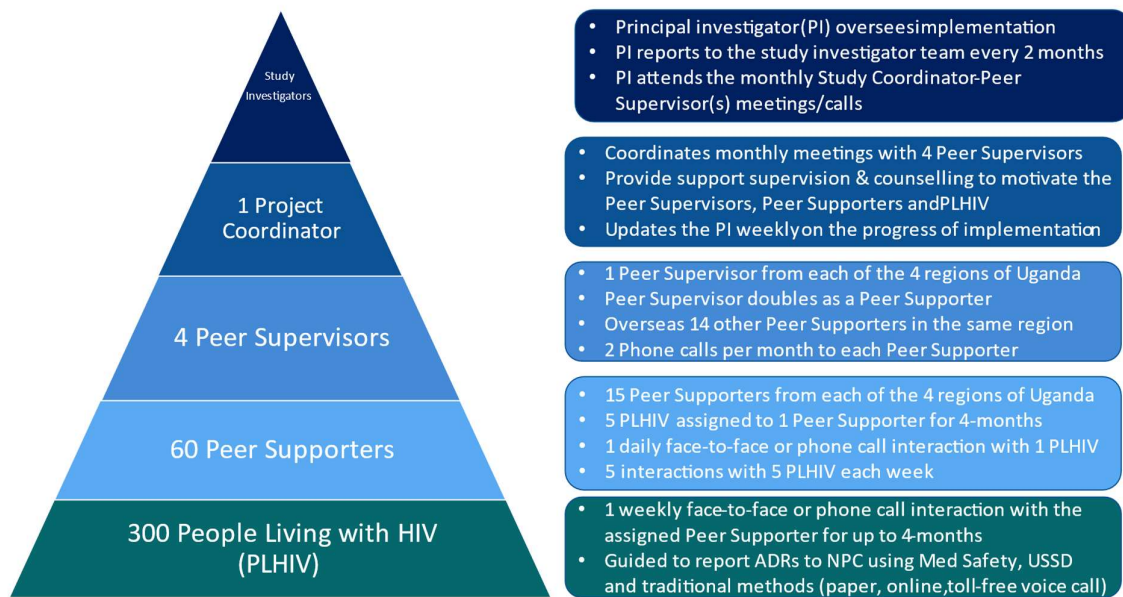


Figure 2. Layers of supervision in the peer support mechanism



23 *Source: Peers for Progress, Global Evidence for Peer Support; Humanizing Healthcare (September 2014)*

24 **Figure 3.** Four key functions of the humanizing healthcare model for peer support as adapted from
25 the framework by Peers for Progress
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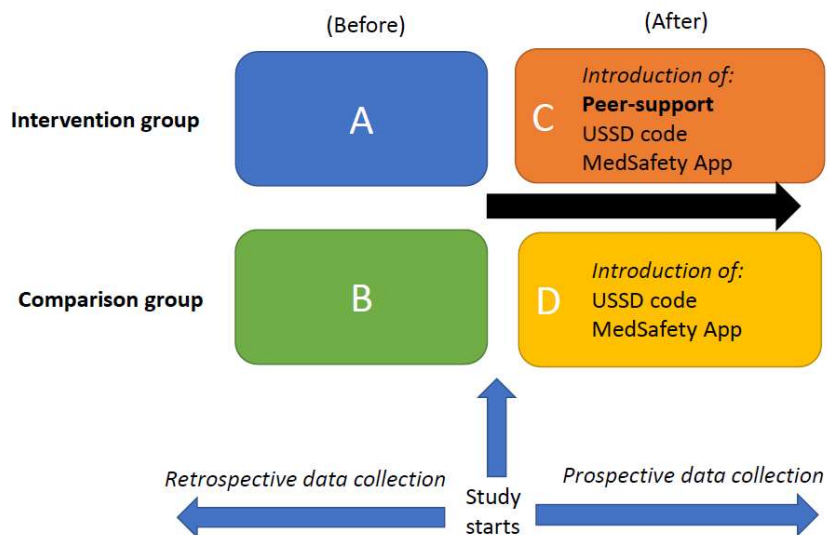
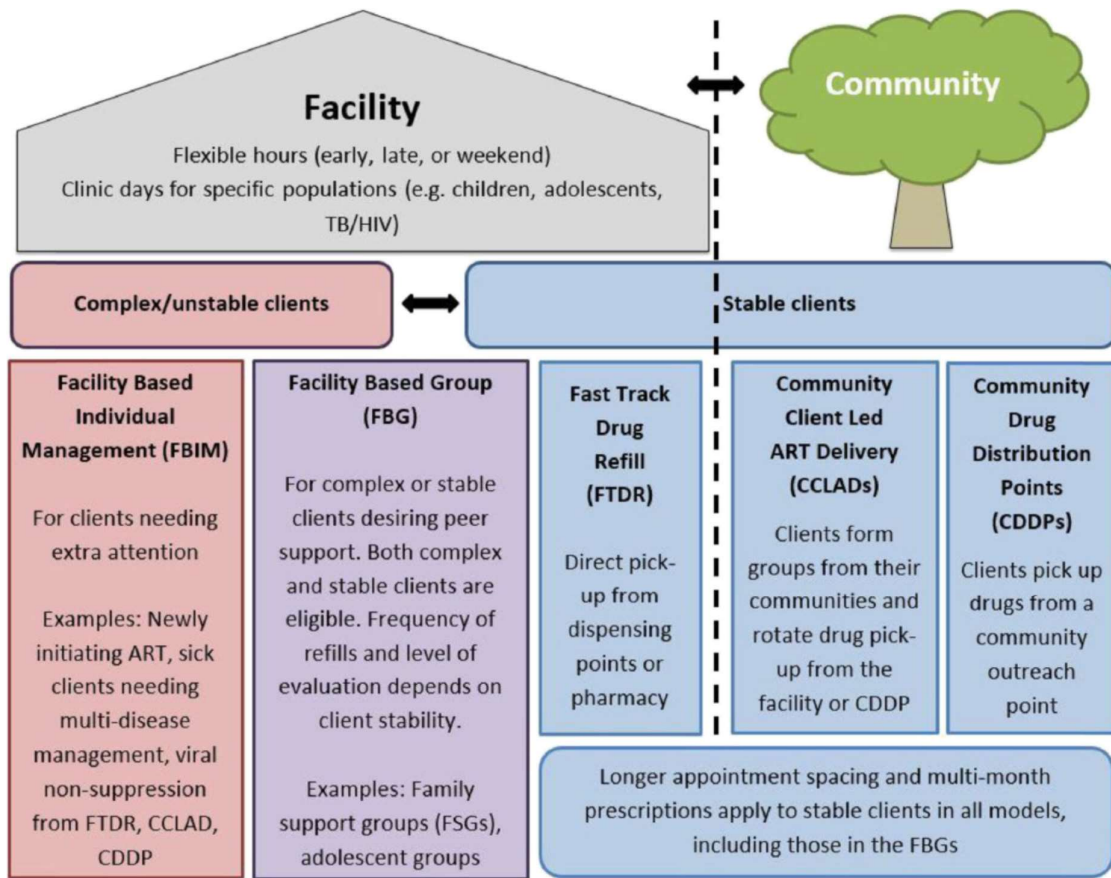


Figure 4. Intervention and comparison groups with two-way comparisons (before-after for each group (A&C, B&D), and between groups after intervention (C&D)).



Source: Ministry of Health, *Implementation Guide for Differentiated TB Services in Uganda* (June 2017).

Figure 5. The five Differentiated Service Delivery models of HIV and TB care in Uganda, 2017.

BMJ Open

Implementation of a peer support intervention to promote the detection, reporting and management of adverse drug reactions in people living with HIV in Uganda: a protocol for a quasi-experimental study

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3 **Implementation of a peer support intervention to promote the detection,**
4 **reporting and management of adverse drug reactions in people living with HIV**
5 **in Uganda: a protocol for a quasi-experimental study**
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Abstract

Introduction: Patients have contributed <1% of spontaneous adverse drug reaction (ADR) reports in Uganda's pharmacovigilance database. Peer support combined with mobile technologies could empower people living with HIV (PLHIV) to report ADRs and improve ADR management through linkage to care. We seek to test the feasibility and effect of a peer support intervention on ADR-reporting by PLHIV receiving combination antiretroviral therapy (cART) in Uganda; identify barriers and facilitators to the intervention; and characterise ADR-reporting and management.

Methods and analysis: This is a quasi-experimental study to be implemented over 4-months at 12 intervention and 12 comparison cART-sites from four geographical regions of Uganda. Per region, two blocks each with a tertiary, secondary and primary care cART-site will be selected by simple random sampling. Blocks per region will be randomly assigned to intervention and comparison arms.

Study units will include cART-sites and PLHIV receiving cART. PLHIV at intervention sites will be assigned to peer supporters to empower them to report ADRs directly to the National Pharmacovigilance Centre (NPC). Peer supporters will be expert clients from among PLHIV and/or recognized community health workers.

Direct patient-reporting of ADRs to NPC will leverage the Med Safety App and toll-free Unstructured Supplementary Service Data interface to augment traditional pharmacovigilance methods.

The primary outcomes are attrition rate measured by number of study participants who remain in the study until the end of follow-up at 4 months; and number of ADR reports submitted to NPC by PLHIV as measured by questionnaire and data abstraction from the national pharmacovigilance database at baseline and 4 months.

Ethics and dissemination: The study received ethical approval from: School of Health Sciences Research and Ethics Committee at Makerere University (MAKSHSREC-2020-64) and Uganda National Council for Science and Technology (HS1206ES). Results will be shared with PLHIV, policy-makers, the public and academia.

Trial registration: ISRCTN75989485

Strengths and limitations of the study

The study will blend a novel peer support intervention with mobile data transmission technologies to promote the detection and reporting of suspected adverse drug reactions (ADRs) by people living with HIV

People living with HIV who experience serious ADRs will be linked directly to health facilities for ADR management

An implementation research approach will be employed to identify the factors that could influence the uptake of peer support in patient-reporting of ADRs while documenting predefined outputs and outcomes relevant to the research objectives

The study will generate pilot data on effect sizes to aid the planning of future randomized controlled trials using peer support to promote patient-reporting of ADRs

Introduction

Adverse drug reactions (ADRs) are a leading cause of morbidity, mortality and increased healthcare costs[1-3]. The timely detection and reporting of ADRs promotes their appropriate management, more accurate prediction and prevention[4]. Pharmacovigilance systems worldwide have identified and led to withdrawal from the market of at least 462 harmful medicines, primarily through passive spontaneous ADR-reporting by healthcare professionals (HCPs)[5], thereby contributing to patient safety. The major drawback of the spontaneous pharmacovigilance system is its reliance on individual HCP motivation. It is estimated that only about 10% of ADRs are reported through the spontaneous pharmacovigilance system, which is a very low rate of ADR-reporting[6-8]. Several factors hinder ADR-reporting by HCPs including medical specialty, lower-level healthcare facility, older HCP age, heavy workloads, shortage of reporting tools, ignorance and fear of litigation[8, 9].

Patient-reporting of suspected ADRs is given little attention in developing countries. Yet, patients are a known complementary source of pharmacovigilance data[10-12]. Patients can make detailed ADR-reports and with similar quality as ADR-reports from HCPs. Patients can also report previously unknown ADRs[13]. Thus, patients are well-placed to participate in ADR-reporting because they have first-hand experience of their own state of health and treatment. Patient involvement in ADR-reporting aligns with the increasing global momentum towards patient-centred healthcare[14]. Yet, patient participation in pharmacovigilance is under-explored with little empirical data, especially in low- and middle-income countries (LMICs). In Uganda, patients' contribution to ADR-reporting is very low indeed and is estimated at less than 1% of the reports in the national pharmacovigilance database (Victoria Nambasa, Pharmacovigilance Manager at National Drug Authority (NDA); personal communication; 6 April 2020).

The quest for expanded avenues to increase the reporting of suspected ADRs has never been more apparent than in Uganda where dolutegravir (DTG) and Isoniazid Preventive Therapy (IPT) have been massively rolled-out since 2018 and 2019, respectively. Anecdotal evidence in Uganda suggests that increased use of DTG and IPT has increased the burden of associated serious ADRs e.g. hyperglycaemia, hepatotoxicity and neuropsychiatric effects[15, 16]; necessitating a more robust pharmacovigilance system that leverages patient-reporting of suspected ADRs to DTG-regimens and/or IPT. This study proposes to test the feasibility and effect of a peer support intervention combined with mobile phone-based tools to promote the reporting of ADRs by people living with HIV (PLHIV) on DTG-based ART and/or IPT in Uganda. If successful, this study will contribute to the development of a more robust pharmacovigilance system to better document serious ADRs in Uganda.

Patient-centred peer support has shown promise in the management of chronic illnesses such as diabetes and mental health[17, 18]; and in improving retention in HIV care and adherence to ART[19, 20]. Thus, peer support could substantially promote the detection, reporting and management of ADRs amongst PLHIV. In the current study, peer support is based on the premise that PLHIV who have previously experienced ADRs linked to ART can – as peer supporters - encourage, mentor and support other similarly affected but less experienced PLHIV to detect and report ADRs[21]. Peer supporters could serve as positive role models to improve the self-efficacy of other PLHIV whom they could guide to identify and report ADRs using the available tools. Direct patient-reporting of ADRs could utilize the Med Safety mobile application, a toll-free Unstructured Supplementary Service Data (USSD) interface and the

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3 traditional pharmacovigilance methods of paper-form, online forms and voice call. The aim
4 remains to have all suspected ADR reports submitted to the National Pharmacovigilance
5 Centre (NPC) database for analysis and subsequent processing. However, those that require
6 clinical management should be brought to the attention of the HCP for appropriate
7 management and prevention[21-23]. From guiding less experienced PLHIV, expert clients
8 serving as peer supporters could equally be empowered to build their own self-esteem[24,
9 25].
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12 Our peer support intervention for strengthening the Ugandan pharmacovigilance system
13 through patient-reporting of ADRs is intended to leverage the available mobile technologies
14 e.g. the USSD platform available for both low-tech non-smartphones and high-tech
15 smartphones[26]; and the Med Safety mobile application for high-tech smartphones[27].
16 USSD is a real-time text-driven technology which allows users to interact directly from their
17 mobile phones by making a selection from a menu. It allows for faster two-way communication
18 of information and enables rapid exchange of data - up to seven times faster than SMS[28].
19 The USSD interface has been a key success factor in the extensive penetration of mobile
20 money banking in rural unbanked sub-Saharan Africa[29]. No Internet connection is needed.
21 This project's toll-free USSD code has been developed by a private Ugandan software
22 company[30]. Med Safety is a smartphone mobile application for ADR-reporting that was
23 recently adapted for LMICs from the prototype app funded by the European Union's Innovative
24 Medicines Initiative – the WEB-RADR project. Adaptation of the mobile app is led by UK's
25 Medicines and Healthcare products Regulatory Agency in collaboration with World Health
26 Organization (WHO) and the WHO Collaborating Centre for International Drug Monitoring, the
27 Uppsala Monitoring Centre (UMC)[31]. Med Safety was launched in Uganda in February 2020.
28 Using both USSD and Med Safety alongside existing pharmacovigilance methods could
29 strengthen peer support-enhanced patient-driven pharmacovigilance in Uganda.
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35 Lastly, the study will use an implementation science approach to evaluate the peer support
36 intervention among PLHIV. Implementation research is critical in identifying factors that could
37 influence uptake of the intervention while documenting predefined outputs and outcomes
38 relevant to the research objectives[32]. Our ultimate goal is to increase patient reporting of
39 ADRs in LMICs such as Uganda with weak pharmacovigilance systems. Hence, this study
40 aims to develop and assess the feasibility of a peer support intervention combined with mobile
41 phone-based tools to promote the detection and reporting of ADRs in PLHIV on DTG-based
42 ART and/or IPT in Uganda. It will identify the barriers and facilitators to implementing the
43 intervention, characterise ADR-reporting and management and estimate the effect of the
44 intervention on ADR-reporting among PLHIV.
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48 **Research hypotheses and objectives**

