Research Article

Home Delivery of Antiretrovirals for HIV Clients amidst Covid-19 and Insecurity Challenges: A Protocol for a Randomized Controlled Trial

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Abstract

Background: Insecurity and Covid-19 has affected access to antiretroviral agents and it has resulted in suboptimal adherence to the antiretroviral therapy which could impact negatively on the overall treatment outcomes.

Objective: This study will evaluate the effectiveness,

cost-benefit, and feasibility of a home-based antiretroviral delivery model in Anambra State, Nigeria.

Method/Design: The study is a randomized, non-blinded, controlled, and parallel-group trial, which will be conducted in two HIV treatment hospitals in Anambra State, Nigeria. Participants will be randomized into the intervention and control arm. Home delivery personnel will be trained to deliver the ARV drugs at 3 monthly intervals to the homes of those in the intervention group while those in the control group (Facility-based services group) will receive ARVs at the HIV treatment hospital. The study was approved by Nnamdi Azikiwe University Teaching Hospital Health Research Ethics Committee (NAUTHHREC) (NAUTH/CS/66/VOL. 13/VER III/ 23/2020/011) on 02/10/2020 and the trial registration number, from Pan Africa Trial registry, is PACTR202004535536808 approved on 08/04/2020, http://www.pactr.org/PACTR202004535536808 The interim analysis will be done on the 12th month and the final analysis will be done on the 24th month.

Results: The interim analysis will be done on the 12th month and the final analysis will be done on the 24th month.

Conclusions: The results of this study could provide the rationale for a larger study involving various geo-political zones in Nigeria to examine the effectiveness of the home delivery model.

Keywords: HIV; ARV; Nigeria; Home delivery; COVID-19; Pandemic

Abbreviations: AIDS: Acquired immunodeficiency syndrome; ARV: Antiretroviral therapy; HIV: Human immunodeficiency virus; RCT: Randomized controlled trial; SPSS: Statistical Package for the Social sciences; VL: Viral load; WHO: World Health Organization; NACA: National Agency for Control of AIDS; SIDSHAS: Strengthening Integrated Delivery of Services on HIV/AIDS; CARC: Community Antiretroviral Refill Club; C-PARP: Community Pharmacy Antiretroviral Refill Programme; HAART: Highly Active Antiretroviral Therapy; HDP: Home delivery Personnel; PLHA: People living with HIV/AIDS

1. Introduction

Eradication of human immunodeficiency virus infection (HIV) offers a huge opportunity to establish a healthy world for the future generation [1], so far, in the past 20 years, enormous global progress has been made against HIV. Success in the fight against HIV has been seen from 2002 to date where the death rate due to AIDS has reduced to 61% globally and the rate of new infections has been reduced by 41% [2]. Unfortunately, setbacks are now been seen as a result of challenges due to insecurity and COVID -19 pandemic, especially in many low-income countries which is the hardest hit of HIV epidemics [2-6]. Poor access and suboptimal adherence to high active antiretroviral therapy (HAART) have a significant impact on the overall treatment outcomes because of the chronic nature of the disease [7]. Hence, continuous access to HIV treatment is very important to achieving the possible eradication of this public health issue [8]. It is worrisome that Africa constitutes about sixty-seven percent (67%) of the global disease burden [9], with about 1.9 million people living with HIV in Nigeria [10]. Nonetheless, only about sixty percent (60%) of the affected adults had access to antiretroviral therapy (ART) in 2019 but a

lesser value was recorded in 2020 due to insecurity and COVID 19 challenges in the country and these disruption patterns tend to reverse the progress made in the fight against HIV[2].

Insecurity has since remained a global problem and has threatened every aspect of development in the world especially in Nigeria [11, 12]. A few years ago, insecurity, banditry, and kidnapping have soared and have continued to have a destructive effect on the Nigerian economy with an overwhelmingly negative impact on the health sector and had since worsened health indices [11]. This is mostly due to inter-connecting religious, ethnic, political, and regional groups in the country [11-14]. The concept of insecurity is cross-cutting and multi-dimensional which has been subject to debates [11-13]. There are different views on insecurity, and some scholars associate it with how it affects individual lives and existence [11]. But Achumba et.al. in 2013 [11, 14] defined insecurity as a state of being subject to danger, exposure to risk, or anxiety i.e a person is said to be secured when such person is not being exposed to any form of danger or risk of physical or moral aggression, accident, theft or deterioration [11, 13]. However, the effect of insecurity on access to HIV care has not been studied in Nigeria but intervention to mitigate such challenges has been applied in some aspects.

