Study Title:

Can the weight gain associated with use of integrase strand inhibitors be halted or reversed with a switch to doravirinE/lamivudine/TEnofovir DF (DeLiTE?)

Protocol version: V 1.4

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GCP Statement

This clinical study will be conducted in accordance with applicable Health Canada regulations, International Conference on Harmonisation (ICH) guidelines on current Good Clinical Practice (GCP), and the Declaration of Helsinki.

Confidentiality Statement

This clinical study protocol contains information which is of a confidential, trade-secret or proprietary nature. The protocol is for the use of Dr. Sharon Walmsley and her designated representatives participating in the investigational trial. It is not to be disclosed to any other person or party without the prior written approval of Dr. Sharon Walmsley

INVESTIGATOR AGREEMENT

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Date: October 19, 2021

This clinical study will be conducted in accordance with applicable Health Canada, ICH guidelines on current GCP, and the Declaration of Helsinki.

I confirm that I have read and understand this protocol and I agree to conduct this clinical study in accordance with the design and specific provisions of the protocol, with the exception of a change intended to eliminate an immediate hazard to participants. Any deviation from the study protocol will be documented in the case report form.

I agree to promptly report to the applicable ethics boards any changes in the research activity and all unanticipated problems involving risks to human participants or others. Additionally, I will not make any changes in the research without prior ethics and sponsor approval, except where necessary to ensure the safety of study participants.

Name Signature Date (dd-mmm-yyyy)

ABBREVIATIONS AND DEFINITIONS

Acronym / Abbreviation	Definition
3TC	Lamivudine
AE	Adverse Event
ARV	Antiretroviral
ASCVD	Atherosclerotic cardiovascular disease
AZT	Zidovudine
BMD	Bone mineral density
BP	Blood pressure
cART	Combination antiretroviral therapy
CBC	Combined blood count
CrCl	Creatinine Clearance
DAIDS	Division of Aids (table for grading severity of adverse events)
DM	Diabetes Mellitus
DOR	Doravirine
DTG	Dolutegravir
DXA	Dual Energy X-ray Absorptiometry
EACS	European AIDS Clinical Society
EFV	Efavirenz
F/TAF or TAF/FTC	Tenofovir alafenamide – coformulated with Emtricitabine
FTC	Emtricitabine
HATS	HIV Adherence Treatment Scale
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
INSTI	Integrase strand inhibitor
LDL	Low density lipoprotein
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PI	Protease Inhibitor
PLWH	People living with HIV
RAL	Raltegravir
SAE	Serious Adverse Event
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil

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1.0 BACKGROUND AND SCIENTIFIC RATIONALE

1.1 Introduction

Advances in the field of HIV therapeutics have led to the universal recommendation of combination antiretroviral therapy (cART) in the treatment of people living with HIV (PLWH) (1). Effective utilization of cART has led to dramatic reductions in HIV-associated morbidity and mortality, improved quality of life, and declining risk of HIV transmission (1). Current guidelines recommend that most individuals with HIV, regardless of CD4 cell count, receive initial therapy with an integrase strand inhibitor (INSTI) based regimen (1). As the HIV therapeutic arsenal has expanded, and efficacy increased to >90% for antiretroviral naïve patients, there has been a renewed focus on differentiating therapy based on factors such as off-target effects and toxicities, convenience, and potential for drug interactions (1). One emerging differentiating factor appears to be weight gain, with early trials implicating an integrase class effect (2).

Is weight gain the result of antiretroviral use?

Whether weight gain is truly consequent to antiretroviral medication and if so, the mechanism for its development is under ongoing investigation. Some instances of weight gain can be attributed to a "return to health" effect amongst those who are underweight with higher viral burdens upon initiating therapy (2, 3). However, in those who are normal or overweight prior to initiating therapy, weight gain above a reasonable "return to health" threshold has been associated with an increase in metabolic and cardiovascular disease risk (2, 3). There is also some suggestion that there may be genetic, racial, or other factors that contribute to its development. For example, in the ADVANCE study the greatest weight gains were observed in African black females (4).

Existing clinical trials vary widely in terms of sample size, demographics, interventions assessed, outcome measures, and follow-up periods (4-12). Integrase inhibitors are the most commonly implicated drug class, and the most clinically relevant due to their first line status (5). However, protease inhibitors (PIs) and more recently, tenofovir alafenamide (TAF) have also been implicated in causing clinically significant weight gain (2, 5, 6, 10). There may also be an interaction effect between the classes. In the recently published ADVANCE trial, triple therapy with dolutegravir (DTG) and emtricitabine (FTC) combined with either TAF or tenofovir disoproxil fumarate (TDF) was compared to the local standard of care regimen of efavirenz/FTC/TDF in a South African population (4). There was significantly more weight gain with DTG-containing regimens, especially in combination with TAF (4).

Existing studies are difficult to compare. Outcome measures that have been utilized to assess weight gain include, but are not limited to, absolute and percent weight gain, BMI changes, and DXA-body composition (4-12). In studies that have employed DXA-body composition scans to assess the nature of weight gain, there have been mixed results (4, 7, 8, 12). In the recently published ADVANCE trial, DXA-body composition scans revealed that males gained mainly lean mass in both the trunk and limbs while females gained significantly more weight overall and a higher proportion of fat vs lean mass in both the trunk and limbs (4). A table summarizing studies of INSTI and TAF-associated weight gain appears in Appendix A.

Is this different than lipodystrophy?

With the introduction of the protease inhibitors, particularly indinavir, in the mid-1990s, a condition "lipodystrophy" was coined based on changes in body habitus that were observed, including central hypertrophy with peripheral atrophy. The central hypertrophy included increases in centripetal fat, often associated with the development of a buffalo hump. The body habitus changes were also associated with metabolic changes including hyperlipidemia, insulin resistance, and metabolic syndrome. The protease inhibitors were implicated but the exact mechanism never elucidated.