49 Research hypotheses:

50 We hypothesize that the patient-centred peer support intervention combined with existing
51 mobile data transmission technologies for promoting the detection, reporting and management
52 of ADRs in PLHIV is feasible and acceptable. We also hypothesize that this peer support
53 intervention combined with mobile data transmission technologies will significantly increase
54 the number of ADR reports submitted to NPC by PLHIV who receive the intervention during
55 4-months of follow-up when compared with PLHIV who do not receive the intervention.
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3 Specific objectives:

- 4 1. To develop a peer support intervention combined with mobile data transmission
5 technologies to promote the detection, reporting and management of ADRs in PLHIV
6 receiving DTG and/or IPT in Uganda
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8 2. To explore the barriers and facilitators to implementation of the peer support
9 intervention combined with mobile data transmission technologies to promote ADR
10 detection, reporting and management among PLHIV on DTG and/or IPT in Uganda
11
12 3. To describe the patterns of ADR-reporting (number, rate, quality, time to reporting,
13 seriousness etc.) by PLHIV receiving DTG and/or IPT in whom the peer support
14 intervention combined with mobile data transmission technologies is implemented in
15 Uganda
16
17 4. To estimate the effect of the peer support intervention combined with mobile data
18 transmission technologies on the rate of ADR-reporting by PLHIV receiving DTG
19 and/or IPT in Uganda
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Methods

Study setting

Uganda has a tiered healthcare system with different levels of healthcare from the National Referral Hospitals which provide tertiary and super-specialized healthcare, through Regional Referral Hospitals (RRHs), General Hospitals, level IV Health Centers (HC IV), level III Health Centers (HC III), to level II Health Centers (HC II) that progressively offer less scope and breadth of health services to out-patient services[33]. HIV treatment and care is provided from HC III and upwards giving a total of 1,832 accredited centers that provide ART services in Uganda. Uganda adopted the Differentiated Service Delivery Models (DSDM), where stable clients have less frequent clinical assessment visits. In 2019, about 80% (1,466/1,832) of the ART accredited sites and 78% (975,675/1,241,478) of PLHIV on ART had access to the DSDM model. An additional, 12% (114,363/975,675) of clients enrolled on DSDM received ART services from the community through Community Drug Distribution Points (CDDP) and Community Client-Led ART Distribution (CCLAD)[34].

Uganda has an estimated 1.46 million PLHIV, of whom prevalence among people aged 15 to 49 years is 5.8% with women having a higher prevalence (7.1%) than men (4.3%). Among the PLHIV, 93% are aged ≥ 15 years and 60% of the HIV-infected adults are women. In 2019, there were 53,413 new HIV infections of which 40,000 were among adults and 21,000 Ugandans died of AIDS-related illnesses[35]. Following the “Test and Treat” policy for HIV adopted in 2016 and scaled up in 2017, the ART coverage was at 89% in 2019. Approximately 96% of PLHIV on ART are taking first-line regimens and >443,000 PLHIV are on TLD. About 17% of PLHIV are ART-naïve at treatment initiation. In 2019, about 41% of TB patients were HIV-positive and 97% of HIV-positive TB patients were receiving ART[35, 36]. By the end of 2019, 477,190 of PLHIV were enrolled on IPT. Strategies to strengthen pharmacovigilance were instituted as part of DTG/IPT roll-out in the 2020 revised Consolidated Guidelines for Prevention and Treatment of HIV and AIDS in Uganda[16]. The guidelines support ADR identification, monitoring and reporting, particularly for DTG and IPT. Pharmacovigilance sentinel sites were established at 18 sentinel sites (RRHs and Centers of Excellence). These ART-sites received training and ADR-reporting tools. ADRs are reported to the NPC at NDA through a paper-based system, online system, toll-free phone line or through NDA's Med Safety App.

For the current study, the authors have divided the country into four geographical regions to establish a sampling framework that leads to selection of national level representation of health facilities and factors that influence provision of care to PLHIV and their pharmacovigilance-related needs. In each region, two blocks of health facilities with ART-sites will be selected of which one block will implement the intervention and the other will serve as the comparison block of health facilities. Each block will consist of an ART-site at a RRH (tertiary care), a HC IV (secondary care) and HC III (primary care), respectively. Therefore, 12 intervention ART-sites will be matched by level of care and region with 12 comparison ART-sites from the four regions of Uganda.

Study design

The study will employ a quasi-experimental design with pre-post and there-there comparisons to measure the preliminary impact of the peer support intervention on ADR-reporting by PLHIV, **Figure 1**. The study will use both quantitative and qualitative methods to triangulate the research findings. The qualitative research methods aim to understand the barriers and

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3 facilitators to implementing the peer support intervention for promoting ADR detection,
4 reporting and management from the perspective of PLHIV and in the context of their interface
5 with Uganda's healthcare system[37] and thus they will be predominantly implemented in the
6 intervention arm. We will explore the experiences of PLHIV in the utilization of the peer support
7 intervention and elicit their preferences to further refine the intervention and implementation
8 strategy.
9

10 11 The intervention

12 The peer support intervention leverages mobile data transmission technologies (Med Safety,
13 USSD) in addition to traditional pharmacovigilance methods (paper, online, voice call). The
14 peer support mechanism has several layers of supervision from the mentored PLHIV, through
15 peer supporters, peer supervisors, study coordinator to study investigators at the top of the
16 hierarchy, see **Figure 2**.
17
18

19 The PLHIV to be mentored in the intervention arm will be assigned to peer supporters to guide
20 their ART care for 4-months. The peer supporters will constitute a mixed group of lay people,
21 namely; i) expert clients who are PLHIV with more experience in the use of ART and, ii)
22 recognized community health workers (CHWs). Most CHWs in Uganda's HIV programs are
23 expert clients. Thus, it is possible to recruit CHWs all of whom are expert clients. Peer
24 supporters in the intervention arm will guide the mentored PLHIV to report ADRs to NPC and
25 improve the latter's healthcare-seeking behaviour. The PLHIV should own mobile phones.
26
27

28 The PLHIV to be mentored will be identified by verbal communication/ written announcements
29 on noticeboards at the study sites and matched with the respective peer supporters of similar
30 age, gender and proximity of residence. The non-random matching of PLHIV to peer
31 supporters is intended to promote easier and faster bonding of the peer-relationships. Five (5)
32 PLHIV will be assigned to one (1) peer supporter from the same community. A weekly
33 (minimum fortnightly) face-to-face/phone call interaction will be held between a peer supporter
34 and each assigned PLHIV. Thus, a peer supporter will be expected to interact with one PLHIV
35 per day and five PLHIV in five days each week. Each PLHIV to be supported will be introduced
36 to an assigned PLHIV by the research team and focal health facility staff. The procedure for
37 the weekly interaction will be illustrated to the PLHIV-peer supporter pair. The mentored PLHIV
38 and peer supporter will be provided with the telephone contacts of the study coordinator/ focal
39 health facility staff whom they could notify at any time when they want to terminate
40 engagement.
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45 Peer supporters will use one-on-one in-person support blended with mobile phone-based
46 interaction to guide each assigned PLHIV to recognize and report suspected ADRs to NPC.
47 The peer supporter will also administer a short weekly questionnaire to each assigned PLHIV
48 regarding ADR experience in the past 1-week.
49

50 This peer support intervention adapts the "humanizing healthcare model" developed by *peers*
51 *for progress*, a group that demonstrates the value and best practices of peer support. The
52 model is based on four functions, namely; assistance in daily management, providing social
53 and emotional support, linking to clinical and community resources and ongoing support[38],
54 see **Figure 3**.
55
56

57 Both the supported PLHIV and peer supporters will be trained on the following aspects: ART;
58 how to live positively with HIV; recognition of suspected ADRs and how to report them via Med
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3 Safety, USSD or traditional methods (paper, online, voice call) to NPC; and about linkage or
4 referral to health facility care e.g. when a serious ADR occurs. The supported PLHIV and peer-
5 supporters will be trained to interact in a manner that ensures confidentiality. The data
6 generated from Med Safety and USSD will be safeguarded according to applicable laws on
7 data protection. The linkage to appropriate care of PLHIV by the peer supporter will aim to; i)
8 promote healthcare-seeking behaviour of the PLHIV, ii) improve the monitoring of HIV
9 treatment (management of serious ADRs, ART adherence, retention in care), iii) enhance
10 timely refill of ART prescriptions and/or, iv) provide for any other special care that PLHIV might
11 require.
12
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14
15 Peer supporters will be separately trained and skilled in interpersonal interaction to be
16 responsive to PLHIV and encourage them to identify and report any suspected ADRs. The
17 training components for peer supporters will include care in chronic illness, ART, adherence
18 to ART, ADRs, ADR-reporting, care-seeking, counselling and facilitative supervision. Training
19 for the peer supporters will take up to three days. It will include a one-day didactic session
20 followed by two days of on-the-job, one-on-one training. In addition to being trained, peer
21 supporters will receive supplementary educational materials. Four follow-up
22 supervisory visits/phone calls at two-week intervals will be conducted by the trainers to
23 reinforce the knowledge, skills and attitudes gained by the peer supporters. Each supported
24 PLHIV will receive one-day's training during his/her clinic visit which will include a didactic
25 session and one-on-one discussion in a non-classroom environment. The trainers will be
26 qualified individuals carefully identified by the project team with the requisite knowledge to
27 offer the training and expertise in adult learning and counselling.
28
29
30

31 The peer support mechanism will have two additional layers of supervision, see **Figure 2**. The
32 first level of additional oversight will be provided by four (4) peer supervisors identified from
33 among the peer supporters at each of the four selected RRHs. Peer supervisors will be
34 seconded by the study sites and collaborating patient safety groups involved in the recruitment
35 of peer supporters. Each peer supervisor will oversee 15 peer supporters in his/her region (10
36 from RRH, 3 from HC IV, 2 from HC III). The peer supervisor will call each peer supporter
37 twice a month. During these 'booster' sessions, the peer supervisor will review, emphasize
38 and re-educate peer supporters on expectations of the intervention e.g. setting and reviewing
39 goals with PLHIV. The second level of oversight will be provided by the project coordinator
40 who will oversee the four (4) peer supervisors whom he/she will meet/call every month. At
41 least one study investigator, mostly the principal investigator, will participate in these
42 meetings/calls. The project coordinator will have the requisite knowledge, skills and
43 competence to train PLHIV and peer supporters. The project coordinator will provide support
44 supervision and counselling to motivate the peer supervisors, peer supporters and PLHIV.
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50 The comparison group

51 PLHIV in the comparison group will be mobile phone owners who will be trained to recognize
52 suspected ADRs and report them to NPC via Med Safety, USSD or the traditional
53 pharmacovigilance methods (paper, online, toll-free voice call) to a peer-supporter, HCP or
54 NPC, see **Figure 4**. Smartphone owners will be guided to install Med Safety for ADR-reporting.
55 PLHIV with non-smartphones or smartphone owners who will not install Med Safety will report
56 ADRs by USSD or the traditional reporting methods. PLHIV in this group will not receive
57 dedicated peer support.
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Study units, participants and selection

Study units and participants:

This study has multiple study units and layers to assess the feasibility of implementation and effect of the intervention on promoting the detection and reporting of suspected ADRs in PLHIV on DTG-based ART and/or IPT in Uganda. From micro to macro-level, the study units include PLHIV receiving DTG-regimens and/or IPT; the pair of PLHIV and peer supporter; the peer supporter; the combination of the PLHIV with peer supporter and ART-site; peer supervisor; the pair of peer supervisor and peer supporter; and the ART-site. At the study ART-site, HCPs and health facility managers will be included. Lastly, the reporting of suspected ADRs by PLHIV, peer supporters, HCPs and ART-sites to the NPC will also be examined.

About 17% of PLHIV are ART-naive, 95% are aged 15 years and older, and 89% receive first-line ART either as treatment-naive or treatment-experienced PLHIV[36].

Eligibility criteria:

Inclusion criteria: Selection of study units will occur at three levels: *First*, eligible PLHIV should i) be aged ≥ 15 years, ii) receive ART at the selected study sites, iii) own a mobile phone (smartphone, basic feature phone) and, iv) provide written/thumb-printed informed consent. Child consent can be given by emancipated minors aged 15 to 17 years in Uganda[39] *Second*, eligible peer supporters (expert clients, CHWs) will be those that are recognized and seconded by the study sites or collaborating patient safety groups. These peer supporters will be those that are attached to the study sites and have already received institutional training in their role as expert clients/CHWs; they should own mobile phones. A focal clinical staff assigned to the study by the health facility administration will approach and recruit the peer supporters. The recruited peer supporters will be screened by the research team to gauge their ability to be peer supporters e.g. the ability to use the Med Safety App/USSD, ability to read and write in English and good interpersonal skills. Satisfactory peer supporters will give written informed consent. Peer supporters will participate only in the intervention arm of the study. *Third*, study health facilities will be selected and enrolled as follows; in each of the four geographical regions, blocks of three health facilities each with an ART-site, including at least a RRH, HC IV and HC III will be created based on the catchment of each RRH. From the created blocks of three health facilities in each region, two blocks will be selected by simple random sampling to participate in the study as the intervention and comparison health facilities, respectively. This will give 24 ART-sites consisting of 12 intervention sites (4 RRHs, 4 HC IVs, 4 HC IIIs) matched by level of care and region with 12 comparison sites (4 RRHs, 4 HC IVs, 4 HC IIIs) selected from the four geographical regions of Uganda.

Exclusion criteria: Exclusion will apply only at the level of PLHIV and CHWs. We shall exclude PLHIV on ART for < 6-months and expert clients/ CHWs who will be unable to commit, from the outset, at least 5-hrs per week to the study for up to 4-months.

Many ADRs happen when starting ART although such PLHIV tend to be unstable on treatment. The priority of this pilot is to understand the dynamics (feasibility and acceptability) of the peer support intervention in a *stable group* of PLHIV on ART (for ≥ 6 months). If found to be feasible, the peer support intervention will be introduced, in future initiatives, to the *unstable group* of PLHIV on ART (for <6 months).

Sample Size and Sampling Considerations

Sample size computation is based on the possible effect of the peer support intervention on the rate of ADR-reporting by PLHIV, with adjustment for clustering. We assume a conservative intra-cluster correlation coefficient of 0.045 and a priori increase of 50% in the rate of ADR-reporting to NDA, from 6 ADR-reports per 100 person-years at baseline[40] to 9 ADR-reports per 100 person-years at end-line evaluation. We assume a standard deviation of 12 ADR-reports per 100 person-years computed from the monthly ADR-reports submitted to NPC for one-year (October 2018 to September 2019). The study is designed to have at least 80% power to estimate an effect size of 1.5. Thus, 126 PLHIV will be required in the intervention arm and 126 PLHIV in the control arm.