In 2020, the world stood still for the COVID-19 pandemic and it impacted the world beyond imagination [2]. The COVID-19 is also known as the coronavirus, It is an ongoing pandemic of corona-virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [15]. It was first identified in December 2019 in Wuhan, China [16] and to date, it has infected more than 135 million people, killed over 2.9 million people, and is projected to plunge up to 115 million people into extreme poverty [2]. Going by the 2020 target, there is a deficit of forty percent of the population of people living with HIV who had access to antiretrovirals (ARV) due to the COVID-19 pandemic [10, 11, 12]. In 2015, the World Health Organization (WHO) modified its CD4 cell count threshold in the treatment guidelines and recom-mended a test-and-treat strategy for all persons living with HIV [17]. This development substantially increased the number of people on ART [18] and with the resultant increased cohort of stable patients; it ensued a huge problem on the already burdened health system, especially in most developing count-ries. Conveniences, long waiting time to receive care and transportation costs were identified as challenges to achieving optimal care in HIV/AIDS management [19, 20]. Similarly, in Nigeria, a report showed that long distances to the service delivery points, transport costs, as well as long waiting times, and in addition insecurity and COVID 19 Pandemic have been identified as barriers to accessing antiretroviral agents in the country [2, 21, 22].

In April 2021, a recent survey by Global Fund showed the extent to which COVID-19 has disrupted health service delivery; it revealed a major decline in HIV care (40%) in over 500 health facilities across Africa and Asia [2]. In line with this, they recom-mended that adaptive mechanisms to increase access to care should be adopted such that stable clients access their therapy conveniently and affordably without necessarily visiting the hospital for HIV care [23, 24]. Delivery of antiretroviral therapy to patients' homes or close to their homes has the potential of

improving adherence to therapy and viral load outcomes due to a significant reduction in waiting time and decongested healthcare facilities [24]. This is seen in the hub and spoke model of differentiated care, where HIV treatment hospitals provide HIV services through established linkages with several secondary facilities within a network, and patients are referred to those services when the indications for such arises [25-28]. Services provided by the secondary facilities include HIV counseling and testing (HCT), ARV re-fill, adherence counseling, and treatment of simple opportunistic infections (OIs) [25-29]. This approach has been successfully applied in some facilities in the UK [30]. Therefore, the development of new and innovative ways to increase access to antiretroviral therapy that would decongest health facilities is of utmost importance [31].

1.1 Study rationale

Different strategies to improve access to ARVs have been piloted by the Strengthening Integrated Delivery of Services on HIV/AIDS (SIDSHAS) in Nigeria. Among these strategies are, the Community Antiretroviral Refill Club (CARC) for patients living in remotes areas with a particular interest in the riverine areas and the Community Pharmacy Antiretroviral Refill Programme (C-PARP) [20]. These programs are targeted at reducing visits to the hospitals by stable clients to decongest the hospitals. Also in response to the disruption caused by COVID-19, countries, and communities are devising new, innovative, and adaptive approaches to enable services to be implemented safely which in the long run will mitigate the negative impacts of COVID-19 on HIV services [2].

1.2 Study objectives

This study is designed to assess the effectiveness, client satisfaction, willingness to pay, and cost-benefit of home-based antiretroviral delivery services in Anambra State, Nigeria.

2. Methods

The SPIRIT guideline was used in reporting the research [32].

2.1 Study design

The study will be a randomized, controlled, and parallel-group balanced (1:1) trial conducted in two facilities in Anambra State, southeast Nigeria. The study aims to evaluate the effectiveness of the antiretroviral home delivery strategy in achieving undetected viral load and the SPIRIT figure was used to illustrate the timeline for the trial (see Figure 1). Participants that meet the inclusion criteria in these two hospitals will be randomly assigned to the intervention or control arm (see Figure 2).