With the introduction of the integrase inhibitors, comparator studies suggested these body habitus and metabolic changes were less common. The PROGRESS trial found significant increases in limb fat distribution but nonsignificant changes in trunk fat when comparing RAL to TDF/FTC (7). In contrast, the STARTMRK trial compared raltegravir (RAL) vs efavirenz (EFV) and found that mean overall fat gain for both trunk and limbs was 19% vs 31%, with the majority of patients in both groups gaining moderately more central fat than limb fat (8).

Trajectory/pattern of weight gain

In contrast to a number of ART-related adverse effects that generally occur during the first year of therapy then decline (i.e. decreased BMD with TDF); weight gain appears to follow a continuous upward trajectory (9). A substudy of the 96-week ADVANCE trial found that body weight gains with DTG/TAF/FTC did not plateau at 96 weeks but rather appeared to be progressively rising (9). While this continuous pattern of weight gain may in part be explained by background weight gain of 0.5-1kg per year associated with normal aging, the ADVANCE study found mean weight gain of 6.3kg in females taking DTG/TAF/FTC at just 48 weeks (4, 9). By week 96, 51% of women on this regimen had experienced a ≥10% body weight increase (4, 9). Overall, aggregate data from existing trials suggests that weight gain is a class effect and that the nature of weight gain and metabolic changes is progressive throughout therapy (4-12).

Metabolic effects

Metabolic impacts of weight changes have been assessed through the measures of new-onset diabetes mellitus (DM), HbA1c, lipid values, and atherosclerotic cardiovascular disease (ASCVD) risk scores (10-12). Rebeiro et al. (2019) investigated ART effect on DM and found that INSTIs, namely raltegravir (RAL), and PIs are associated with an increased risk of incident DM compared to NNRTIs (10). Schafer et al. (2019) looked at virologically-suppressed PLWH switching from TDF to TAF as part of combination therapy and found significant increases in total cholesterol, LDL, and ASCVD risk scores (11). Blood pressure effects were investigated by KerchBerger et al. (2019), who found that there was a significant rise in systolic and diastolic blood pressure in PLWH who were switched to or received add-on therapy with an INSTI (12). Overall, numerous studies have shown that ART-related weight gain may impact metabolic parameters that have been implicated in increased risk of morbidity and mortality. This represents an area of growing focus in a cohort of PLWH that are living longer than ever before.

1.2 Study agent

The agent for this study is Delstrigo, a combination product that contains 100mg of doravirine (DOR), 300mg of lamivudine (3TC), and 300mg of tenofovir disoproxil fumarate (TDF).

Doravirine (DOR) is a novel NNRTI that has established efficacy in treatment-naïve adults with HIV-1 (13,14). In addition, as demonstrated by the DRIVE-SHIFT trial, doravirine as part of a fixed dose combination tablet with 3TC and TDF (Delstrigo) has demonstrated noninferiority to a regimen of 2 NRTIs plus an NNRTI, boosted PI, or boosted ETG (13). Delstrigo contains TDF and has the advantage of easy administration owing to once-daily dosing, no evidence of CYP enzyme induction/inhibition, and no food, gastric pH, or chelation interactions (14,15). Within the above study, Delstrigo was shown to have a favorable safety profile over 48 weeks of follow-up and was associated with a substantially significant decrease in fasting lipid levels (including total cholesterol, LDL, and triglycerides) compared to baseline regimens that included a PI (13). Doravirine-based regimens are now included in the European AIDS Clinical Society (EACS) treatment guidelines for antiretroviral-naïve adults, with no restrictions in terms of baseline CD4 or viral load (https://eacs.sanfordguide.com/art/initial-regimens-arv-naive-adults). Doravirine-based combinations are also classified by the U.S. Department of Health and Human Services as a recommended initial regimen in certain clinical situations.(https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/11/what-to-start)

1.3 Rationale for this Study

A primary question that remains unaddressed by existing trials is whether weight gain and metabolic effects are permanent or reversible. Furthermore, the significance of these effects as they apply to medication adherence, quality of life, and clinical outcomes has yet to be assessed. Trials suggest that weight gain may be progressive throughout therapy and may increase risk of cardiovascular events in an aging HIV+ cohort by increasing risk factors (i.e. elevated lipids, BP, and blood glucose). **The trajectory of weight gain has yet to be quantified and no therapeutic alternatives have been substantiated in those who experience extreme weight gain and associated morbidity**. While all clinicians may concede that extreme weight gain is an undesirable adverse effect of therapy, without evidence to suggest that it impacts clinical outcomes or quality of life for patients, there may be hesitation to switch from otherwise effective, stable therapy. This hesitation may be compounded by the fact that there is no good evidence to suggest that any particular alternative agent may successfully change or reverse the trajectory of drug-associated weight gain.

A key benefit of Delstrigo for the purposes of investigating (and potentially slowing/reversing) antiretroviral-associated weight gain in PLWH is that it excludes drug classes previously implicated in causing weight gain, namely INSTIs, PIs, and TAF. In a recent pooled analysis of 3 doravirine studies, the proportion of participants with ≥10% increase in body weight was not significantly different in the doravirine group as compared to those in the darunavir and efavirenz arms (16). Median changes in weight were also not significantly different among the groups, with an increase of 1.5kg in DOR, 0.7kg in DRV, and 1.0 in EFV through 96 weeks (16).