Since the caseload for each peer supporter will be 5 PLHIV in the intervention arm, 60 peer supporters (15 from each of the 4 regions) will be responsible for 300 PLHIV on DTG and/or IPT. Thus, the peer support arm will include 300 PLHIV and the control arm 300 PLHIV all of whom should own functional mobile phones (smartphone or non-smartphone or both). Thus, a total of 600 PLHIV will be enrolled; 400 from RRHs, 120 from HC IVs and 80 from HC IIIs.

The PLHIV will be enrolled consecutively until the required sample size is attained. Smartphone owners will be guided to install Med Safety for ADR-reporting. We assume that 7 in 10 PLHIV at the ART-sites will have mobile phones and only one in 10 will possess smartphones[41]. Thus, only up to 10% (or 60) of PLHIV with smartphones will be helped (with maximal support from peer supporters) to download Med Safety. The rest of the 540 PLHIV without smartphones or smartphone owners who will not install Med Safety will report ADRs by USSD or the traditional methods.

Study variables

Primary outcomes: Feasibility of the peer support intervention - attrition rate recorded as the number of study participants who remain in the study until the end of follow-up at 4 months; Number of suspected ADR reports submitted to NPC by PLHIV as measured by questionnaire and data abstracted from the national pharmacovigilance database at baseline and 4 months

Other process/output/outcome variables:

1. Acceptability of the peer support intervention measured using a questionnaire and qualitative interviews at 4 months post-intervention
2. Barriers/facilitators of the peer support intervention measured using a questionnaire during the intervention and qualitative interviews at 4 months post-intervention
3. Fidelity to the peer support intervention measured using a questionnaire and qualitative interviews at 4 months post-intervention
4. Rate of ADR-reporting to NPC by PLHIV as measured by questionnaire and data abstraction from the national pharmacovigilance database at baseline and 4 months
5. Quality of ADR-reports by PLHIV measured by questionnaire and data abstraction from the national pharmacovigilance database at baseline and 4 months
6. Time to ADR-reporting to NPC by PLHIV since enrolment measured by questionnaire and data abstraction from the national pharmacovigilance database during 4 months
7. Time from ADR onset to registration in the national pharmacovigilance database measured by questionnaire and data abstraction from the database during 4 months
8. Health-related quality of life measured by questionnaire at baseline and 4 months
9. Management of ADRs recorded using a questionnaire during the 4 months
10. Number of PLHIV linked to health facilities by peer supporters for ADR management as measured by questionnaire during the 4-month intervention period

11. Health-seeking behaviour measured using a questionnaire at baseline and 4 months
12. Self-efficacy to report ADRs measured by questionnaire at baseline and 4 months
13. Self-reported ART adherence measured by questionnaire at baseline and 4 months
14. Mood (positive/ negative affect) measured by questionnaire at baseline and 4 months

Patient and Public Involvement

Direct involvement of PLHIV in the detection and reporting of suspected ADRs, and patient safety groups in recruitment of PLHIV, will have value in improving the public's awareness of ADRs and the available pharmacovigilance tools (Med Safety, USSD, toll-free voice call, etc.). Together, these will be essential for ensuring that changes to clinical practice to promote patient safety based on our work are acceptable to the public.

The study team will work with PLHIV to assess whether the available pharmacovigilance tools meet their needs, to identify potential improvements and to understand facilitators and barriers to using these pharmacovigilance tools. Wider public input into the refinement of the tools and mechanisms to encourage uptake will add value to our work. This work will also be of value to the wider public as Med Safety can be used to report ADRs to any drug, and users can receive drug safety information directly from NPC.

Data management and statistical analysis

Quantitative data

Data collection and management: Baseline and end-line semi-structured questionnaires will be administered to the PLHIV and peer supporters (expert clients) in the intervention arm and PLHIV only in the comparison arm.

The baseline questionnaire will record socio-demographics (age, sex, monthly income, education level, residence) of all study participants. Clinical details (ART adherence; ADRs; ART-regimen; ART-status i.e. first-line, second-line, third-line; duration on ART; comorbidities) and healthcare-seeking behaviour of study PLHIV will be measured. Data will be transmitted to a password-protected online database via the Open Data Kit (ODK) suite of tools. Participating PLHIV will be asked at enrolment if they experienced suspected ADRs in the 4-months preceding the study. The self-reported suspected ADRs will be corroborated with additional information on documented suspected ADRs from retrospective clinical chart review of the 4-month period prior to study enrolment. The clinical charts will be accessed by the health facility staff.

Additional data collection for the intervention group: On a weekly basis for up to 4-months, peer supporters will inquire from each assigned PLHIV (during a 1 hour face-to-face or phone call interaction) if he/she experienced one or more suspected ADR(s) and if the ADR had any impact on quality of life and/or ART adherence. Peer supporters will document if the ADR(s) was/were reported; and, if reported, by which means (Med Safety, USSD, voice call, other methods). Peer supporters will document all ADRs experienced by the PLHIV during the previous 1-week (using a tool designed to capture the medicines and ADRs); and will guide the PLHIV to report ADRs directly to NPC using the available pharmacovigilance methods. Active surveillance of ADRs linked to DTG and/or IPT will be prioritized but ADRs linked to other medicines will also be documented. PLHIV who experience serious ADRs will be linked directly to the health facilities where they receive ART for ADR management. Peer supporters will refer serious ADR cases to peer supervisors who will, in turn, refer these cases to focal clinical staff assigned to the study by the health facility administration; usually stationed at

1
2
3 triage to connect the cases to clinicians. We will document the management of serious and
4 non-serious ADRs (number of serious and non-serious ADR cases referred for health facility
5 management; actions taken by health facilities in the management of serious and non-serious
6 ADRs e.g. stopping treatment, changing treatment, continuing treatment with adherence
7 counselling, doing nothing, etc.).

8
9 The end-line questionnaire for PLHIV will measure their healthcare-seeking behaviour, linkage
10 to care for ADR management and adherence to ART. The PLHIV will also be asked to report
11 their experiences while receiving peer support to assess the intervention's feasibility and
12 acceptability (e.g. user satisfaction). The study will also assess the participants' experiences
13 when using the various pharmacovigilance methods (Med Safety, USSD, toll-free voice call,
14 etc.). We shall assess the ease of use, language and costs of the available pharmacovigilance
15 methods (Med Safety, USSD, toll-free voice call, etc) alongside peer support.
16
17

18
19 **Med Safety App and USSD data collection:** PLHIV will submit ADR-reports via Med Safety
20 and/or USSD with initial assistance from peer supporters. Each app-based ADR-report will be
21 automatically converted into the standard E2B (R2) format prior to its receipt in the Vigilance
22 Hub[42]. The app is hosted by Uganda's NDA which manages the reported ADR data. For
23 USSD reporting, PLHIV will dial the USSD code and answer a set of questions. The data will
24 be stored in real-time on a dashboard accessible to the project staff.
25

26
27 **Statistical analysis:** All ADR-data in both the national and project databases and received
28 from the study sites during the study period will be exported into Stata version 15.0 MP for
29 descriptive analysis – frequencies, proportions and their 95% confidence intervals (StataCorp
30 LLC, College Station, Texas). Duplicate ADR-reports will be identified and analysed
31 accordingly. Summary estimates will be reported by pharmacovigilance method (Med Safety,
32 USSD, toll-free voice call, etc.).
33

34
35 To assess the feasibility to retain peer supporters and PLHIV, we shall compute the attrition
36 rate which is the proportion of study participants who remain in the study until the end of follow-
37 up at 4 months.
38

39
40 The number of suspected ADRs reported to NPC by the PLHIV overall and in each study arm
41 will be described by subgroup: serious ADR (yes/no); peer supporter guided (yes/no); DTG-
42 linked (yes/no); IPT-linked (yes/no); DTG/IPT-linked (yes/no); linked to other medicines
43 (yes/no); level of reporting (PLHIV, peer supporter, HCP, health facility) etc.
44

45
46 The rate of ADR-reporting (m_a) by PLHIV (per site, overall) per completed-month (m_1) of follow-
47 up will be computed as follows: $m_a = [n_a \text{ reports}/(N_a \text{ completed-months of follow-up})]$, where
48 n_a is the number of reported ADRs and N_a the number of completed-months of follow-up.
49 Reporting rates of same-day ADR-onsets will be documented; and time from ADR-onset to
50 registration in the national database recorded for all other events[33]. Time to ADR-reporting
51 to NPC for a PLHIV will be the time from the day a PLHIV is enrolled into the peer support
52 intervention to the time he/she reports the first suspected ADR to NPC. Time-to-event data
53 will be analysed by survival analysis techniques.
54

55
56 We will explore the influence of level of care on the uptake of the peer support intervention in
57 Uganda's healthcare system - such as whether rolling it out at primary care facilities or tertiary
58 hospitals influences uptake.
59
60

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3 The change in outcome measures (e.g.) between pre- and post-intervention in PLHIV will be
4 assessed using a linear mixed model with random effect for peer supporter. Random effect
5 will be included to account for clustering of PLHIV with peer supporters. The ICC will be
6 estimated from this model. Since supporters are a mixed population of expert clients and
7 CHWs, a stratified analysis will be conducted. To aid the planning of future randomized
8 controlled trials from this pilot's data, we shall report effect sizes.
9
10

11 Qualitative data

12 **Data collection:** Post-intervention, a combination of focus group discussions (FDGs), in-
13 depth interviews (IDIs) and Key Informant Interviews (KIIs) will be conducted with purposively
14 selected study participants. A lead qualitative researcher will be assisted by two well-trained
15 research assistants. Semi-structured interviews informed by the Consolidated Framework for
16 Implementation Research (CFIR)[43] will be used to elicit participants' perspectives on the
17 facilitators and barriers to implementing the peer support intervention at four purposively
18 selected health facilities.
19
20

21 We will conduct six FDGs with three categories of PLHIV in the intervention arm; two with
22 those enrolled in Community Drug Distribution Points (CDDPs), two in Community Client-Led
23 ART Delivery (CCLAD) and two in facility-based ART delivery models.
24
25

26 A total of 12 IDIs will be conducted with peer supporters (expert clients, CHWs) attached to
27 each of the three ART delivery models; a) CDDP, b) CCLAD, c) Facility-Based, see **Figure 5**.
28
29

30 Four KIIs will be conducted with HCPs/facility managers with insights in the implementation
31 experience of the peer support intervention at their respective host facilities from an
32 organizational-context.
33

34 As a first step, participants will complete a written informed consent form. We will then capture
35 baseline characteristics: age, gender and educational level. A CFIR-informed semi-structured
36 guide will be used for the interviews. The semi-structured guide will explore participants'
37 experiences with the peer support intervention, their preferences and suggestions for
38 improvement of the intervention and the challenges encountered in using USSD and/or Med
39 Safety. On average, the duration of the FDGs and IDIs will be approximately 45-60 min. The
40 FDGs, IDIs and KIIs will be conducted until theoretical saturation is reached. Theoretical
41 saturation means that no new knowledge is generated and all aspects of a theory are covered.
42 All the data generated from the focus groups and interviews will be explored for themes and
43 sub-themes.
44
45
46

47 **Guiding qualitative analytical framework:** The CFIR will be adopted as the overall guiding
48 analytical framework for this study. The CFIR is a comprehensive 'meta-theoretical'
49 implementation research framework compiled from more than 20 sources and is cross-cutting
50 in more than 13 scientific disciplines; it guides systematic assessment of multi-level
51 implementation settings to identify factors that influence intervention implementation and
52 effectiveness [44]. The CFIR informs the conceptualization of this study, will guide the
53 development of data collection tools and will serve as an overarching deductive thematic
54 framework in analysis of study findings and the overall synthesis and interpretation of results
55 for this study. The CFIR is widely-applied because of its multi-level, 'ecological' dimensions
56 on multi-faceted influences on healthcare intervention implementation outcomes[45]. The
57 CFIR has been applied across diverse interventions and varied content fields[44].
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3 More specifically, the CFIR-derived domains that will guide the study are the following:

4 *Intervention characteristics:* Implementation of the peer support intervention could potentially
5 be impacted by factors including its perceived effectiveness in ADR-reporting, relative
6 advantages over alternative reporting approaches, adaptability in varied resource-constrained
7 settings, trialability, complexity, design quality and presentation, and cost-effectiveness.
8
9

10 *Outer setting:* external influences on implementation of peer support may include external
11 policies and incentives, socio-cultural belief systems, peer pressure dynamics and socio-
12 economic context.
13

14 *Inner setting:* characteristics of the implementing organization (or host health facility) such as
15 organizational culture, the relative priority assigned to the peer support intervention (including
16 funding support), presence of intervention 'champions', availability of supportive administrative
17 or physical infrastructure, congruence with host organization's mission and vision, quality of
18 leadership support and implementation climate(s).
19
20

21 *Characteristics of individuals:* Patients' beliefs, knowledge, level of income, self-efficacy, and
22 personal attributes that may affect the implementation and uptake of the peer support
23 intervention.
24
25

26 *Process of implementation:* Influences on implementation outcomes may derive from different
27 implementation phases involved in roll-out of the peer support strategy such as degree and
28 quality of involvement of primary beneficiaries in designing the intervention, planning,
29 execution, degree of effectiveness of monitoring and evaluation strategies and presence of
30 key intervention stakeholders and influencers including opinion leaders, stakeholder
31 engagement, and intervention champions.
32
33

34 The CFIR will be used to identify barriers and facilitators of the peer support intervention for
35 promoting ADR-reporting by PLHIV.
36

37 **Data analysis:** Our qualitative data analysis will follow the procedures recommended by Miles
38 & Huberman (1994)[46]. Interviews and FGDs will be audio-recorded and transcribed verbatim
39 into text transcripts by three research assistants (and translated into English where
40 necessary). Data will be analysed, in an iterative process, involving four major steps:
41
42

43 a) *Data familiarization:* An experienced qualitative researcher and one other investigator will
44 read the interview transcripts multiple times for data familiarization.
45

46 b) *Developing a coding framework:* We shall adopt the five CFIR-derived domains
47 (*Intervention characteristics, outer setting, inner setting, characteristics of individuals, and*
48 *process of implementation*) as an overarching deductive thematic framework, combined with
49 an inductive approach based on the data[47].
50

51 c) *Data abstraction:* The coded data will be categorized into thematic categories.
52
53

54 d) *Overall interpretation and synthesis:* Our overall synthesis of study findings will adopt a
55 team-based process of peer-debriefing involving all investigators to resolve disagreements in
56 interpretation of study findings.
57
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59
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Quality assurance

To ensure uniform study procedures and high-quality data, all research assistants recruited for the study will receive face-to-face training on the following: the informed consent process, participant interviewing techniques, confidentiality issues, pharmacovigilance, use of the Med Safety App, use of the USSD, ADRs, use of the Open Data Kit (ODK) software for data entry into an online password-protected database; and qualitative and quantitative study designs, among others.

The FGDs and KIs will be led by an expert in qualitative research. Research assistants with prior training in qualitative research methods will also be hired for the qualitative study component. All research assistants will receive face-to-face training in both qualitative and quantitative research methods.

Questionnaire data will be transmitted through ODK to an online database by the research assistants while still in the field. The study statistician will check the online data for integrity and contact field staff as soon as possible while still in the field to correct any data entry errors. Prior to entry into ODK, all research assistants shall be required to cross-check the data on study questionnaires to eliminate errors and ensure data completeness.