	Study period																							
Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Enrolment																									
SCBH																									
Eligibility Criteria	X	x	x																						
Randomization			x																						
Informed consent	X	x	x																						
IMH																									
Eligibility Criteria	X	x	x																						
Randomization			x																						
Informed consent	X	x	x																						
Baseline Assessment																									
SCBH																									
Viral Load	X	x	x	x																					
Case form	X	x	x	x																					
IMH																									
Recruitment	X	x	x	X																					
Viral Load	X	x	x	x																					
Case form	X	x	x	x																					
Intervention																									
SCBH																									
ART Home delivery	X			X			X			x			X			x			X			X			
Structured interview	X			X			X			X			X			X			X			X			
Viral load assessment							X			X			X			X			X			X			
Case form	X			x			x			X			x			X			x			X			
IMH																									
ART Home delivery	X			X			X			X			X			x			X			x			
Structured interview	X			X			X			X			X			X			X			X			
Viral load assessment							X						X						X						
Case form	X			x			X			X			x			X			x			X			
Exit from trial																									
SCBH																									
ART Home delivery																									X
Structured interview																									X
Viral load assessment																									x
Case form																									X
IMH																									
ART Home delivery																									X
Structured interview																									X
Viral load																									X
Case form																									X

Figure 1: Trial Schedule.