Although there could be hesitation with switching to a TDF-containing regimen due to concerns of increased nephrotoxicity compared to TAF, we argue that this is low risk in light of the meta-analysis by Hill et al. (2018). In this analysis of 11 randomized head-to-head studies comparing TDF versus TAF, it was found that risks associated with TDF are higher only when TDF is used

in a boosted regimen including ritonavir or cobicistat (14). No significant differences in HIV RNA suppression rates or clinical safety endpoints were demonstrated between unboosted TAF and unboosted TDF (14).

1.4 Potential risks and benefits to participants

In a study that compared Delstrigo to efavirenz/emtricitabine/tenofovir DF over the course of 96 weeks, the most frequent side effects (>1%) shown in the DRIVE-AHEAD trial among 364 participants who took Delstrigo were:

- Nausea (5%)
- Diarrhea (3%)
- Vomiting (2%)
- Tiredness (4%)
- Dizziness (7%)
- Headache (4%)
- Drowsiness (3%)
- Abnormal dreams (5%)
- Insomnia (4%)
- Nightmares (2%)
- Rash (2%)

Some other rare but possible side effects with Delstrigo include:

- Bone loss
- New onset or worsening kidney impairment (and Fanconi syndrome)
- Lactic acidosis
- Severe hepatomegaly with steatosis
- Pure red cell aplasia
- Severe acute exacerbation of hepatitis B in patients co-infected with HIV-1 and HBV
- Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome can occur during the initial phase of combined antiretroviral treatment. Patients may develop an inflammatory response to indolent or residual opportunistic infections. Patients may necessitate further evaluation and treatment. As this is a switch study, patients will not be in the initial phase of cART. Therefore this reaction is unlikely.

<u>Lamivudine (3TC)</u>

In clinical studies of lamivudine in combination with zidovudine and efavirenz (EFV) in patients with HIV-1, the most frequent adverse events reported include:

- Malaise and fatigue
- Headache
- Abdominal discomfort and pain
- Nasal signs and symptoms

- Viral respiratory infection
- Dizziness
- Sleep disorders
- Musculoskeletal pain
- Myalgia
- Diarrhea
- Cough
- Skin Rashes
- Depressive disorders
- Nausea and vomiting
- Throat and tonsil discomfort and pain
- Fever or chills
- Arthralgia

Other common (1-10%) adverse effects from lamivudine, zidovudine and efavirenz treatment include: dyspepsia, hyposalivation, oral ulceration, muscle pain, muscle atrophy/weakness/tiredness, mood disorders, taste disturbances, sexual function disturbances, temperature regulation disturbances, sweating, rash, and pruritus.

Tenofovir DF (TDF, Viread®)

Tenofovir DF has been studied in more than 12,000 HIV-infected adults for as long as 480 weeks in some patients. Common potential side effects identified in patients who received at least one dose of tenofovir DF 300 mg include diarrhea, nausea, vomiting, flatulence (intestinal gas), and dizziness. Those side effects were often mild or moderate in severity, and did not lead to discontinuation of tenofovir DF.[33]

In addition to side effects reported from clinical trials the following side effects have also been identified after tenofovir DF was approved by the FDA and Health Canada in HIV-infected patients treated with combination therapy that has included tenofovir DF and other anti-HIV drugs. Because post marketing (after regulatory licensing) reactions are reported voluntarily from a patient population of uncertain size, it is not always possible to reliably estimate how frequently these side effects occurred, or establish a causal relationship to tenofovir DF. The side effects which have been reported with tenofovir DF when taken with other anti-HIV drugs include:

- allergic reaction
- rash
- abdominal pain
- pancreatitis
- shortness of breath
- weakness
- abnormalities of hepatic (liver) function and hepatitis (inflammation of liver).

Cases of lactic acidosis, hepatosteatosis, including fatal cases, were reported in HIV-infected patients treated with anti-retroviral agents similar to tenofovir DF. The symptoms of lactic acidosis include weakness, nausea, vomiting, and unexpected and uncommon abdominal pain.

Symptoms of liver problems include:

- yellowing of the skin or whites of the eyes
- dark urine
- light colored bowel movements
- nausea
- loss of appetite
- lower abdominal pain

Cases of kidney damage have been reported in patients taking tenofovir DF who already have atherosclerosis, or specific kidney disease, and patients who, while receiving tenofovir DF, were also taking medications that may cause damage to the kidneys. Kidney damage has also been reported in patients without any of these factors. In addition, continuous or sudden kidney failure, abnormal kidney function, inflammation of the kidneys, protein in the urine, excessive urination,

nephrogenic diabetes insipidus, and increased creatinine have also been reported in patients taking tenofovir DF.

Bone toxicity, including a decrease in bone mineral density was seen in animals following treatment with tenofovir DF. Decreases in bone mineral density have been seen in humans. The risk of bone fractures associated with these types of changes is unknown.

Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Allergic Reaction Risks

As with taking any drug, there is a risk of allergic reaction.

Blood Draws

Drawing blood from a vein may cause local pain, bruising, occasional light-headedness, fainting, and very rarely, infection at the site of the blood draw.

DXA

Changes in body fat composition have been observed in HIV-infected patients taking certain antiretrovirals. An X-Ray called dual energy X-ray absorptiometry, or a DXA scan, will be performed on the abdomen to measure changes in body fat. The radiation exposure is lower than with a chest x-ray. The DXA scans are considered, in general, less harmful than a standard x-ray.[31] A DXA scan usually takes about 30 minutes.

2.0 STUDY SYNOPSIS

This pilot intervention study is designed to provide preliminary data on whether switching patients with weight gain on an INSTI-based regimen to a combination of doravirine/tenofovir disoproxil fumarate/lamivudine (DOR/3TC/TDF, an NNRTI-based regimen) for one year can slow down or even reverse weight gain. Combined these data will then be used to inform the design and sample size of a larger switch study. This study will be conducted at the University Health Network Toronto General Immunodeficiency Clinic.