Results uptake and use

Outcomes/Impact/Outreach: The peer support intervention is expected to increase patient-reporting of ADRs to NPC. It is anticipated that the patients will subsequently; i) find it easier and faster to report ADRs (including DTG- and IPT-related reactions) anywhere and at any time using their mobile phones and, ii) receive medication-safety alerts directly from NPC to their phones. We expect this project to promote pharmacovigilance in Uganda by improving; i) the exchange of medication-safety information between patients, peer supporters, HCPs and NPC, ii) the awareness of pharmacovigilance by patients and the public through the mobile phone and other awareness campaigns and, iii) the rate of ADR-reporting by patients.

Potential impact on policy or programs: This project could foster the increased involvement of patients in pharmacovigilance activities and improve the efficiency of pharmacovigilance systems in Uganda with real-time monitoring of DTG and INH safety in PLHIV in the first instance, thus, increasing the volume of analysable data for quick decision-making by both clinicians and policy makers.

We expect to promote collaboration between consumers/public and the NPC, national AIDS Control Program - Ministry of Health and the National TB and Leprosy Control Programme (NTLP). The accumulation of relevant medication-safety data from spontaneous and active ADR-reports permits robust detection of safety signals at the national and international levels.

Scalability: After this pilot project, we expect the peer support intervention to be tested in a nationwide randomized controlled trial; and the USSD and Med Safety App to be modified accordingly and implemented at all 1,832 ART-sites in Uganda to complement the existing active and passive pharmacovigilance methods for ART and TB treatment. We hope to embed peer support in routine pharmacovigilance practice to promote the detection and reporting of ADRs by PLHIV in Uganda. The Med Safety App is available in English and will be subsequently translated into other local languages according to need.

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3 The USSD and Med Safety are potentially invaluable tools for the pharmacovigilance of drugs
4 used for other diseases e.g. non-communicable diseases like cancers, diabetes mellitus,
5 hypertension etc.
6

7
8 Peer support, USSD and Med Safety will be scaled-up to support spontaneous ADR-reporting
9 in both public and private health facilities at all levels of healthcare ranging from hospitals,
10 medical centres and clinics to pharmacies and drug shops, not least, the general public.
11

12 The pharmacovigilance data at NPC could be linked with the patients' clinical data at ART-
13 sites, stock consumption data from the Supply Management Chain system; and the electronic
14 Health Management Information System. Machine learning/artificial intelligence analytical
15 techniques could then be used on big data in the near future to foster improved systems.
16

17
18 *Sustainability:* Peer support to promote the detection and reporting of ADRs by PLHIV can be
19 embedded in the HIV/AIDS program of Uganda just as community engagement programmes
20 have been successful in Maternal and Child Health programmes; and are being rolled out in
21 the COVID-19 Community Engagement Strategy and the Young people and Adolescent Peer
22 Support Model for improving HIV care and treatment outcomes for Adolescents and young
23 PLHIV of 2019 in Uganda[48, 49]. The USSD and Med Safety will be integrated into NPC's
24 routine pharmacovigilance functions to complement existing pharmacovigilance methods.
25 Regional pharmacovigilance centres have pharmacovigilance focal persons who will continue
26 to support the NPC. All ADR-reports received by NPC are reviewed and submitted into an
27 existing national medication-safety database. The equipped peer supporters are a valuable
28 resource for scaling up peer support in the ART-sites after the study is concluded.
29
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31
32 The USSD interface and Med Safety will be freely available. Med Safety can be downloaded
33 and installed from both Google Play and Apple iOS stores. NPC pays the salaries of its full-
34 time pharmacovigilance staff who receive and process the reported medication-safety data.
35

36 The research collaboration between Makerere University's Department of Pharmacology,
37 Department of Pharmacy, NPC, ACP, MHRA and other stakeholders will continue to source
38 for additional research grants to support the future scale-up of evidence-based digital
39 pharmacovigilance in Uganda. The findings could be helpful to other countries to inform their
40 own pharmacovigilance activities.
41
42

43 **Dissemination**

44
45 Med Safety users will immediately benefit from the app's two-way communication functionality
46 as they will receive medication-safety alerts from NPC in addition to their submission to NPC
47 of ADR-reports.
48

49 We plan to present the project's research findings at local stakeholders' workshops organized
50 to ensure the balanced representation of HCPs, administrators, policy makers, patient safety
51 groups, the public and other local and international partners. At least one policy brief will be
52 prepared from this work. We shall also disseminate the results at three or more local and
53 international conferences, engage the public through local and international television
54 channels, and through social media (Facebook, Twitter, WhatsApp, blogging etc.). We shall
55 publish at least two manuscripts in internationally-recognized peer-reviewed journals.
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Ethical and environmental considerations

The study received ethical approval from the School of Health Sciences Research and Ethics Committee at Makerere University College of Health Sciences (MAKSHSREC-2020-64); and was registered with the Uganda National Council for Science and Technology (HS1206ES). Administrative clearance will be obtained from participating ART-sites and written/thumb-printed informed consent from participating PLHIV and expert clients/CHWs. We consider the introduction of USSD and Med Safety for ADR-reporting to be a minimal risk intervention. However, we shall remind participants to mind their own confidentiality which could be lost due to phone sharing. On the contrary, participants in the intervention group could potentially benefit from peer-support. We received a waiver of consent from the ethics committee to access anonymized clinical and medication data of PLHIV at the health facilities. The data will be extracted by staff of the respective health facilities. Applicable international laws on data protection will be observed as well as the Data Protection and Privacy Act, 2019 of the Republic of Uganda[50].

Risk management

Small number of patients ($\leq 10\%$) expected to own functional smartphones: Our main goal is to demonstrate that Med Safety can be downloaded and used by PLHIV, which we can achieve without the requirement for strict sample size and power calculations. Also, we shall use the USSD which can work on both basic low-tech mobile phones and high-tech smartphones.

Duplicate ADR-reports: Duplicates will be identified by the NPC staff and study statistician.

Loss to follow-up of peer supporters and PLHIV: A major goal is to demonstrate the feasibility of peer support for PLHIV to get involved in ADR-reporting. The study will provide preliminary data on the magnitude of loss to follow-up to be expected in future studies.

Compromise in data quality by the research assistants: The research assistants will be trained by the study team. Questionnaire data will be transmitted online immediately using ODK – thus giving a chance to the centrally located statistician to verify data integrity.

COVID-19: We shall observe the SOPs of social distancing, washing hands and wearing masks by study participants and investigators to minimise the risk of spreading COVID-19. The pandemic could limit face-to-face contact but is also an opportunity to show how more remote engagement can support pharmacovigilance in a developing country setting. Remote engagement could be more cost-effective to support participants through phone calls and other forms of online interaction.

Collaboration

MHRA adapted Med Safety for Uganda with NDA's approval. The NPC staff at NDA, where NPC is located, will participate in this project. Involvement of the ACP in this pharmacovigilance project will promote the integration of peer support-driven pharmacovigilance in the HIV care and treatment programme of Uganda. The Department of Pharmacology & Therapeutics and Department of Pharmacy, Makerere University conceived this project and will coordinate the study. The WHO contracted MHRA to adapt the app for Uganda and will, together with UMC, provide technical support.

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5 version of the manuscript. All authors read and approved the final manuscript.
6

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16

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18

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Figures

Figure 1. Before-after and there-there quasi-experimental study design for a peer support intervention to improve adverse drug reaction reporting by people living with HIV in Uganda

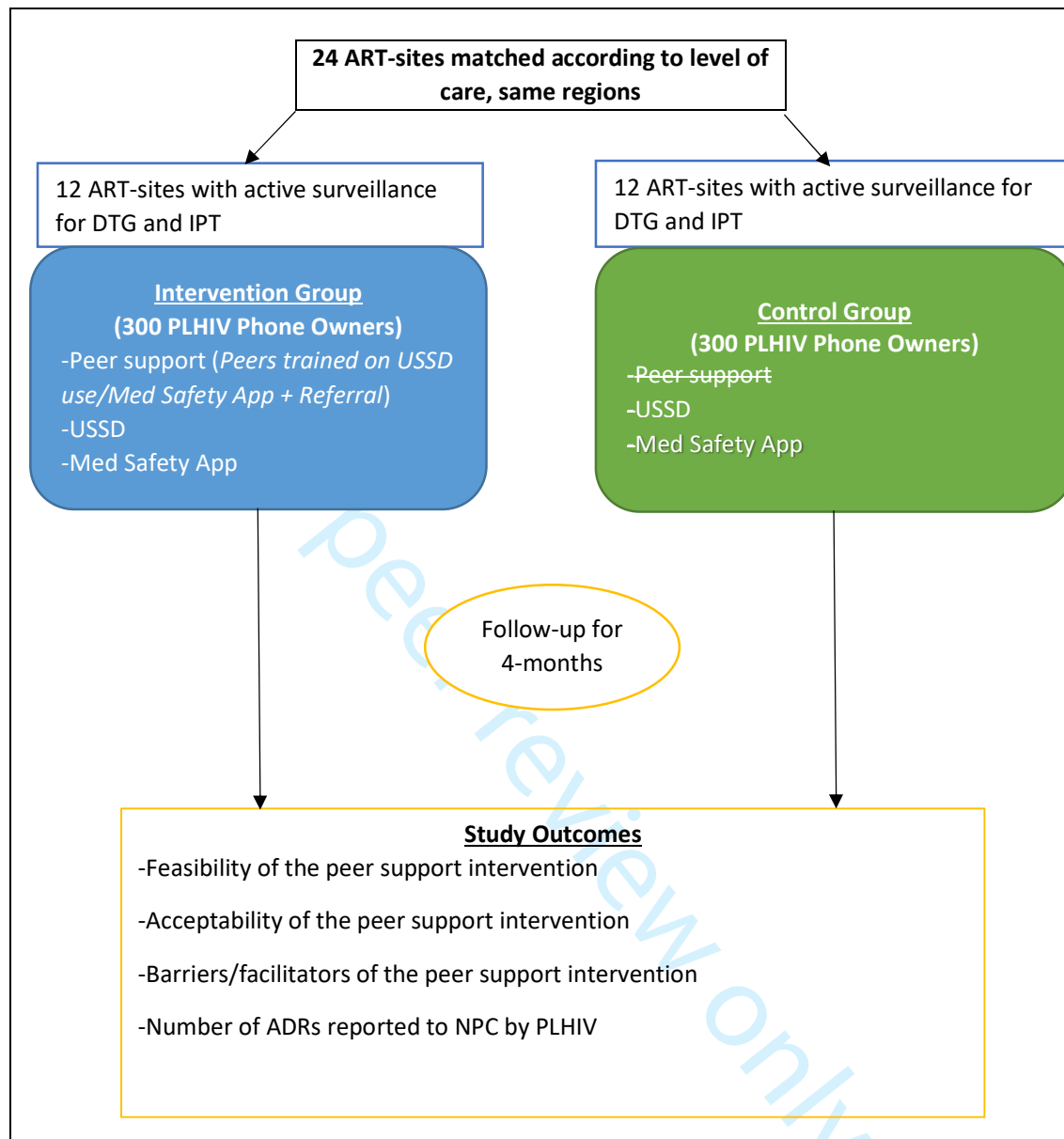
Figure 2: Layers of supervision in the peer support mechanism

Figure 3. Four key functions of the humanizing healthcare model for peer support as adapted from the framework by Peers for Progress

Figure 4. Intervention and comparison groups with two-way comparisons (before-after for each group (A&C, B&D), and between groups after intervention (C&D).

Figure 5. The five Differentiated Service Delivery models of HIV and TB care in Uganda, 2017.

For peer review only



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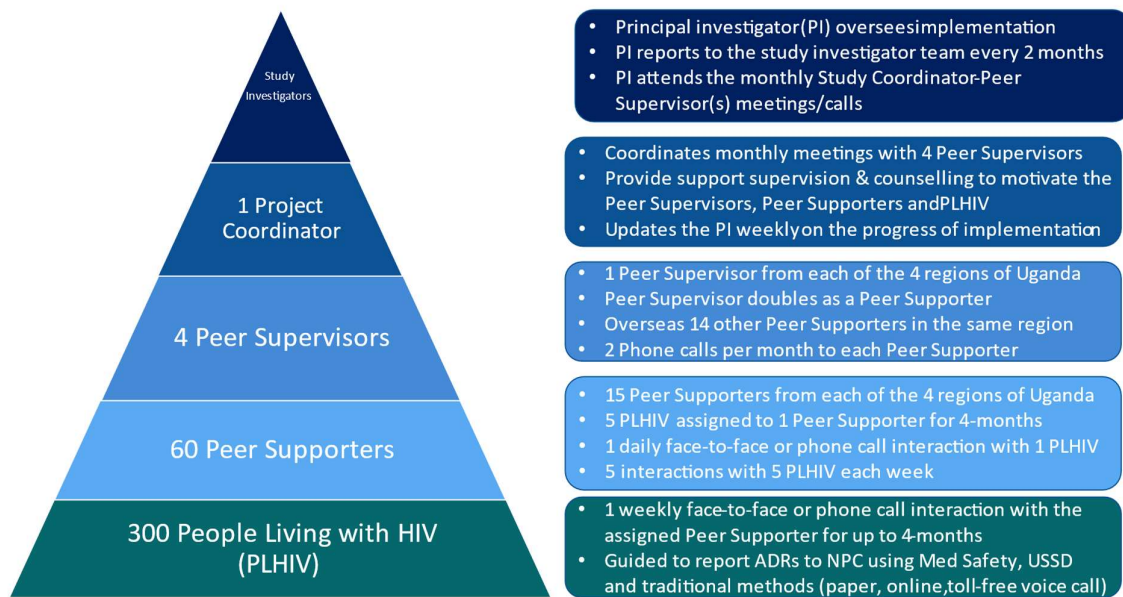


Figure 2. Layers of supervision in the peer support mechanism



23 *Source: Peers for Progress, Global Evidence for Peer Support; Humanizing Healthcare (September 2014)*