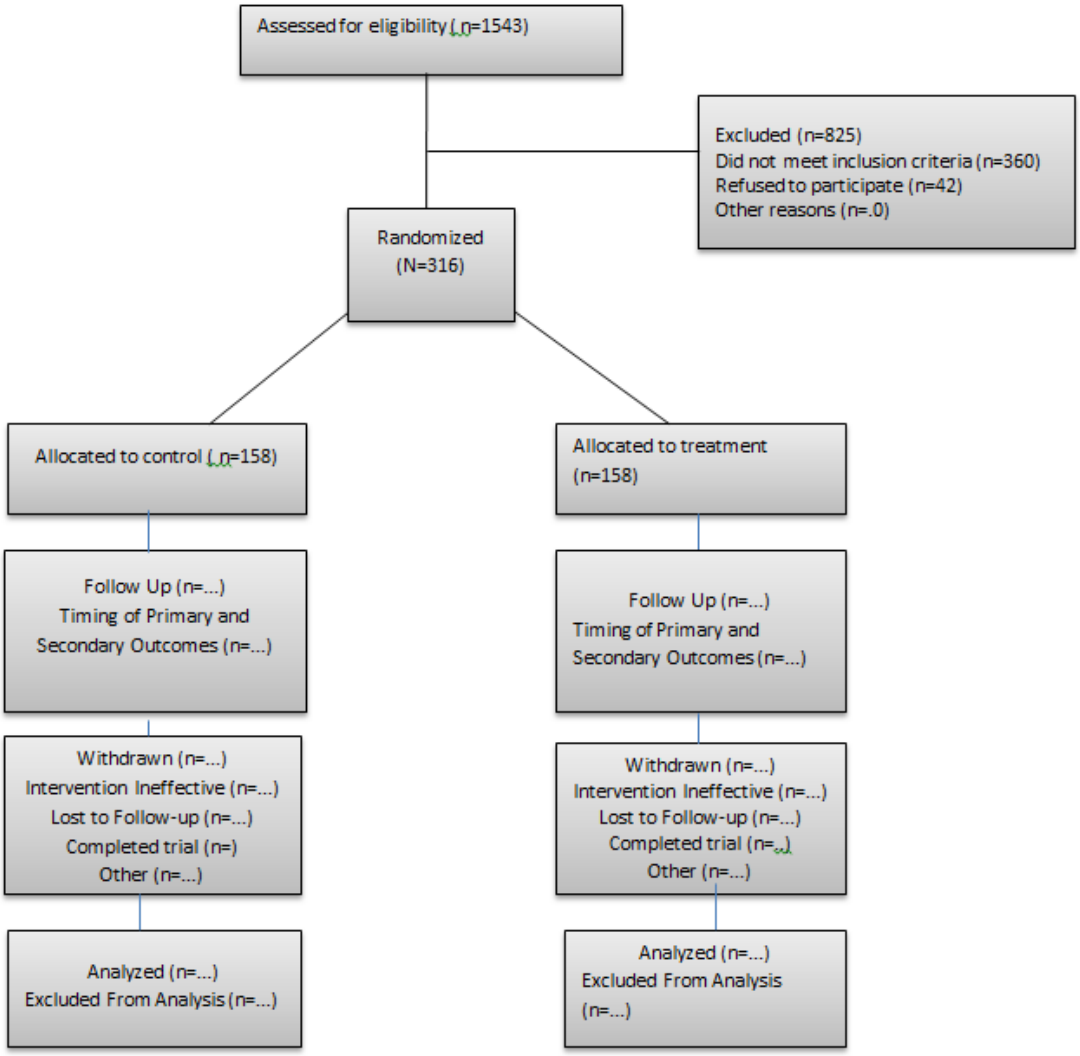

Figure 2: Flow diagram for the Randomized control Trial.

2.2 Study setting

The study setting will be in Anambra state which is one of the five states in the south-eastern geopolitical zone in Nigeria. It is bounded in the northeast by Enugu state, in the east by Enugu and Abia states, in the west by Delta state while in the South and Northwest by Imo and Kogi states respectively. The State is mainly inhabited by Igbo-speaking people who are mostly Christians. Most members of the population are farmers, civil servants, artisans, and businessmen, and women [33]; with a projected population of approximately 4,177,828 (50.7% males and 49.3% females) [34]. Interestingly, about 60.5% of these populations are of ages 15-65 years [35]. Awka is the state's capital and there are 21 local government areas in the state out of which five are urban; five are semi-urban while eleven are rural [35] and the state has an HIV prevalence rate of 2.4% [33].

2.3 Eligibility criteria

Inclusion criteria include all stable participants who

commenced ART for ≥ 6months and have suppressed viral load of ≤ 1000 copies per milliliter of blood. Participants will be excluded if they: were pregnant at the time of enrolment, aged < 18years, were defaulters (i.e. those with missed appointments), had undetected viral load, or viral load <20 copies per milliliter of blood, withdrew consent, and reside outside the state.

2.4 Intervention

Enrolled participants will be directed to the research assistant responsible for introducing the study to the enrolees and they will consent to the study by signing the consent form. Those that give their consent will be sent to the physician after collecting information that will aid home delivery of their drugs including delivery points, preferred day of the week, and most available phone numbers among others. The physician will then, examine the participants' latest viral load from his/her folder and then request a baseline viral load.

Based on the physician's recommendation that an enrolled participant qualifies for home delivery, the home delivery personnel (HDP) will deliver a three-month pre-packaged ARV in a suitable package form with a participant identifier to the participant's chosen delivery point using a delivery motorcycle. The delivery points are jointly decided by the participant and the HDP and the drugs are to be delivered in a way to ensure confidentiality. Participants in the intervention arm will be advised to visit the hospital every six months for viral load and CD4+ cell count unless there is a problem requiring the physician's attention. After each delivery, the HDPs will report back to the physician who then decides on whether to schedule the patient on appointment. Participants in the intervention arm will be provided with a phone number to call in case of emergency or urgent consultation needs before the next appointtment schedule. The participant will also be referred to Nnamdi Azikwe Teaching hospital for further care in a case of non-negligent and/or harm and it will be reported to the Nnamdi Azikiwe University Teaching Hospital Ethics Committee and National Agency for Food and Drug Administration (NAFDAC) pharmacovigilance center. In the control arm, the participants will receive their drugs in the HIV treatment hospital as usual but assess the viral load and CD4 count every six months as in the intervention group. Routine data will be collected and the patient is at liberty to withdraw from the trial at any time.