3.0 STUDY HYPOTHESIS

We hypothesize that switching from an INSTI-containing regimen to Delstrigo will stabilize or even reverse the trajectory of weight gain in virally-suppressed PLWH.

4.0 STUDY OBJECTIVES

4.1 Primary objective:

To determine how many active patients in our clinic who have gained ≥10% body weight on a current INSTI-containing regimen would be eligible for our proposed switch study to DOR/TDF/3TC. We will determine how many of those approached accept enrollment and complete the protocol.

4.2. Secondary Objectives

To determine changes in absolute weight, weight trajectory, BMI and waist circumference after 1 year following regimen switch. To determine nature of weight gain (lean vs fat mass), impact of weight gain on body image and medication adherence, and impact of weight gain on fasting glucose, insulin resistance (HOMA), and lipid values. To determine efficacy, safety, and tolerability of DOR/TDF/3TC as a switch strategy in virally suppressed patients who have gained ≥10% body weight on a current INSTI-containing regimen.

5.0 STUDY DESIGN

This study is an open-label, exploratory switch study from INSTI-containing regimens to DOR/TDF/3TC.

5.1 Study population:

Participants will be selected from the patient population of the Toronto General Hospital Immunodeficiency Clinic. The charts of active patients currently on INSTI-containing regimens and experiencing a ≥10% weight gain identified will be further reviewed to determine the proportion that meet the remainder of the eligibility criteria for the intervention study. A current version of the consent form is included in Appendix B.

5.2 Intervention:

Switch from current INSTI based ARV to Delstrigo (doravirine, 3TC, TDF) for 12 months.

5.3 Primary endpoints:

1. Identify number of active patients in our clinic who meet eligibility criteria, and of those approached, how many accepted enrollment and completed the study protocol.
2. Identify reasons for study ineligibility/study refusal among clinic patients on INSTI-containing regimen who have experienced weight gain.
3. Identify factors associated with early study discontinuation.

5.4 Secondary endpoints

1. To determine the change in absolute weight, relative weight change per year (i.e. weight trajectory), waist circumference, and BMI category from baseline to one year following the switch from the INSTI-containing regimen to DOR/TDF/3TC.
2. To determine the proportion of participants who maintain viral suppression (HIV RNA < 50 copies/ml) after a switch to DOR/TDF/3TC.
3. To assess safety and tolerability of the DOR/TDF/3TC combination.

5.5 Exploratory endpoints

To determine the impact from baseline to one year following the switch from the INSTI-containing regimen to DOR/TDF/3TC on DXA body scans, body image questionnaires, fasting glucose, insulin resistance (HOMA), and lipid values.

5.6 Justification of endpoints:

Absolute weight, BMI, waist circumference, metabolic effects:

Patients who experience weight gain while on an INSTI-based regimen have generally shown an increasing and progressive increase in weight, with some studies showing increases up to 96 weeks with no plateau (9). Absolute weight change over the course of the trial will be compared to weight change from baseline while on the INSTI-based regimen to examine if the patient's rate of weight gain is altered.

BMI category increases are significantly associated with cardiovascular mortality. A shift to a lower BMI category would demonstrate a change in overall health and cardiovascular risk in these patients who have been put at an increased risk due to their ART.

Measurement of waist circumference is recommended as an important vital sign in clinical practice, and provides additional information for assessment and management of cardiometabolic risk associated with increased adiposity in adults.

The metabolic effects of ART-related weight gain include increased lipid values, atherosclerotic cardiovascular disease (ASCVD) risk scores, blood pressure, incident diabetes mellitus, and hemoglobin A1c values (10-12). These metabolic parameters are associated with increased risk of morbidity and mortality.

Use of DXA body composition scan:

The whole-body DXA scan allows for rapid and non-invasive assessment of body composition—including fat mass, lean mass, and bone mineral mass—with relatively low radiation exposure (28). DXA body scans have been used in numerous studies investigating ART-related weight gain in PLWH in order to quantify the nature of the weight gained (4, 7, 8). This information is vital to determining clinical relevance as raw changes in weight do not directly translate into increased risk of adverse clinical outcomes (i.e. diabetes, CVD) (28, 29). Srikanthan et al. (2016) performed DXA body scans of 6,541 participants with CVD (defined by confirmation of coronary artery disease, cerebrovascular disease, hypertension, or congestive heart failure) to determine how body composition and CVD might be linked. In assessing both cardiovascular mortality outcomes and death from natural causes, they found that risk was significantly lower in participants with a high muscle/low fat composition as compared to those with a low muscle/low fat composition (29). Across the board, a higher proportion of lean mass was associated with lower risk of morbidity and mortality, even in those considered "overweight" or "obese" according to their BMI (29). If Delstrigo is able to change or reverse the trajectory of weight gain in PLWH, it will be valuable to assess change in body composition and how it may ultimately impact clinical outcomes.