24 **Figure 3.** Four key functions of the humanizing healthcare model for peer support as adapted from
25 the framework by Peers for Progress
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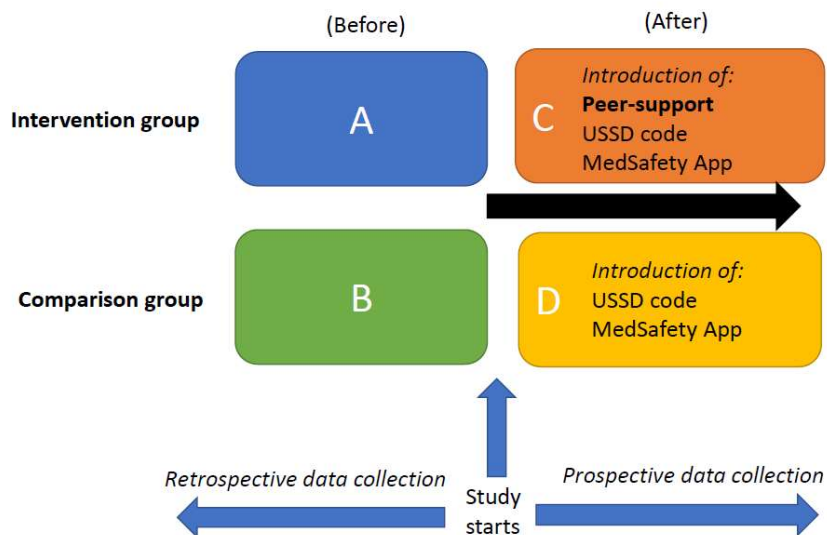
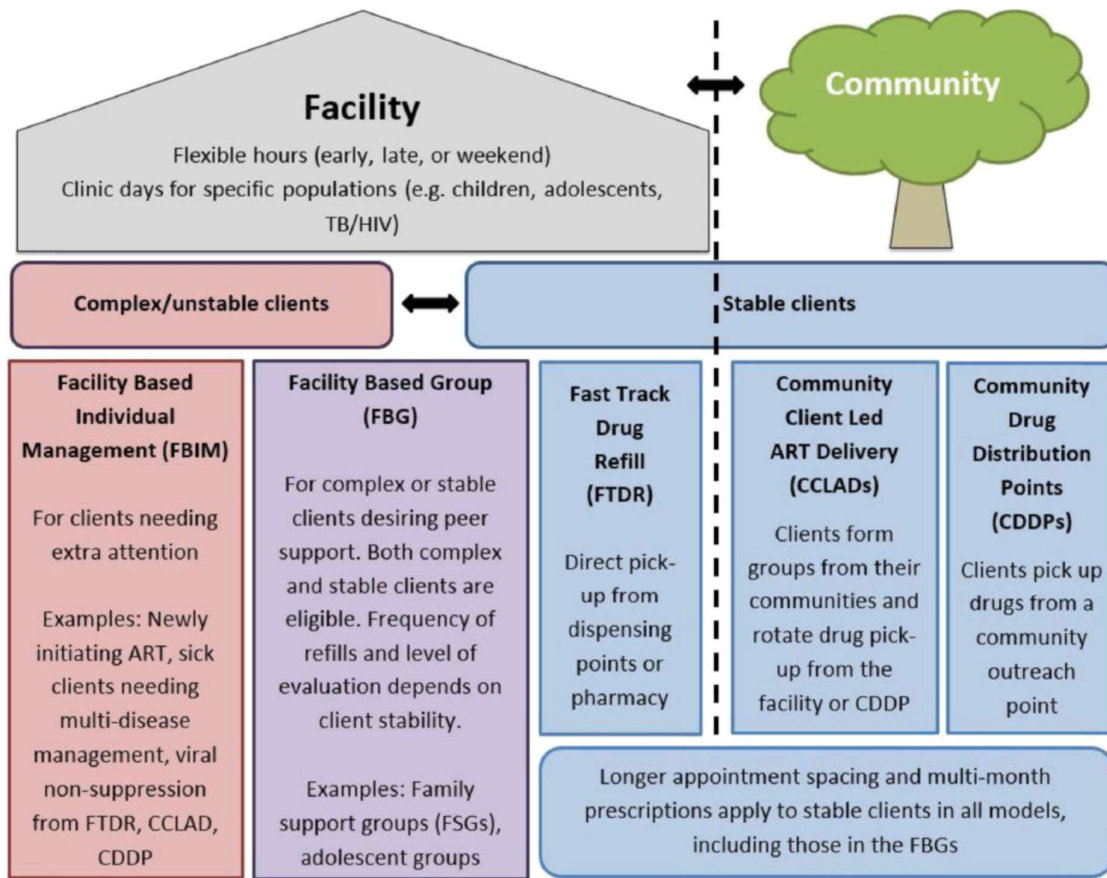


Figure 4. Intervention and comparison groups with two-way comparisons (before-after for each group (A&C, B&D), and between groups after intervention (C&D)).



Source: Ministry of Health, *Implementation Guide for Differentiated TB Services in Uganda* (June 2017).

Figure 5. The five Differentiated Service Delivery models of HIV and TB care in Uganda, 2017.

BMJ Open

Implementation of a peer support intervention to promote the detection, reporting and management of adverse drug reactions in people living with HIV in Uganda: a protocol for a quasi-experimental study

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Keywords:	Adverse events < THERAPEUTICS, SOCIAL MEDICINE, Epidemiology < INFECTIOUS DISEASES, Pharmacology < TROPICAL MEDICINE

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3 **Implementation of a peer support intervention to promote the detection,**
4 **reporting and management of adverse drug reactions in people living with HIV**
5 **in Uganda: a protocol for a quasi-experimental study**
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Abstract

Introduction: Patients have contributed <1% of spontaneous adverse drug reaction (ADR) reports in Uganda's pharmacovigilance database. Peer support combined with mobile technologies could empower people living with HIV (PLHIV) to report ADRs and improve ADR management through linkage to care. We seek to test the feasibility and effect of a peer support intervention on ADR-reporting by PLHIV receiving combination antiretroviral therapy (cART) in Uganda; identify barriers and facilitators to the intervention; and characterise ADR-reporting and management.

Methods and analysis: This is a quasi-experimental study to be implemented over 4-months at 12 intervention and 12 comparison cART-sites from four geographical regions of Uganda. Per region, two blocks each with a tertiary, secondary and primary care cART-site will be selected by simple random sampling. Blocks per region will be randomly assigned to intervention and comparison arms.

Study units will include cART-sites and PLHIV receiving cART. PLHIV at intervention sites will be assigned to peer supporters to empower them to report ADRs directly to the National Pharmacovigilance Centre (NPC). Peer supporters will be expert clients from among PLHIV and/or recognized community health workers.

Direct patient-reporting of ADRs to NPC will leverage the Med Safety App and toll-free Unstructured Supplementary Service Data interface to augment traditional pharmacovigilance methods.

The primary outcomes are attrition rate measured by number of study participants who remain in the study until the end of follow-up at 4 months; and number of ADR reports submitted to NPC by PLHIV as measured by questionnaire and data abstraction from the national pharmacovigilance database at baseline and 4 months.

Ethics and dissemination: The study received ethical approval from: School of Health Sciences Research and Ethics Committee at Makerere University (MAKSHSREC-2020-64) and Uganda National Council for Science and Technology (HS1206ES). Results will be shared with PLHIV, policy-makers, the public and academia.

Trial registration: ISRCTN75989485

Strengths and limitations of the study

The study will blend a novel peer support intervention with mobile data transmission technologies to promote the detection and reporting of suspected adverse drug reactions (ADRs) by people living with HIV

People living with HIV who experience serious ADRs will be linked directly to health facilities for ADR management

An implementation research approach will be employed to identify the factors that could influence the uptake of peer support in patient-reporting of ADRs while documenting predefined outputs and outcomes relevant to the research objectives

The study will generate pilot data on effect sizes to aid the planning of future randomized controlled trials using peer support to promote patient-reporting of ADRs

Introduction

Adverse drug reactions (ADRs) are a leading cause of morbidity, mortality and increased healthcare costs[1-3]. The timely detection and reporting of ADRs promotes their appropriate management, more accurate prediction and prevention[4]. Pharmacovigilance systems worldwide have identified and led to withdrawal from the market of at least 462 harmful medicines, primarily through passive spontaneous ADR-reporting by healthcare professionals (HCPs)[5], thereby contributing to patient safety. The major drawback of the spontaneous pharmacovigilance system is its reliance on individual HCP motivation. It is estimated that only about 10% of ADRs are reported through the spontaneous pharmacovigilance system, which is a very low rate of ADR-reporting[6-8]. Several factors hinder ADR-reporting by HCPs including medical specialty, lower-level healthcare facility, older HCP age, heavy workloads, shortage of reporting tools, ignorance and fear of litigation[8, 9].

Patient-reporting of suspected ADRs is given little attention in developing countries. Yet, patients are a known complementary source of pharmacovigilance data[10-12]. Patients can make detailed ADR-reports and with similar quality as ADR-reports from HCPs. Patients can also report previously unknown ADRs[13]. Thus, patients are well-placed to participate in ADR-reporting because they have first-hand experience of their own state of health and treatment. Patient involvement in ADR-reporting aligns with the increasing global momentum towards patient-centred healthcare[14]. Yet, patient participation in pharmacovigilance is under-explored with little empirical data, especially in low- and middle-income countries (LMICs). In Uganda, patients' contribution to ADR-reporting is very low indeed and is estimated at less than 1% of the reports in the national pharmacovigilance database (Victoria Nambasa, Pharmacovigilance Manager at National Drug Authority (NDA); personal communication; 6 April 2020).

The quest for expanded avenues to increase the reporting of suspected ADRs has never been more apparent than in Uganda where dolutegravir (DTG) and Isoniazid Preventive Therapy (IPT) have been massively rolled-out since 2018 and 2019, respectively. Anecdotal evidence in Uganda suggests that increased use of DTG and IPT has increased the burden of associated serious ADRs e.g. hyperglycaemia, hepatotoxicity and neuropsychiatric effects[15, 16]; necessitating a more robust pharmacovigilance system that leverages patient-reporting of suspected ADRs to DTG-regimens and/or IPT. This study proposes to test the feasibility and effect of a peer support intervention combined with mobile phone-based tools to promote the reporting of ADRs by people living with HIV (PLHIV) on DTG-based ART and/or IPT in Uganda. If successful, this study will contribute to the development of a more robust pharmacovigilance system to better document serious ADRs in Uganda.

Patient-centred peer support has shown promise in the management of chronic illnesses such as diabetes and mental health[17, 18]; and in improving retention in HIV care and adherence to ART[19, 20]. Thus, peer support could substantially promote the detection, reporting and management of ADRs amongst PLHIV. In the current study, peer support is based on the premise that PLHIV who have previously experienced ADRs linked to ART can – as peer supporters - encourage, mentor and support other similarly affected but less experienced PLHIV to detect and report ADRs[21]. Peer supporters could serve as positive role models to improve the self-efficacy of other PLHIV whom they could guide to identify and report ADRs using the available tools. Direct patient-reporting of ADRs could utilize the Med Safety mobile application, a toll-free Unstructured Supplementary Service Data (USSD) interface and the

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3 traditional pharmacovigilance methods of paper-form, online forms and voice call. The aim
4 remains to have all suspected ADR reports submitted to the National Pharmacovigilance
5 Centre (NPC) database for analysis and subsequent processing. However, those that require
6 clinical management should be brought to the attention of the HCP for appropriate
7 management and prevention[21-23]. From guiding less experienced PLHIV, expert clients
8 serving as peer supporters could equally be empowered to build their own self-esteem[24,
9 25].
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12 Our peer support intervention for strengthening the Ugandan pharmacovigilance system
13 through patient-reporting of ADRs is intended to leverage the available mobile technologies
14 e.g. the USSD platform available for both low-tech non-smartphones and high-tech
15 smartphones[26]; and the Med Safety mobile application for high-tech smartphones[27].
16 USSD is a real-time text-driven technology which allows users to interact directly from their
17 mobile phones by making a selection from a menu. It allows for faster two-way communication
18 of information and enables rapid exchange of data - up to seven times faster than SMS[28].
19 The USSD interface has been a key success factor in the extensive penetration of mobile
20 money banking in rural unbanked sub-Saharan Africa[29]. No Internet connection is needed.
21 This project's toll-free USSD code has been developed by a private Ugandan software
22 company[30]. Med Safety is a smartphone mobile application for ADR-reporting that was
23 recently adapted for LMICs from the prototype app funded by the European Union's Innovative
24 Medicines Initiative – the WEB-RADR project. Adaptation of the mobile app is led by UK's
25 Medicines and Healthcare products Regulatory Agency in collaboration with World Health
26 Organization (WHO) and the WHO Collaborating Centre for International Drug Monitoring, the
27 Uppsala Monitoring Centre (UMC)[31]. Med Safety was launched in Uganda in February 2020.
28 Using both USSD and Med Safety alongside existing pharmacovigilance methods could
29 strengthen peer support-enhanced patient-driven pharmacovigilance in Uganda.
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35 Lastly, the study will use an implementation science approach to evaluate the peer support
36 intervention among PLHIV. Implementation research is critical in identifying factors that could
37 influence uptake of the intervention while documenting predefined outputs and outcomes
38 relevant to the research objectives[32]. Our ultimate goal is to increase patient reporting of
39 ADRs in LMICs such as Uganda with weak pharmacovigilance systems. Hence, this study
40 aims to develop and assess the feasibility of a peer support intervention combined with mobile
41 phone-based tools to promote the detection and reporting of ADRs in PLHIV on DTG-based
42 ART and/or IPT in Uganda. It will identify the barriers and facilitators to implementing the
43 intervention, characterise ADR-reporting and management and estimate the effect of the
44 intervention on ADR-reporting among PLHIV.
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48 **Research hypotheses and objectives**

49 Research hypotheses:

50 We hypothesize that the patient-centred peer support intervention combined with existing
51 mobile data transmission technologies for promoting the detection, reporting and management
52 of ADRs in PLHIV is feasible and acceptable. We also hypothesize that this peer support
53 intervention combined with mobile data transmission technologies will significantly increase
54 the number of ADR reports submitted to NPC by PLHIV who receive the intervention during
55 4-months of follow-up when compared with PLHIV who do not receive the intervention.
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3 Specific objectives:

- 4 1. To develop a peer support intervention combined with mobile data transmission
5 technologies to promote the detection, reporting and management of ADRs in PLHIV
6 receiving DTG and/or IPT in Uganda
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8 2. To explore the barriers and facilitators to implementation of the peer support
9 intervention combined with mobile data transmission technologies to promote ADR
10 detection, reporting and management among PLHIV on DTG and/or IPT in Uganda
11
12 3. To describe the patterns of ADR-reporting (number, rate, quality, time to reporting,
13 seriousness etc.) by PLHIV receiving DTG and/or IPT in whom the peer support
14 intervention combined with mobile data transmission technologies is implemented in
15 Uganda
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17 4. To estimate the effect of the peer support intervention combined with mobile data
18 transmission technologies on the rate of ADR-reporting by PLHIV receiving DTG
19 and/or IPT in Uganda
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Methods

Study setting

Uganda has a tiered healthcare system with different levels of healthcare from the National Referral Hospitals which provide tertiary and super-specialized healthcare, through Regional Referral Hospitals (RRHs), General Hospitals, level IV Health Centers (HC IV), level III Health Centers (HC III), to level II Health Centers (HC II) that progressively offer less scope and breadth of health services to out-patient services[33]. HIV treatment and care is provided from HC III and upwards giving a total of 1,832 accredited centers that provide ART services in Uganda. Uganda adopted the Differentiated Service Delivery Models (DSDM), where stable clients have less frequent clinical assessment visits. In 2019, about 80% (1,466/1,832) of the ART accredited sites and 78% (975,675/1,241,478) of PLHIV on ART had access to the DSDM model. An additional, 12% (114,363/975,675) of clients enrolled on DSDM received ART services from the community through Community Drug Distribution Points (CDDP) and Community Client-Led ART Distribution (CCLAD)[34].

Uganda has an estimated 1.46 million PLHIV, of whom prevalence among people aged 15 to 49 years is 5.8% with women having a higher prevalence (7.1%) than men (4.3%). Among the PLHIV, 93% are aged ≥ 15 years and 60% of the HIV-infected adults are women. In 2019, there were 53,413 new HIV infections of which 40,000 were among adults and 21,000 Ugandans died of AIDS-related illnesses[35]. Following the "Test and Treat" policy for HIV adopted in 2016 and scaled up in 2017, the ART coverage was at 89% in 2019. Approximately 96% of PLHIV on ART are taking first-line regimens and >443,000 PLHIV are on TLD. About 17% of PLHIV are ART-naïve at treatment initiation. In 2019, about 41% of TB patients were HIV-positive and 97% of HIV-positive TB patients were receiving ART[35, 36]. By the end of 2019, 477,190 of PLHIV were enrolled on IPT. Strategies to strengthen pharmacovigilance were instituted as part of DTG/IPT roll-out in the 2020 revised Consolidated Guidelines for Prevention and Treatment of HIV and AIDS in Uganda[16]. The guidelines support ADR identification, monitoring and reporting, particularly for DTG and IPT. Pharmacovigilance sentinel sites were established at 18 sentinel sites (RRHs and Centers of Excellence). These ART-sites received training and ADR-reporting tools. ADRs are reported to the NPC at NDA through a paper-based system, online system, toll-free phone line or through NDA's Med Safety App.