2.5 Home delivery personnel training

The community health extension worker (4 staff, who are also staff in the hospital) will serve as the home delivery personnel (HDP), and they will undergo a 5-day training based on the following guidelines: (1) the National ART training curriculum, (2) World Health Organization (WHO) guideline on management of stigma, (3) World Health Organization consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach and (4) WHO community home delivery manual. The HDPs will be trained on how to maintain utmost confidentiality when delivering the medication. They will also be trained on how to interview the participants and monitor for adherence to antiretroviral therapy during the drug delivery. The training will be carried out by an expert on HIV services.

2.6 Outcomes

The primary outcome measure will be the difference

between the HIV viral load suppression from ≤ 1000 copies per milliliter of blood to undetected viral load at the baseline, at 6, 12, 18, and 24 months in both the intervention and the control arms. The secondary outcome will measure patient satisfaction, the patient's willingness to pay, and the cost-benefit of the home delivery model.

2.7 Sample size

The sample size for this study was calculated using a web-based Sample Size Calculator of the Clinical and Translational Science Institute, University of Califonia, San Fransico [36]. The sample size calculation was based on the proportion of participants with viral load suppression of less than or equal to 1000 copies per milliliter of blood. Based on a two-sided significance level of 5% and assuming a standard deviation of 50% (increase in undetected viral load in the intervention arm compared to the control arm), the outcome in the population to be 50% and an effect size of 0.5, a minimal sample size of 264 participants was calculated to be appropriate for the study. To account for possible dropouts and loss to follow-up, an extra 20% of the calculated sample was added to the minimal sample size of 264. This resulted in a sample size of 316 participants (158 participants per group).

2.8 Randomization

Three hundred and Sixteen (316) participants living with HIV, (158 from each hospital) receiving care in the two randomly selected hospitals in Anambra and that met the eligibility criteria will be recruited for the study. Research Randomizer, a web-based computer random numbers generator will be used to generate two sets of numbers ranging from 1 – 316 [37]. Each set will contain 158 numbers. Set 1 will represent the intervention arm while setting 2 will represent the control arm. Participants will be identified by sequential numbers, according to the order of recruitment. The allocation sequence will be conducted by an individual uninvolved in sampling and data analysis, (using the participants' identification number) and verifying which arm the participant belongs to. On the other hand, home delivery of antiretroviral which is the intervention in question would be impossible to blind since the home delivery personnel would deliver the medications to the participants at home.

2.9 Data collection techniques

Baseline data will be collected by a trained research assistant at each of the respective recruitment centers, whereas the follow-up data will be collected by the home delivery personnel. The study tools for the secondary outcome will be pretested using a pilot study at another hospital that offers ART comprehensive services. This hospital will be located in another part of the country. Random checks will be conducted by the researchers to ensure completeness.

2.10 Statistical analysis

Statistical analysis will be conducted using IBM SPSS for Windows, Version 23 (NY, USA; IBM Corp). Descriptive statistics will be used to describe the demographic and clinical characteristics. A 2-sided p-value of 0.05 will be used to indicate statistical significance. Descriptive statistics will be used to evaluate differences in demographic and clinical characteristics. Categorical variables will be expressed as frequencies or percentages and quantitative variables as means and standard deviations or medians and interquartile ranges. An intention-to-treat analysis will be conducted. A secondary per-

protocol analysis will also be conducted. The latter includes only those participants who completed the treatment protocol originally allocated, providing results on the efficacy of the trial. Intention-to-treat analysis will only be reported if the result differs markedly from per-protocol analysis. Within-group and between-group comparisons of proportional data will be analyzed using the $\chi 2$ test or Fisher's exact test were appropriate. Within groups comparison of the mean of continuous measurement between the intervention group and control group will be conducted using Paired sample t-tests or Wilcoxon signed-rank tests. Between groups comparison of the mean of continuous measurement between the intervention group and control group will be conducted using Student's t-test or Wilcoxon signed-rank tests.