Use of body image questionnaires:

In order to obtain a complete picture of ART-related weight gain in PLWH, impact on quality of life must be considered. While the degree and nature of weight gain may impact clinical outcomes, it may also have a significant bearing on patient satisfaction with therapy. Few studies looking at

ART-related weight gain have assessed self-reported weight gain and none have assessed impact on body image, self-esteem, and overall quality of life. Bhagwat et al. (2018) used a subjective measure of self-reported abdominal change ("gained a lot"/"gained some"/"no change or lost in size") in addition to objective measures of weight gain (i.e. waist circumference) in an effort to add context to raw weight gain data (30). In a similar vein, the FRAM study provided participants with a self-administered questionnaire on body fat changes to compare self-perceived changes with those identified by research associates upon examination (31). Since this was originally applied to investigation of ART-associated "lipodystrophy" in the early 2000's, we will adapt it to be relevant to modern concerns of fat change in the context of significant weight gain with implicated ARTs. Assessing how self-reported weight gain influences factors related to quality of life is complicated by the lack of body image questionnaires that have been validated for use in HIV positive populations. However, the body weight, image, and self-esteem (B-WISE) evaluation questionnaire has been validated for the assessment of weight gain associated with psychotropic drug use (32). This 12-item, self-administered questionnaire can be applied for our purposes to obtain a more holistic picture of the impact of weight gain in PLWH. It may also be of benefit for monitoring the impact of switching to Delstrigo to see if any potential effect on trajectory of weight gain may also influence participant body image and self-esteem. Both questionnaires will be short (Appendix D).

6.0 ELIGIBILITY CRITERIA

6.1 Inclusion Criteria – all criteria must be met

1. Age 18 years or older
2. Documented HIV-1 infection **by means of any <u>one</u> of the following**:
    i. **Documentation of HIV diagnosis in the medical record by a licensed health care provider;**

    ii. **OR HIV-1 RNA detection by a licensed HIV-1 RNA assay demonstrating >1000 RNA copies/mL;**

    iii. **OR any licensed HIV screening antibody and/or HIV antibody/antigen combination assay confirmed by a second licensed HIV assay such as a HIV-1 Western blot confirmation or HIV rapid Multispot antibody differentiation assay.**

3. On current Integrase Strand Transfer Inhibitor (INSTI) based regimen for at least 1 year and less than 5 years prior to screening
4. Significant weight gain since initiation of the current INSTI-based regimen (>10% of baseline body weight)
5. Viral load of <200 copies/mL for > 6 consecutive months prior to screening (single viral blips <200 copies/mL accepted if re-suppressed)
6. Documentation of weight, glycemia, cholesterol, and blood pressure (BP) history within the last year.

7. Signed Informed Consent Form (Appendix B) and willing to comply with the protocol.
8. Using proper contraception if of child bearing age and potential.

6.2 Exclusion Criteria - if any are present the participant cannot be included

1. Pregnancy or desire to become pregnant within the next year
2. Failure to use adequate contraception during the study if of child-bearing potential.
3. Any underlying documented ART resistance to doravirine, tenofovir disoproxil fumarate, or lamivudine
4. Prior virologic failure
5. Concomitant drugs that interact with doravirine
6. Initiated on concomitant drugs known to cause weight gain within the last 6 months (i.e. antidepressants and antipsychotics)
7. Concomitant drugs known to cause nephrotoxicity
8. History of renal toxicity or renal events while on TDF therapy.
9. Creatinine clearance (CrCL) < 50 mL/min
10. Inability to read/understand English

7.0 STUDY EVALUATIONS AND PROCEDURES

7.1 Study Eligibility and Participation

A screening log and enrollment log will be used to record all subjects screened for eligibility. Information recorded will include Subject ID, date of screening, eligibility for enrollment. Of those eligible who consent to enrollment, the date of consent and version of the Informed Consent Form will be recorded. Reasons for ineligibility or declining to participate in the study will be recorded. The screening log will not contain any identifying information. Subjects will be tracked separately on logs which are only accessed by the research coordinator and the principle investigator.

7.2 Clinical Evaluations

Once a candidate for screening has been identified, study details will be carefully discussed with the potential participant. The participant will be asked to read and sign the approved informed consent form (Appendix B) prior to any assessments being performed.

Medical history, documented HIV test results, and demographic information will be obtained at the screening visit. Data will be collected on age, race, HIV risk factor, smoking history, diet, exercise habits (Appendix K), illicit drug use, alcohol, steroid use, ARV history, past medical illness, medications, weight, and body mass index. Weight and waist circumference will be measured according to protocols defined in Appendices F and G, respectively.

Routine investigations will include viral load, CD4, CD8, haematology, biochemistry, lipids, endocrinology, renal monitoring. Hepatitis B and C status will be recorded.

A complete physical exam, including vital signs will also be performed at the screening visit. A brief targeted physical exam, including vital signs, will be performed at subsequent visits. Information pertaining to medication review and adverse events will be collected as indicated in Appendix C.

A complete history of antiretroviral therapy including time of starting ART and type of drugs will be recorded. While on the study, ART switching, adherence to ART (Appendix E) or stopping ART for any reasons will also be documented.

7.3 Participant Identification Number Assignment

Participant Identification (ID) numbers will be assigned sequentially to each participant who is eligible to participate in the study. Participants who are not eligible for the study will not be assigned a Participant ID Number. The Participant ID Number will consist of a three digit number according to chronological order of entry. Details for assigning Participant ID Numbers will be provided in the Operations Manual. Log(s) should be completed to capture all participants who have consented and who have been assigned a participant identification number. If a patient discontinues from the study the Participant ID Number will not be reused.

The Participant ID Numbers will be used for identification of participants in the source documentation, CRFs, and laboratory samples. This will ensure that participant data and laboratory samples will be identified and tracked.

7.4 Imaging

Participants will complete DXA scans at the UHN site.

7.5 Laboratory Evaluations

Blood samples will be obtained for clinical laboratory evaluations on the days specified in Appendix C. Routine investigations will include HIV viral load, CD4 cell counts, complete blood count (CBC) with differential and measurements of hepatic (AST, ALT, ALP, GGT, bilirubin, albumin) and renal function (creatinine, GFR, urinalysis, urine albumin, Ur albumin/Cr, and Ur Protein/cr), urine and serum phosphate), calcium, fasting glucose, hemoglobin A1c, and lipid profiles (triglyceride, LDL, HDL, TC/HDL). Plasma HIV RNA levels will be measured at local laboratories with a lower limit of detection as per current assays. (This may be < 50/ml, < 40/ml or viral load not detected). Clinical laboratory evaluations for hematology, biochemistry, CD4/CD8, viral load and serology will be performed at the UHN laboratory.