For the current study, the authors have divided the country into four geographical regions to establish a sampling framework that leads to selection of national level representation of health facilities and factors that influence provision of care to PLHIV and their pharmacovigilance-related needs. In each region, two blocks of health facilities with ART-sites will be selected of which one block will implement the intervention and the other will serve as the comparison block of health facilities. Each block will consist of an ART-site at a RRH (tertiary care), a HC IV (secondary care) and HC III (primary care), respectively. Therefore, 12 intervention ART-sites will be matched by level of care and region with 12 comparison ART-sites from the four regions of Uganda.

Study design

The study will employ a quasi-experimental design with pre-post and there-there comparisons to measure the preliminary impact of the peer support intervention on ADR-reporting by PLHIV, **Figure 1**. The study will use both quantitative and qualitative methods to triangulate the research findings. The qualitative research methods aim to understand the barriers and

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3 facilitators to implementing the peer support intervention for promoting ADR detection,
4 reporting and management from the perspective of PLHIV and in the context of their interface
5 with Uganda's healthcare system[37] and thus they will be predominantly implemented in the
6 intervention arm. We will explore the experiences of PLHIV in the utilization of the peer support
7 intervention and elicit their preferences to further refine the intervention and implementation
8 strategy.
9

10 11 The intervention

12 The peer support intervention leverages mobile data transmission technologies (Med Safety,
13 USSD) in addition to traditional pharmacovigilance methods (paper, online, voice call). The
14 peer support mechanism has several layers of supervision from the mentored PLHIV, through
15 peer supporters, peer supervisors, study coordinator to study investigators at the top of the
16 hierarchy, see **Figure 2**.
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19 The PLHIV to be mentored in the intervention arm will be assigned to peer supporters to guide
20 their ART care for 4-months. The peer supporters will constitute a mixed group of lay people,
21 namely; i) expert clients who are PLHIV with more experience in the use of ART and, ii)
22 recognized community health workers (CHWs). Most CHWs in Uganda's HIV programs are
23 expert clients. Thus, it is possible to recruit CHWs all of whom are expert clients. Peer
24 supporters in the intervention arm will guide the mentored PLHIV to report ADRs to NPC and
25 improve the latter's healthcare-seeking behaviour. The PLHIV should own mobile phones.
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28 The PLHIV to be mentored will be identified by verbal communication/ written announcements
29 on noticeboards at the study sites and matched with the respective peer supporters of similar
30 age, gender and proximity of residence. The non-random matching of PLHIV to peer
31 supporters is intended to promote easier and faster bonding of the peer-relationships. Five (5)
32 PLHIV will be assigned to one (1) peer supporter from the same community. A weekly
33 (minimum fortnightly) face-to-face/phone call interaction will be held between a peer supporter
34 and each assigned PLHIV. Thus, a peer supporter will be expected to interact with one PLHIV
35 per day and five PLHIV in five days each week. Each PLHIV to be supported will be introduced
36 to an assigned PLHIV by the research team and focal health facility staff. The procedure for
37 the weekly interaction will be illustrated to the PLHIV-peer supporter pair. The mentored PLHIV
38 and peer supporter will be provided with the telephone contacts of the study coordinator/ focal
39 health facility staff whom they could notify at any time when they want to terminate
40 engagement.
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45 Peer supporters will use one-on-one in-person support blended with mobile phone-based
46 interaction to guide each assigned PLHIV to recognize and report suspected ADRs to NPC.
47 The peer supporter will also administer a short weekly questionnaire to each assigned PLHIV
48 regarding ADR experience in the past 1-week.
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50 This peer support intervention adapts the "humanizing healthcare model" developed by *peers*
51 *for progress*, a group that demonstrates the value and best practices of peer support. The
52 model is based on four functions, namely; assistance in daily management, providing social
53 and emotional support, linking to clinical and community resources and ongoing support[38],
54 see **Figure 3**.
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57 Both the supported PLHIV and peer supporters will be trained on the following aspects: ART;
58 how to live positively with HIV; recognition of suspected ADRs and how to report them via Med
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3 Safety, USSD or traditional methods (paper, online, voice call) to NPC; and about linkage or
4 referral to health facility care e.g. when a serious ADR occurs. The supported PLHIV and peer-
5 supporters will be trained to interact in a manner that ensures confidentiality. The data
6 generated from Med Safety and USSD will be safeguarded according to applicable laws on
7 data protection. The linkage to appropriate care of PLHIV by the peer supporter will aim to; i)
8 promote healthcare-seeking behaviour of the PLHIV, ii) improve the monitoring of HIV
9 treatment (management of serious ADRs, ART adherence, retention in care), iii) enhance
10 timely refill of ART prescriptions and/or, iv) provide for any other special care that PLHIV might
11 require.
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15 Peer supporters will be separately trained and skilled in interpersonal interaction to be
16 responsive to PLHIV and encourage them to identify and report any suspected ADRs. The
17 training components for peer supporters will include care in chronic illness, ART, adherence
18 to ART, ADRs, ADR-reporting, care-seeking, counselling and facilitative supervision. Training
19 for the peer supporters will take up to three days. It will include a one-day didactic session
20 followed by two days of on-the-job, one-on-one training. In addition to being trained, peer
21 supporters will receive supplementary educational materials. Four follow-up
22 supervisory visits/phone calls at two-week intervals will be conducted by the trainers to
23 reinforce the knowledge, skills and attitudes gained by the peer supporters. Each supported
24 PLHIV will receive one-day's training during his/her clinic visit which will include a didactic
25 session and one-on-one discussion in a non-classroom environment. The trainers will be
26 qualified individuals carefully identified by the project team with the requisite knowledge to
27 offer the training and expertise in adult learning and counselling.
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31 The peer support mechanism will have two additional layers of supervision, see **Figure 2**. The
32 first level of additional oversight will be provided by four (4) peer supervisors identified from
33 among the peer supporters at each of the four selected RRHs. Peer supervisors will be
34 seconded by the study sites and collaborating patient safety groups involved in the recruitment
35 of peer supporters. Each peer supervisor will oversee 15 peer supporters in his/her region (10
36 from RRH, 3 from HC IV, 2 from HC III). The peer supervisor will call each peer supporter
37 twice a month. During these 'booster' sessions, the peer supervisor will review, emphasize
38 and re-educate peer supporters on expectations of the intervention e.g. setting and reviewing
39 goals with PLHIV. The second level of oversight will be provided by the project coordinator
40 who will oversee the four (4) peer supervisors whom he/she will meet/call every month. At
41 least one study investigator, mostly the principal investigator, will participate in these
42 meetings/calls. The project coordinator will have the requisite knowledge, skills and
43 competence to train PLHIV and peer supporters. The project coordinator will provide support
44 supervision and counselling to motivate the peer supervisors, peer supporters and PLHIV.
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50 The comparison group

51 PLHIV in the comparison group will be mobile phone owners who will be trained to recognize
52 suspected ADRs and report them to NPC via Med Safety, USSD or the traditional
53 pharmacovigilance methods (paper, online, toll-free voice call) to a peer-supporter, HCP or
54 NPC, see **Figure 4**. Smartphone owners will be guided to install Med Safety for ADR-reporting.
55 PLHIV with non-smartphones or smartphone owners who will not install Med Safety will report
56 ADRs by USSD or the traditional reporting methods. PLHIV in this group will not receive
57 dedicated peer support.
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Study units, participants and selection

Study units and participants:

This study has multiple study units and layers to assess the feasibility of implementation and effect of the intervention on promoting the detection and reporting of suspected ADRs in PLHIV on DTG-based ART and/or IPT in Uganda. From micro to macro-level, the study units include PLHIV receiving DTG-regimens and/or IPT; the pair of PLHIV and peer supporter; the peer supporter; the combination of the PLHIV with peer supporter and ART-site; peer supervisor; the pair of peer supervisor and peer supporter; and the ART-site. At the study ART-site, HCPs and health facility managers will be included. Lastly, the reporting of suspected ADRs by PLHIV, peer supporters, HCPs and ART-sites to the NPC will also be examined.

About 17% of PLHIV are ART-naive, 95% are aged 15 years and older, and 89% receive first-line ART either as treatment-naive or treatment-experienced PLHIV[36].

Eligibility criteria:

Inclusion criteria: Selection of study units will occur at three levels: *First*, eligible PLHIV should i) be aged ≥ 15 years, ii) receive ART at the selected study sites, iii) own a mobile phone (smartphone, basic feature phone) and, iv) provide written/thumb-printed informed consent. Child consent can be given by emancipated minors aged 15 to 17 years in Uganda[39] *Second*, eligible peer supporters (expert clients, CHWs) will be those that are recognized and seconded by the study sites or collaborating patient safety groups. These peer supporters will be those that are attached to the study sites and have already received institutional training in their role as expert clients/CHWs; they should own mobile phones. A focal clinical staff assigned to the study by the health facility administration will approach and recruit the peer supporters. The recruited peer supporters will be screened by the research team to gauge their ability to be peer supporters e.g. the ability to use the Med Safety App/USSD, ability to read and write in English and good interpersonal skills. Satisfactory peer supporters will give written informed consent. Peer supporters will participate only in the intervention arm of the study. *Third*, study health facilities will be selected and enrolled as follows; in each of the four geographical regions, blocks of three health facilities each with an ART-site, including at least a RRH, HC IV and HC III will be created based on the catchment of each RRH. From the created blocks of three health facilities in each region, two blocks will be selected by simple random sampling to participate in the study as the intervention and comparison health facilities, respectively. This will give 24 ART-sites consisting of 12 intervention sites (4 RRHs, 4 HC IVs, 4 HC IIIs) matched by level of care and region with 12 comparison sites (4 RRHs, 4 HC IVs, 4 HC IIIs) selected from the four geographical regions of Uganda.

Exclusion criteria: Exclusion will apply only at the level of PLHIV and CHWs. We shall exclude PLHIV on ART for < 6-months and expert clients/ CHWs who will be unable to commit, from the outset, at least 5-hrs per week to the study for up to 4-months.

Many ADRs happen when starting ART although such PLHIV tend to be unstable on treatment. The priority of this pilot is to understand the dynamics (feasibility and acceptability) of the peer support intervention in a *stable group* of PLHIV on ART (for ≥ 6 months). If found to be feasible, the peer support intervention will be introduced, in future initiatives, to the *unstable group* of PLHIV on ART (for <6 months).

Sample Size and Sampling Considerations

Sample size computation is based on the possible effect of the peer support intervention on the rate of ADR-reporting by PLHIV, with adjustment for clustering. We assume a conservative intra-cluster correlation coefficient of 0.045 and a priori increase of 50% in the rate of ADR-reporting to NDA, from 6 ADR-reports per 100 person-years at baseline[40] to 9 ADR-reports per 100 person-years at end-line evaluation. We assume a standard deviation of 12 ADR-reports per 100 person-years computed from the monthly ADR-reports submitted to NPC for one-year (October 2018 to September 2019). The study is designed to have at least 80% power to estimate an effect size of 1.5. Thus, 126 PLHIV will be required in the intervention arm and 126 PLHIV in the control arm.

Since the caseload for each peer supporter will be 5 PLHIV in the intervention arm, 60 peer supporters (15 from each of the 4 regions) will be responsible for 300 PLHIV on DTG and/or IPT. Thus, the peer support arm will include 300 PLHIV and the control arm 300 PLHIV all of whom should own functional mobile phones (smartphone or non-smartphone or both). Thus, a total of 600 PLHIV will be enrolled; 400 from RRHs, 120 from HC IVs and 80 from HC IIIs.

The PLHIV will be enrolled consecutively until the required sample size is attained. Smartphone owners will be guided to install Med Safety for ADR-reporting. We assume that 7 in 10 PLHIV at the ART-sites will have mobile phones and only one in 10 will possess smartphones[41]. Thus, only up to 10% (or 60) of PLHIV with smartphones will be helped (with maximal support from peer supporters) to download Med Safety. The rest of the 540 PLHIV without smartphones or smartphone owners who will not install Med Safety will report ADRs by USSD or the traditional methods.

Study variables

Primary outcomes: Feasibility of the peer support intervention - attrition rate recorded as the number of study participants who remain in the study until the end of follow-up at 4 months; Number of suspected ADR reports submitted to NPC by PLHIV as measured by questionnaire and data abstracted from the national pharmacovigilance database at baseline and 4 months

Other process/output/outcome variables:

1. Acceptability of the peer support intervention measured using a questionnaire and qualitative interviews at 4 months post-intervention
2. Barriers/facilitators of the peer support intervention measured using a questionnaire during the intervention and qualitative interviews at 4 months post-intervention
3. Fidelity to the peer support intervention measured using a questionnaire and qualitative interviews at 4 months post-intervention
4. Rate of ADR-reporting to NPC by PLHIV as measured by questionnaire and data abstraction from the national pharmacovigilance database at baseline and 4 months
5. Quality of ADR-reports by PLHIV measured by questionnaire and data abstraction from the national pharmacovigilance database at baseline and 4 months
6. Time to ADR-reporting to NPC by PLHIV since enrolment measured by questionnaire and data abstraction from the national pharmacovigilance database during 4 months
7. Time from ADR onset to registration in the national pharmacovigilance database measured by questionnaire and data abstraction from the database during 4 months
8. Health-related quality of life measured by questionnaire at baseline and 4 months
9. Management of ADRs recorded using a questionnaire during the 4 months
10. Number of PLHIV linked to health facilities by peer supporters for ADR management as measured by questionnaire during the 4-month intervention period

11. Health-seeking behaviour measured using a questionnaire at baseline and 4 months
12. Self-efficacy to report ADRs measured by questionnaire at baseline and 4 months
13. Self-reported ART adherence measured by questionnaire at baseline and 4 months
14. Mood (positive/ negative affect) measured by questionnaire at baseline and 4 months

Patient and Public Involvement

Direct involvement of PLHIV in the detection and reporting of suspected ADRs, and patient safety groups in recruitment of PLHIV, will have value in improving the public's awareness of ADRs and the available pharmacovigilance tools (Med Safety, USSD, toll-free voice call, etc.). Together, these will be essential for ensuring that changes to clinical practice to promote patient safety based on our work are acceptable to the public.

The study team will work with PLHIV to assess whether the available pharmacovigilance tools meet their needs, to identify potential improvements and to understand facilitators and barriers to using these pharmacovigilance tools. Wider public input into the refinement of the tools and mechanisms to encourage uptake will add value to our work. This work will also be of value to the wider public as Med Safety can be used to report ADRs to any drug, and users can receive drug safety information directly from NPC.

Data management and statistical analysis

Quantitative data

Data collection and management: Baseline and end-line semi-structured questionnaires will be administered to the PLHIV and peer supporters (expert clients) in the intervention arm and PLHIV only in the comparison arm.