Patient satisfaction will be analyzed by adopting a validated questionnaire used in a pilot study conducted in St. Mary Hospital Gwagwalada i.e the Satisfaction with Antiretroviral Home Delivery (SAHD questionnaire). The patients will be asked to respond to five categories of questionnaire items: patient demographic characteristics, Health education by the Home delivery personnel (HDP), Convenience of refill, Confidentiality, and general satisfaction level. Patient satisfaction level with home delivery will be rated on a five-point scale (ranging from 'strongly disagree to strongly agree. The patient satisfaction will be analyzed by the Chi-square test. Contingent valuation approach using the payment card technique will be used to estimate patients' average maximum willingness-to-pay for the home delivery service. All the resources consumed in providing the home delivery will be calculated from the health provider's perspective. The cost-benefit ratio of the home delivery service will be calculated by dividing benefits over costs, referred to as a benefit-cost ratio (BCR). A ratio greater than 1 demonstrates a positive return on investment.

2.11 Program steering committee (PSC)

The program steering committee's role in this trial is to monitor and evaluate all the steps in research. PSC consists of five members including two patient representatives whose sole responsibility in this trial is to offer surveillance for this research.

2.12 Data monitoring committee (DMC)

The data monitoring committee consists of an independent statistician, nurse, pharmacist, clinician, and patient. The DMC reviews the data and offers advice to other committees in the trial. The DMC will also coordinate the stopping of the trial when the data has been collected. The statistician conduct a conditional power analysis of interim results or Bayesian predictive probabilities [38] will be done to identify if there is a significant difference between treatment groups, this will help the DMC make informed steps on how to end the trial. They communicate to the other trial committees to ensure that all aspect of disagreement is addressed before stopping the trial. The research assistant is responsible for the collation of trial data and entry into the trial database. To ensure confidentiality, the trial database will be protected by a password. The research assistant will carry out data verification and validation. The major risk that may occur in this study is the exposure of patient personal information. To curtail this risk, patient data will be pseudo-anonymized and treated with the utmost confidentiality.

2.13 Ethics and dissemination

Nnamdi Azikiwe University Teaching Hospital Health Research Ethics Committee (NAUTHHREC) approved this study (NAUTH/CS/66/VOL.13/VER III/23/2020/011). The trial will be conducted per the principles outlined in the Declaration of Helsinki. All identifiable data will be handled with the strictest confidentiality. Participants will fill the informed consent form and will be informed that they are free to withdraw at any time during any phase of the trial. Dissemination plans involve holding advocacy meetings with stakeholders in HIV care, publishing study outcome in an open-access peer-review journal (with an impact factor), and presentation of the outcome at an international conference.

2.14 Clinical trial registration

This trial is registered in the WHO International Clinical Trials Registry on 8th April 2020 through the WHO International Registry Network with the registration number, PACTR202004535536808.

3. Discussion

The home delivery model improves patients' choice for care as well as minimizes interruption to patients' HIV care [39] especially during the COVID-19 pandemic and state of insecurity that has consistently threatened the lives of the populace. This research offers a reliable option to assess the outcome of this model in the wellbeing of HIV patients. Nevertheless, related data in Nigeria on the effect of this model during the current COVID-19 and insecurity challenges is lacking. The results from this study will provide more option adoptions in this COVID-19 and insecurity challenges in this part of the globe.

We admit that this study protocol could have a potential limitation, as two HIV/AIDS sites in Nigeria would be used to access the impact of this model which may not allow for generalization of the study findings and the study cannot be blinded from both the participants and the Home delivery personnel in this study because the patient receives their ARVs at home which may not be without inherent potential bias. To curtail this potential risk we use a large sample size and randomization was to reduce inherent bias to the barest minimum.

Trial Status

The version number of this Clinical study trial is V 2.1, as various modifications have been made especially to the title on the 29th August 2021, and notification has been sent to the ethics committee. The trial is expected to begin on December 1, 2021, and the recruitment will be completed approximately on Jan 30, 2022.

Availability of Data and Materials

The data used and/or analyzed during this study are available from the corresponding author on reasonable request.

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Competing Interests

The authors declare that they have no competing interest

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Author Contributions

NA, OE, OOD, UIB and SN designed the trial. NA, UIB, ANI, OKO and EIO drafted the first protocol. All authors participated in reviewing the protocol. NA and OO submitted the protocol for ethical clearance. All authors read and approved the final version of the protocol.

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