7.6 Stored Research Samples

Blood samples will be aliquoted, frozen and stored in order to perform biomarker testing at a later date. As this field is rapidly evolving, not all tests are currently known or developed but the frozen samples will be used only for HIV research purposes and testing related to this study. The samples will not be made available to any commercial enterprise. Stored samples will be identified only by a code number and will be destroyed after 10

years. A separate consent form for the collection and storage of these samples will be obtained.

7.7 Adherence

For self-reports of adherence will use the Visual Analogue Scale[44] (VAS last week and/or last month) which measures item ratings by participants in percentile terms from 0 to 100% and using a descriptor, for subjective perception of adherence in the last day, week, two weeks, and month (Appendix E). We will corroborate self-reported measure with objective outcome measurements such as returned pill counts.

7.8 Body Image Questionnaires (Appendix D)

- Body Weight, Image, and Self-Esteem (B-WISE) evaluation questionnaire
- Adjusted questionnaire from the FRAM study

8.0 STUDY VISITS

8.1 Screening visit:

The screening visit is anticipated to require 1-2 hours of the participant's time. During this visit the following will take place:

- Informed Consent
- Assign Participant ID Number
- Demographic Information
- Medical History
- Physical Exam
- Vital Signs including height, weight and determination of BMI
- HIV Viral load (within 1 month of screening date)
- CD4 and CD8 levels
- Serum Pregnancy test
- Hepatitis B and C (only if not previously tested)
- Hematology and biochemistry: CBC with differential, liver profile (AST, ALT, serum creatinine, Urinalysis, GFR, Urine albumin/creatinine, urine protein/creatinine), lipid profile (within 1 month of screening date)
- Medication Review
- Review of Eligibility Criteria
- DXA scan will be scheduled before baseline visit. (DXA scan should be completed prior to Baseline Visit).

8.2 Baseline Visit for Participants

Day 1- Week 0 (no more than 30 days after screening visit date)

This visit must occur within 30 days of the screening visit. (**Note:** If baseline visit is within 2 weeks of screening lab work, then available screening lab results may be used and **duplicate** lab work need not be recollected). This visit is anticipated to require 1 hour of

the participant's time. A baseline visit should be scheduled if the eligibility criteria met, at which the following events will take place:

- Confirmation that eligibility criteria have been met
- Confirm DXA Scan has been completed.
- Urine Pregnancy test (if premenopausal) and FSH if postmenopausal
- Targeted Physical Exam including waist circumference
- Vital Signs
- Diet & exercise habits over the previous 3 months (Appendix K)
- Framingham Cardiovascular Risk Score
- Hematology and biochemistry: CBC with differential and liver profile (AST, ALT), serum creatinine, calcium, phosphate, Urinalysis, GFR, Urine albumin/creatinine, urine protein/creatinine, lipids- cholesterol, LDL, HDL, TG, fasting glucose, hemoglobin A1c)
- CD4/CD8
- HIV Viral Load
- Research Blood Sample
- Study Drug dispensation
- Body image questionnaires (Appendix D)
- Medication review
- Body composition (lean mass, fat mass, and bone mineral mass) will be determined from the screening DXA

8.3 Follow-up Visits for Participants

Follow-up visits will occur at weeks 12, 24, 36, and a final visit at week 48. Accepted windows around study visits are +/- 7 days. Patient weight and waist circumference will be measured every 3 months until study completion at 12 months according to the protocols outlined in Appendix F & Appendix G. Routine laboratory work will also be done every 3 months, including HIV RNA, CD4, CD8, liver transaminases, renal function, fasting glucose, hemoglobin A1c and a standard lipid panel. Medication adherence will be assessed every 3 months using the Visual Analogue Scale (VAS) (Appendix E) and AE based on DAIDS criteria (Appendix H) will be documented as well as any changes in clinical conditions, diet or exercise habits or medications over the past 3 months (Appendix K), and pill counts of returned study drug. The procedures will last about 60 minutes per visit.

Drug dispensation will be done every 3 months during the regular visits at W0, W12, W24, and W36.

8.4 Final Study Visit (Week 48 +/- 14 days)

The duration of the study is 1 year per participant. Participants will be recruited during the first year of the study and will be followed for 48 weeks. The final visit will be the participant's last follow-up visit and the following assessments will take place:

- Complete Physical Exam including weight and waist circumference
- Vital Signs
- Hematology and biochemistry: CBC with differential and liver profile (AST, ALT), serum creatinine, calcium, phosphate, Urinalysis, GFR, Urine albumin/creatinine, urine protein/creatinine, lipids- cholesterol, LDL, HDL, TG, fasting glucose, hemoglobin A1c, CD4/CD8
- HIV Viral Load
- Research Blood Samples
- Documentation of any changes in clinical conditions, diet or exercise habits over the past 3 months (Appendix K)
- Medication review: ART and Other Concomitant Medications
- Adherence questionnaire (Appendix E)
- DXA imaging
- Body image questionnaires (Appendix D)

To collect any information on potential adverse event reaction, patients will be called 4 weeks after their last visit at 48 weeks +/- 7 days.

8.5 Early Termination

If a participant withdraws from the study early, documentation for reason of early termination is required. Investigations will be completed as per final visit. If they agree, participants will continue to be followed even if they decide to stop the study medication

8.6 Re-contact of Participants after Study Termination

Study results will be made known to the investigators. As per UHN practices and IRB/REB requirements, investigators will be responsible for disseminating the information to participants who participated in the study.