The baseline questionnaire will record socio-demographics (age, sex, monthly income, education level, residence) of all study participants. Clinical details (ART adherence; ADRs; ART-regimen; ART-status i.e. first-line, second-line, third-line; duration on ART; comorbidities) and healthcare-seeking behaviour of study PLHIV will be measured. Data will be transmitted to a password-protected online database via the Open Data Kit (ODK) suite of tools. Participating PLHIV will be asked at enrolment if they experienced suspected ADRs in the 4-months preceding the study. The self-reported suspected ADRs will be corroborated with additional information on documented suspected ADRs from retrospective clinical chart review of the 4-month period prior to study enrolment. The clinical charts will be accessed by the health facility staff.

Additional data collection for the intervention group: On a weekly basis for up to 4-months, peer supporters will inquire from each assigned PLHIV (during a 1 hour face-to-face or phone call interaction) if he/she experienced one or more suspected ADR(s) and if the ADR had any impact on quality of life and/or ART adherence. Peer supporters will document if the ADR(s) was/were reported; and, if reported, by which means (Med Safety, USSD, voice call, other methods). Peer supporters will document all ADRs experienced by the PLHIV during the previous 1-week (using a tool designed to capture the medicines and ADRs); and will guide the PLHIV to report ADRs directly to NPC using the available pharmacovigilance methods. Active surveillance of ADRs linked to DTG and/or IPT will be prioritized but ADRs linked to other medicines will also be documented. PLHIV who experience serious ADRs will be linked directly to the health facilities where they receive ART for ADR management. Peer supporters will refer serious ADR cases to peer supervisors who will, in turn, refer these cases to focal clinical staff assigned to the study by the health facility administration; usually stationed at

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3 triage to connect the cases to clinicians. We will document the management of serious and
4 non-serious ADRs (number of serious and non-serious ADR cases referred for health facility
5 management; actions taken by health facilities in the management of serious and non-serious
6 ADRs e.g. stopping treatment, changing treatment, continuing treatment with adherence
7 counselling, doing nothing, etc.).

8
9 The end-line questionnaire for PLHIV will measure their healthcare-seeking behaviour, linkage
10 to care for ADR management and adherence to ART. The PLHIV will also be asked to report
11 their experiences while receiving peer support to assess the intervention's feasibility and
12 acceptability (e.g. user satisfaction). The study will also assess the participants' experiences
13 when using the various pharmacovigilance methods (Med Safety, USSD, toll-free voice call,
14 etc.). We shall assess the ease of use, language and costs of the available pharmacovigilance
15 methods (Med Safety, USSD, toll-free voice call, etc) alongside peer support.
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19 **Med Safety App and USSD data collection:** PLHIV will submit ADR-reports via Med Safety
20 and/or USSD with initial assistance from peer supporters. Each app-based ADR-report will be
21 automatically converted into the standard E2B (R2) format prior to its receipt in the Vigilance
22 Hub[42]. The app is hosted by Uganda's NDA which manages the reported ADR data. For
23 USSD reporting, PLHIV will dial the USSD code and answer a set of questions. The data will
24 be stored in real-time on a dashboard accessible to the project staff.
25

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27 **Statistical analysis:** All ADR-data in both the national and project databases and received
28 from the study sites during the study period will be exported into Stata version 15.0 MP for
29 descriptive analysis – frequencies, proportions and their 95% confidence intervals (StataCorp
30 LLC, College Station, Texas). Duplicate ADR-reports will be identified and analysed
31 accordingly. Summary estimates will be reported by pharmacovigilance method (Med Safety,
32 USSD, toll-free voice call, etc.).
33

34
35 To assess the feasibility to retain peer supporters and PLHIV, we shall compute the attrition
36 rate which is the proportion of study participants who remain in the study until the end of follow-
37 up at 4 months.
38

39
40 The number of suspected ADRs reported to NPC by the PLHIV overall and in each study arm
41 will be described by subgroup: serious ADR (yes/no); peer supporter guided (yes/no); DTG-
42 linked (yes/no); IPT-linked (yes/no); DTG/IPT-linked (yes/no); linked to other medicines
43 (yes/no); level of reporting (PLHIV, peer supporter, HCP, health facility) etc.
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46 The rate of ADR-reporting (m_a) by PLHIV (per site, overall) per completed-month (m_1) of follow-
47 up will be computed as follows: $m_a = [n_a \text{ reports}/(N_a \text{ completed-months of follow-up})]$, where
48 n_a is the number of reported ADRs and N_a the number of completed-months of follow-up.
49 Reporting rates of same-day ADR-onsets will be documented; and time from ADR-onset to
50 registration in the national database recorded for all other events[33]. Time to ADR-reporting
51 to NPC for a PLHIV will be the time from the day a PLHIV is enrolled into the peer support
52 intervention to the time he/she reports the first suspected ADR to NPC. Time-to-event data
53 will be analysed by survival analysis techniques.
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56 We will explore the influence of level of care on the uptake of the peer support intervention in
57 Uganda's healthcare system - such as whether rolling it out at primary care facilities or tertiary
58 hospitals influences uptake.
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3 The change in outcome measures (e.g.) between pre- and post-intervention in PLHIV will be
4 assessed using a linear mixed model with random effect for peer supporter. Random effect
5 will be included to account for clustering of PLHIV with peer supporters. The ICC will be
6 estimated from this model. Since supporters are a mixed population of expert clients and
7 CHWs, a stratified analysis will be conducted. To aid the planning of future randomized
8 controlled trials from this pilot's data, we shall report effect sizes.
9
10

11 Qualitative data

12 **Data collection:** Post-intervention, a combination of focus group discussions (FDGs), in-
13 depth interviews (IDIs) and Key Informant Interviews (KIIs) will be conducted with purposively
14 selected study participants. A lead qualitative researcher will be assisted by two well-trained
15 research assistants. Semi-structured interviews informed by the Consolidated Framework for
16 Implementation Research (CFIR)[43] will be used to elicit participants' perspectives on the
17 facilitators and barriers to implementing the peer support intervention at four purposively
18 selected health facilities.
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21 We will conduct six FDGs with three categories of PLHIV in the intervention arm; two with
22 those enrolled in Community Drug Distribution Points (CDDPs), two in Community Client-Led
23 ART Delivery (CCLAD) and two in facility-based ART delivery models.
24
25

26 A total of 12 IDIs will be conducted with peer supporters (expert clients, CHWs) attached to
27 each of the three ART delivery models; a) CDDP, b) CCLAD, c) Facility-Based, see **Figure 5**.
28
29

30 Four KIIs will be conducted with HCPs/facility managers with insights in the implementation
31 experience of the peer support intervention at their respective host facilities from an
32 organizational-context.
33

34 As a first step, participants will complete a written informed consent form. We will then capture
35 baseline characteristics: age, gender and educational level. A CFIR-informed semi-structured
36 guide will be used for the interviews. The semi-structured guide will explore participants'
37 experiences with the peer support intervention, their preferences and suggestions for
38 improvement of the intervention and the challenges encountered in using USSD and/or Med
39 Safety. On average, the duration of the FDGs and IDIs will be approximately 45-60 min. The
40 FDGs, IDIs and KIIs will be conducted until theoretical saturation is reached. Theoretical
41 saturation means that no new knowledge is generated and all aspects of a theory are covered.
42 All the data generated from the focus groups and interviews will be explored for themes and
43 sub-themes.
44
45
46

47 **Guiding qualitative analytical framework:** The CFIR will be adopted as the overall guiding
48 analytical framework for this study. The CFIR is a comprehensive 'meta-theoretical'
49 implementation research framework compiled from more than 20 sources and is cross-cutting
50 in more than 13 scientific disciplines; it guides systematic assessment of multi-level
51 implementation settings to identify factors that influence intervention implementation and
52 effectiveness [44]. The CFIR informs the conceptualization of this study, will guide the
53 development of data collection tools and will serve as an overarching deductive thematic
54 framework in analysis of study findings and the overall synthesis and interpretation of results
55 for this study. The CFIR is widely-applied because of its multi-level, 'ecological' dimensions
56 on multi-faceted influences on healthcare intervention implementation outcomes[45]. The
57 CFIR has been applied across diverse interventions and varied content fields[44].
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3 More specifically, the CFIR-derived domains that will guide the study are the following:

4 *Intervention characteristics:* Implementation of the peer support intervention could potentially
5 be impacted by factors including its perceived effectiveness in ADR-reporting, relative
6 advantages over alternative reporting approaches, adaptability in varied resource-constrained
7 settings, trialability, complexity, design quality and presentation, and cost-effectiveness.
8
9

10 *Outer setting:* external influences on implementation of peer support may include external
11 policies and incentives, socio-cultural belief systems, peer pressure dynamics and socio-
12 economic context.
13

14 *Inner setting:* characteristics of the implementing organization (or host health facility) such as
15 organizational culture, the relative priority assigned to the peer support intervention (including
16 funding support), presence of intervention 'champions', availability of supportive administrative
17 or physical infrastructure, congruence with host organization's mission and vision, quality of
18 leadership support and implementation climate(s).
19
20

21 *Characteristics of individuals:* Patients' beliefs, knowledge, level of income, self-efficacy, and
22 personal attributes that may affect the implementation and uptake of the peer support
23 intervention.
24
25

26 *Process of implementation:* Influences on implementation outcomes may derive from different
27 implementation phases involved in roll-out of the peer support strategy such as degree and
28 quality of involvement of primary beneficiaries in designing the intervention, planning,
29 execution, degree of effectiveness of monitoring and evaluation strategies and presence of
30 key intervention stakeholders and influencers including opinion leaders, stakeholder
31 engagement, and intervention champions.
32
33

34 The CFIR will be used to identify barriers and facilitators of the peer support intervention for
35 promoting ADR-reporting by PLHIV.
36

37 **Data analysis:** Our qualitative data analysis will follow the procedures recommended by Miles
38 & Huberman (1994)[46]. Interviews and FGDs will be audio-recorded and transcribed verbatim
39 into text transcripts by three research assistants (and translated into English where
40 necessary). Data will be analysed, in an iterative process, involving four major steps:
41
42

43 a) *Data familiarization:* An experienced qualitative researcher and one other investigator will
44 read the interview transcripts multiple times for data familiarization.
45

46 b) *Developing a coding framework:* We shall adopt the five CFIR-derived domains
47 (*Intervention characteristics, outer setting, inner setting, characteristics of individuals, and*
48 *process of implementation*) as an overarching deductive thematic framework, combined with
49 an inductive approach based on the data[47].
50

51 c) *Data abstraction:* The coded data will be categorized into thematic categories.
52
53

54 d) *Overall interpretation and synthesis:* Our overall synthesis of study findings will adopt a
55 team-based process of peer-debriefing involving all investigators to resolve disagreements in
56 interpretation of study findings.
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Quality assurance

To ensure uniform study procedures and high-quality data, all research assistants recruited for the study will receive face-to-face training on the following: the informed consent process, participant interviewing techniques, confidentiality issues, pharmacovigilance, use of the Med Safety App, use of the USSD, ADRs, use of the Open Data Kit (ODK) software for data entry into an online password-protected database; and qualitative and quantitative study designs, among others.

The FGDs and KIs will be led by an expert in qualitative research. Research assistants with prior training in qualitative research methods will also be hired for the qualitative study component. All research assistants will receive face-to-face training in both qualitative and quantitative research methods.

Questionnaire data will be transmitted through ODK to an online database by the research assistants while still in the field. The study statistician will check the online data for integrity and contact field staff as soon as possible while still in the field to correct any data entry errors. Prior to entry into ODK, all research assistants shall be required to cross-check the data on study questionnaires to eliminate errors and ensure data completeness.

Results uptake and use

Outcomes/Impact/Outreach: The peer support intervention is expected to increase patient-reporting of ADRs to NPC. It is anticipated that the patients will subsequently; i) find it easier and faster to report ADRs (including DTG- and IPT-related reactions) anywhere and at any time using their mobile phones and, ii) receive medication-safety alerts directly from NPC to their phones. We expect this project to promote pharmacovigilance in Uganda by improving; i) the exchange of medication-safety information between patients, peer supporters, HCPs and NPC, ii) the awareness of pharmacovigilance by patients and the public through the mobile phone and other awareness campaigns and, iii) the rate of ADR-reporting by patients.

Potential impact on policy or programs: This project could foster the increased involvement of patients in pharmacovigilance activities and improve the efficiency of pharmacovigilance systems in Uganda with real-time monitoring of DTG and INH safety in PLHIV in the first instance, thus, increasing the volume of analysable data for quick decision-making by both clinicians and policy makers.

We expect to promote collaboration between consumers/public and the NPC, national AIDS Control Program - Ministry of Health and the National TB and Leprosy Control Programme (NTLP). The accumulation of relevant medication-safety data from spontaneous and active ADR-reports permits robust detection of safety signals at the national and international levels.

Scalability: After this pilot project, we expect the peer support intervention to be tested in a nationwide randomized controlled trial; and the USSD and Med Safety App to be modified accordingly and implemented at all 1,832 ART-sites in Uganda to complement the existing active and passive pharmacovigilance methods for ART and TB treatment. We hope to embed peer support in routine pharmacovigilance practice to promote the detection and reporting of ADRs by PLHIV in Uganda. The Med Safety App is available in English and will be subsequently translated into other local languages according to need.

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2
3 The USSD and Med Safety are potentially invaluable tools for the pharmacovigilance of drugs
4 used for other diseases e.g. non-communicable diseases like cancers, diabetes mellitus,
5 hypertension etc.
6

7
8 Peer support, USSD and Med Safety will be scaled-up to support spontaneous ADR-reporting
9 in both public and private health facilities at all levels of healthcare ranging from hospitals,
10 medical centres and clinics to pharmacies and drug shops, not least, the general public.
11

12 The pharmacovigilance data at NPC could be linked with the patients' clinical data at ART-
13 sites, stock consumption data from the Supply Management Chain system; and the electronic
14 Health Management Information System. Machine learning/artificial intelligence analytical
15 techniques could then be used on big data in the near future to foster improved systems.
16

17
18 *Sustainability:* Peer support to promote the detection and reporting of ADRs by PLHIV can be
19 embedded in the HIV/AIDS program of Uganda just as community engagement programmes
20 have been successful in Maternal and Child Health programmes; and are being rolled out in
21 the COVID-19 Community Engagement Strategy and the Young people and Adolescent Peer
22 Support Model for improving HIV care and treatment outcomes for Adolescents and young
23 PLHIV of 2019 in Uganda[48, 49]. The USSD and Med Safety will be integrated into NPC's
24 routine pharmacovigilance functions to complement existing pharmacovigilance methods.
25 Regional pharmacovigilance centres have pharmacovigilance focal persons who will continue
26 to support the NPC. All ADR-reports received by NPC are reviewed and submitted into an
27 existing national medication-safety database. The equipped peer supporters are a valuable
28 resource for scaling up peer support in the ART-sites after the study is concluded.
29
30

31
32 The USSD interface and Med Safety will be freely available. Med Safety can be downloaded
33 and installed from both Google Play and Apple iOS stores. NPC pays the salaries of its full-
34 time pharmacovigilance staff who receive and process the reported medication-safety data.
35

36 The research collaboration between Makerere University's Department of Pharmacology,
37 Department of Pharmacy, NPC, ACP, MHRA and other stakeholders will continue to source
38 for additional research grants to support the future scale-up of evidence-based digital
39 pharmacovigilance in Uganda. The findings could be helpful to other countries to inform their
40 own pharmacovigilance activities.
41
42

43 **Dissemination**

44
45 Med Safety users will immediately benefit from the app's two-way communication functionality
46 as they will receive medication-safety alerts from NPC in addition to their submission to NPC
47 of ADR-reports.
48

49 We plan to present the project's research findings at local stakeholders' workshops organized
50 to ensure the balanced representation of HCPs, administrators, policy makers, patient safety
51 groups, the public and other local and international partners. At least one policy brief will be
52 prepared from this work. We shall also disseminate the results at three or more local and
53 international conferences, engage the public through local and international television
54 channels, and through social media (Facebook, Twitter, WhatsApp, blogging etc.). We shall
55 publish at least two manuscripts in internationally-recognized peer-reviewed journals.
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Ethical and environmental considerations

The study received ethical approval from the School of Health Sciences Research and Ethics Committee at Makerere University College of Health Sciences (MAKSHSREC-2020-64); and was registered with the Uganda National Council for Science and Technology (HS1206ES). Administrative clearance will be obtained from participating ART-sites and written/thumb-printed informed consent from participating PLHIV and expert clients/CHWs. We consider the introduction of USSD and Med Safety for ADR-reporting to be a minimal risk intervention. However, we shall remind participants to mind their own confidentiality which could be lost due to phone sharing. On the contrary, participants in the intervention group could potentially benefit from peer-support. We received a waiver of consent from the ethics committee to access anonymized clinical and medication data of PLHIV at the health facilities. The data will be extracted by staff of the respective health facilities. Applicable international laws on data protection will be observed as well as the Data Protection and Privacy Act, 2019 of the Republic of Uganda[50].