8.7 Schedule of Procedures

Please refer to Appendix C.

9.0. STUDY DRUG

Participants will take a single tablet of Delstrigo (DOR 100 mg, 3TC 300mg, TDF 300mg) once daily orally.

Study drug will be donated by Merck. Study drug will be packaged in bottles containing 30 tablets, silica gel desiccant and polyester packing material. Each bottle will be enclosed with a polypropylene screw cap. To ensure stability the drug should not be stored in any

other container than that supplied. The study drug bottles will be labelled to meet all the applicable requirements of the EU guidelines to good manufacturing practice, Health Canada and the US food and drug administration. The bottles should be stored at a controlled room temperature of 25C (77F) with excursions permitted to between 15C and 30C). Storage conditions will be specified on the labels.

Until dispensed to participants, all bottles of study drug will be stored in a securely locked area, accessible only to authorized study personnel.

9.1 Study Drug Accountability

The investigator is responsible to ensure adequate accountability of all used and unused study products. The investigator or designated central pharmacy will acknowledge receipt of the study drugs from Merck after reviewing the shipment's content and condition. The investigator or designee will be responsible for maintaining an accurate inventory of the dates and quantities of all study drugs received, dispensed and returned. Each dose of the study drug administered by the qualified study centre personnel will be accurately recorded on logs which indicate the date and quantity of all doses dispensed. These logs will be available for inspection by study monitors. Study medication supplies must be accounted for by the study monitor prior to destruction or return.

10. EARLY TERMINATION

Participation in the study will be terminated early if: the participant refuses further treatment and/or follow-up evaluations; the study staff or participant's medical provider determines that further participation in the study would be detrimental to the participant's health or well-being; the participant is non-compliant with the study requirements in a manner that is either detrimental to her health or interferes with the validity of the study results; the patient has viral failure and requires an alternative antiretroviral regimen (the viral load that requires a change in therapy will be at discretion of the investigator); the patient becomes pregnant; or the sponsor terminates the study.

11. ASSESSMENT OF SAFETY

11.1 Adverse Events (AEs)

Adverse events (AEs) are defined as any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study medication/intervention. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug/intervention, whether or not it is related to the medication/intervention.

Toxicities will be graded on a 4-point scale according to standard guidelines outlined in the "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events" [48][Appendix H]. In general, grade 1 and 2 events will not be considered adverse

events, but details should be documented in the source documents. Fractures will be considered and captured as an adverse event regardless of grading.

Stable chronic conditions which are present prior to clinical study entry and do not worsen are not considered adverse events and will be accounted for in the participant's medical history.

Participants who have an adverse event should be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. It is up to the clinician to determine that the AE is either resolved or that is has reached a stable state, after which no further follow-up is necessary. There should also be source documentation to support this determination.

There are no recorded moderate to severe intensity adverse reactions that occur ≥2% in those receiving Delstrigo.

11.2 Recording/ Documentation of AEs

At each contact with the participant, information regarding adverse events will be elicited by appropriate questioning and examinations, and will be recorded immediately on a source document (e.g., progress notes, laboratory reports, survey tools, and data collection tools). The start date, stop date, severity of each reportable event, and the PI's judgment of the AE's relationship to the study medication/intervention will also be recorded in the case report form (CRF).

11.3 Serious Adverse Events (SAEs)

A Serious Adverse Event is defined as an AE meeting one of the following:

- Death during the period of protocol-defined surveillance
- Life Threatening Event (immediate risk of death at the time of the event)
- In-patient hospitalization or prolongation of existing hospitalization during the period of protocol-defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity
- Any other important medical event that may not result in one of the above outcomes may be considered a serious adverse event when: based upon appropriate medical judgment, the event may jeopardize the participant, and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse or any event of possible drug-induced liver injury with hyperbilirubinemia defined as ALT>3xULN and bilirubin >2xULN (>35% direct)

Any AE that occurs between baseline and 30 days following the last study visit at Week 48 (or at the time of early discontinuation of the participant from the study for any reason)

is to be recorded in the source documentation (patient will be called). Surveillance for AEs will end at 30 days following Week 48. If an SAE is ongoing at the time a participant discontinues/completes the trial the SAE will be followed until the Investigator agrees that the event is satisfactorily resolved, becomes chronic, or that no further follow-up is required.

11.4 AE/SAE Grading, Relationship Assignment and Reporting Procedures

11.4.1 AE/SAE Grading

The intensity (severity) of each adverse/serious event will be graded according to the toxicity table and toxicity guidelines provided by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Appendix H). The DAIDS Table will be provided with the Operations Manual.

11.4.2 Relationship Assessment

For all collected AEs (including SAEs), the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in

which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not related: The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

11.4.3 SAE Reporting Procedures

The Investigator or designee must report any SAE occurring in a patient receiving study drug to the Sponsor within 24 hours, even if the SAE is not drug-related. This should be done by telephone and by sending a faxed or emailed copy of the Serious Adverse Event form plus other supporting documentation, as required.

SAEs will be reported to:

Immunodeficiency Clinic

University Health Network

Attention: Rosemarie Clarke, Research Nurse Manager

Phone: 416-340-4800 ext. 6723 or 416-340-5077
Fax: 416-340-9105

E-mail: rosemarie.clarke@uhn.ca

All additional follow-up evaluations must also be reported as soon as possible in the same manner. All SAEs will be followed until the Investigator agrees that the event is satisfactorily resolved, becomes chronic, or that no further follow-up is required.

The Sponsor or designee will be responsible for notifying the relevant authorities of any reportable SAE as outlined in the Canadian Food and Drug Regulations and ICH Guidelines.