Risk management

Small number of patients ($\leq 10\%$) expected to own functional smartphones: Our main goal is to demonstrate that Med Safety can be downloaded and used by PLHIV, which we can achieve without the requirement for strict sample size and power calculations. Also, we shall use the USSD which can work on both basic low-tech mobile phones and high-tech smartphones.

Duplicate ADR-reports: Duplicates will be identified by the NPC staff and study statistician.

Loss to follow-up of peer supporters and PLHIV: A major goal is to demonstrate the feasibility of peer support for PLHIV to get involved in ADR-reporting. The study will provide preliminary data on the magnitude of loss to follow-up to be expected in future studies.

Compromise in data quality by the research assistants: The research assistants will be trained by the study team. Questionnaire data will be transmitted online immediately using ODK – thus giving a chance to the centrally located statistician to verify data integrity.

COVID-19: We shall observe the SOPs of social distancing, washing hands and wearing masks by study participants and investigators to minimise the risk of spreading COVID-19. The pandemic could limit face-to-face contact but is also an opportunity to show how more remote engagement can support pharmacovigilance in a developing country setting. Remote engagement could be more cost-effective to support participants through phone calls and other forms of online interaction.

Collaboration

MHRA adapted Med Safety for Uganda with NDA's approval. The NPC staff at NDA, where NPC is located, will participate in this project. Involvement of the ACP in this pharmacovigilance project will promote the integration of peer support-driven pharmacovigilance in the HIV care and treatment programme of Uganda. The Department of Pharmacology & Therapeutics and Department of Pharmacy, Makerere University conceived this project and will coordinate the study. The WHO contracted MHRA to adapt the app for Uganda and will, together with UMC, provide technical support.

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5 version of the manuscript. All authors read and approved the final manuscript.
6

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12

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14 are responsible for the views expressed in this publication and they do not necessarily
15 represent the decisions, policies or views of WHO.
16

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18

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20

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22

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Figures

Figure 1. Before-after and there-there quasi-experimental study design for a peer support intervention to improve adverse drug reaction reporting by people living with HIV in Uganda

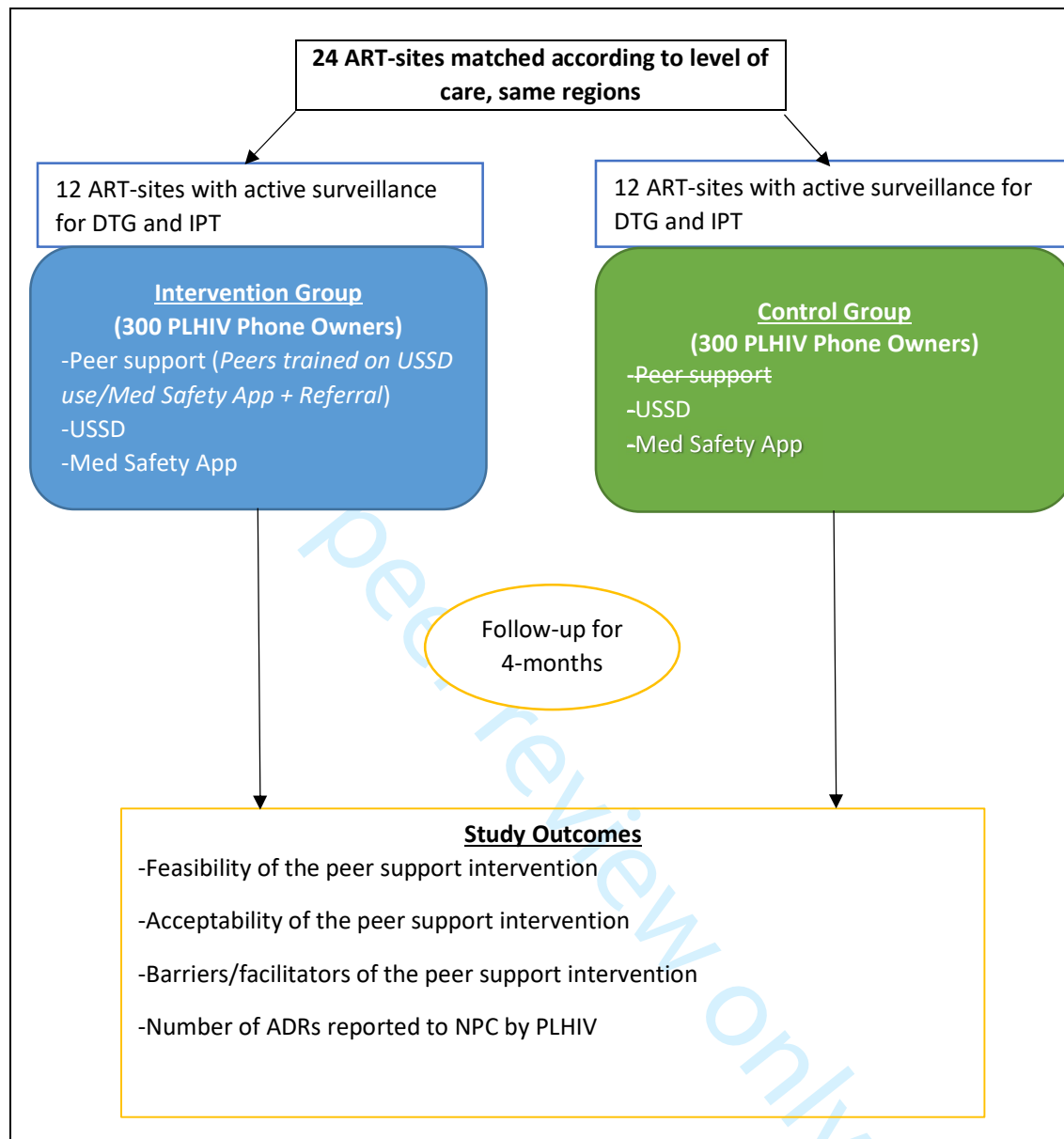
Figure 2: Layers of supervision in the peer support mechanism

Figure 3. Four key functions of the humanizing healthcare model for peer support as adapted from the framework by Peers for Progress

Figure 4. Intervention and comparison groups with two-way comparisons (before-after for each group (A&C, B&D), and between groups after intervention (C&D).

Figure 5. The five Differentiated Service Delivery models of HIV and TB care in Uganda, 2017.

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Figure 1. Before-after and there-there quasi-experimental study design for a peer support intervention to improve adverse drug reaction reporting by people living with HIV in Uganda

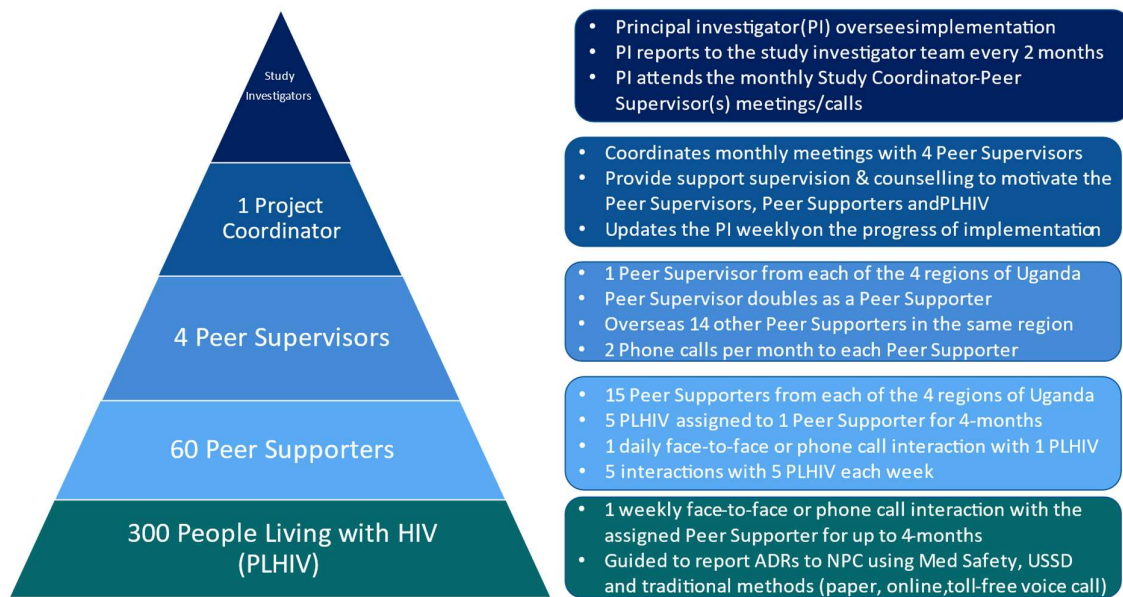


Figure 2. Layers of supervision in the peer support mechanism



23 *Source: Peers for Progress, Global Evidence for Peer Support; Humanizing Healthcare (September 2014)*

24 **Figure 3.** Four key functions of the humanizing healthcare model for peer support as adapted from
25 the framework by Peers for Progress
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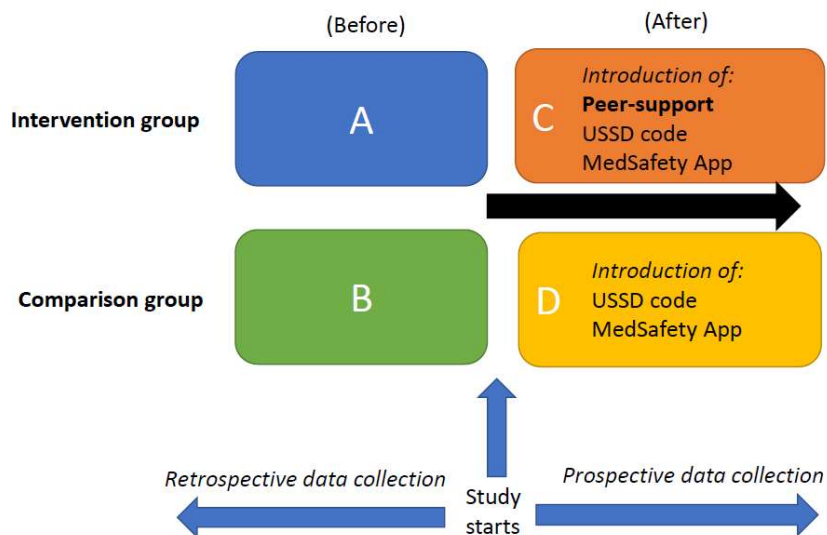
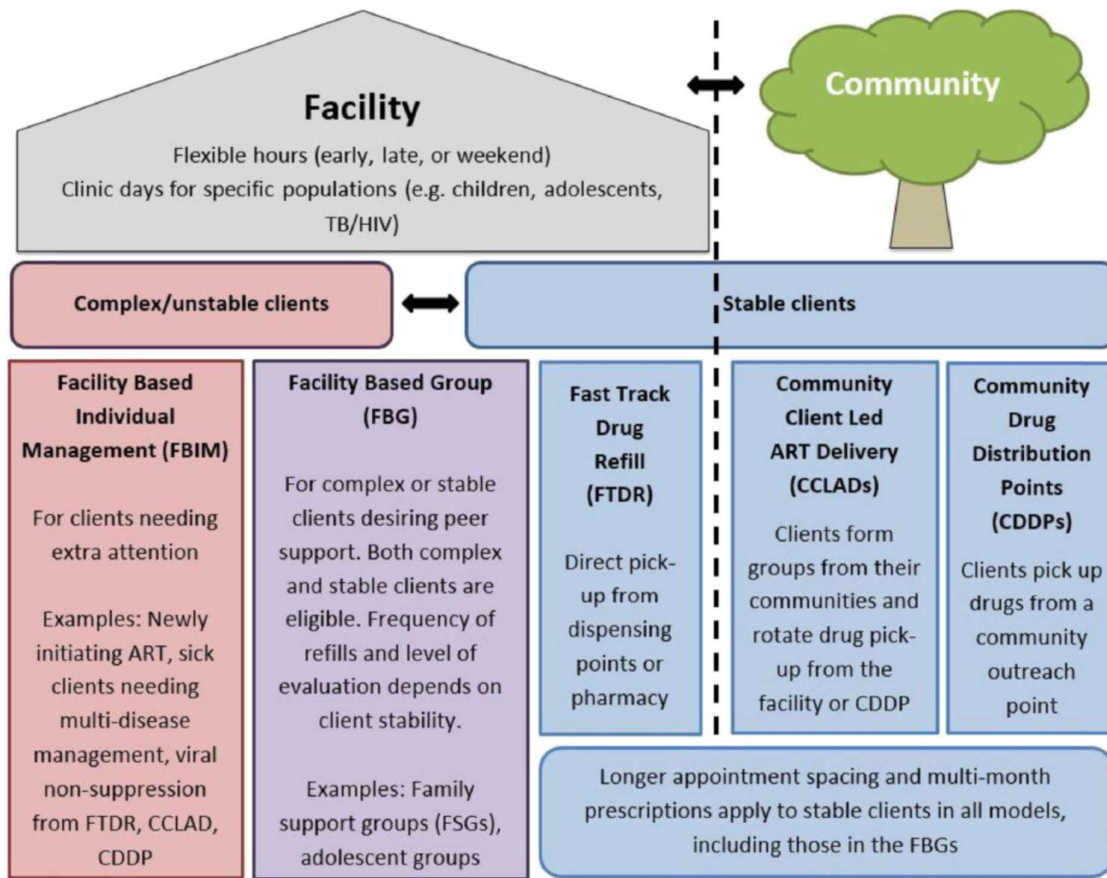


Figure 4. Intervention and comparison groups with two-way comparisons (before-after for each group (A&C, B&D), and between groups after intervention (C&D)).



Source: Ministry of Health, *Implementation Guide for Differentiated TB Services in Uganda* (June 2017).

Figure 5. The five Differentiated Service Delivery models of HIV and TB care in Uganda, 2017.