11.5 AEs/SAEs monitoring

Any AE/SAE that occurs between baseline and the time the participant departs the study at the end of the final follow-up visit (or at the time of early discontinuation of the participant from the study for any reason) will be captured and recorded in the source documentation. At each contact with the participant, the investigator (or designate) must seek information on adverse events by specific questioning and, as appropriate, by examination.

Adverse events that had previously been reported by the study participant will also be reassessed for duration, intensity and possible reoccurrence. Assessment of safety will include clinical observation and monitoring of routine hematology and biochemistry.

Surveillance for AEs will end 30 days post Week 48 (or at the time of early discontinuation of the participant from the study for any reason). If an SAE is ongoing at the time a participant discontinues/completes the study, the SAE will be followed up until the

Investigator agrees that the event is satisfactorily resolved, becomes chronic, or that no further follow-up is required.

11.6 Toxicities/ Adverse Event Management

In the event of a discontinuation of Delstrigo for suspected renal impairment, or other clinically significant chemistry elevations, participants should not restart Delstrigo due to the risk of a recurrent reaction; such participants should be withdrawn from study and seek/be reviewed for alternative antiretroviral therapy. If they agree, participants will continue to be followed for the duration of the study.

11.7 Management of HIV Virologic failure.

Virologic failure must be considered for any patient with plasma HIV RNA ≥50 c/mL at any time following randomization. For the purposes of clinical management in this study, virologic failure is defined as:

Two consecutive plasma HIV RNA ≥50 c/mL within four weeks of the initial suspected virologic failure.

Cases of confirmed virologic failure will trigger genotypic virologic resistance testing, including non-nucleoside reverse transcriptase resistance testing, when plasma HIV RNA >400c/mL. The virologic failure definition is intended for guidance and Investigators should use their discretion as to the most appropriate clinical management of their patients. The choice of antiretroviral therapy will be left to the discretion of the treating physician. In some cases, e.g. if there is no evidence of acquired resistance to the current regimen, treatment may be continued with increased efforts at adherence support.

11.8 Pregnancy Management

Patients who are pregnant will be excluded from the study, as pregnancy is associated with weight gain which would be a confounder for this study. Additionally, the safety of the study drug in pregnancy is unknown. There is no data are available on the placental transfer of DOR in humans, and insufficient data to assess for teratogenicity in humans.

11.9 Action to be taken if pregnancy occurs

Any participant who becomes pregnant during the study must be immediately withdrawn from the study because, as stated above, weight gain in pregnancy would be a confounding factor and the effects of the drug during pregnancy are not known. Management of the patient after removal from the study will handled by their treating physician.

12. TRIAL MANAGEMENT

12.1 Local Coordination

The principal investigator will be responsible for recruiting study personnel, obtaining UHN REB/IRB approval, ensuring clinic staff are informed about the study, and supervising study activities. The study personnel will be responsible for: identifying participants; obtaining informed consent; conducting study visits; ensuring participants

have regular follow-up; encouraging attendance at visits; telephoning participants if visits are missed; and collecting participant data. A study manual will outline methods for CRF completion and record management. Personnel will also be trained on study procedures prior to and during the study.

13.0 DETAILS OF STATISTICAL ANALYSIS

13.1. Sample size considerations

As this is a pilot study it is not powered to meet statistical significance for the primary or secondary endpoints but is chosen as a convenience sample upon which preliminary data can be obtained. We estimate 800 active patients currently on an INSTI-containing regimen at our clinic. If we approach 40 eligible patients, we estimate 70% acceptance rate with a 95% confidence interval (CI) of +/- 14%. Reaching our target enrollment of 25 patients means that we will be able to estimate a 90% completion rate with a 95% CI of +/- 12%.

13.2 Primary analysis:

The following proportions and their 95% confidence intervals will be calculated: 1) the proportion of patients on INSTI-containing regimens that are eligible for the study, 2) the proportion of eligible patients approached who agree to participate, and 3) the proportion of those who sign consent who complete the protocol.

13.3 Secondary analyses:

Wilcoxon Signed Rank Tests will be used to compare patients' absolute weight and waist circumference between baseline and 12 months on DOR/TDF/3TC. Relative weight change per year (i.e. weight trajectory) while on INSTI and while on DOR/TDF/3TC will be calculated and compared using a Wilcoxon Signed Rank Test. McNemar's test will be used to compare BMI categories between baseline and 12 months on DOR/TDF/3TC. Retrospective (from Part 1) and prospective measures of weight will be used in univariable GEE models to estimate weight change over time before and after switching to DOR/TDF/3TC. GEE models are flexible to different follow-up schedules and thus allow for missed visits and loss to follow up. The number of participants with viral failure will be recorded.

Exploratory analyses: For the following outcomes with repeated measures, univariable GEE models will be used to estimate the trajectory of change after switching to DOR/TDF/3TC: CD4 count, CD8 count, liver transaminases, renal function, fasting glucose, insulin resistance (HOMA) and a standard lipid panel. Wilcoxon Signed Rank Tests will be used to compare DXA body scan results and body image questionnaires between baseline and 12 months on DOR/TDF/3TC.

13.4. Interim analysis:

no interim analyses are planned

13.5 Feasibility: Of approximately 1500 active patients at the Immunodeficiency Clinic, 98% are currently on antiretroviral treatment, and 91% have a viral load below 40 copies/mL. Over 1000 patients (over 2/3) are on treatment with an INSTI.

13.6 Timeline: 6-12 months for start- up and ethics approval, 6-9 months for enrollment; 12 months for follow-up; 6 months for analysis/write-up (Appendix I)

13.7. Loss to follow-up: We expect that 10% of patients will drop out before 48 weeks. Primary analyses will be conducted assuming data are missing at random. Pattern mixture models and selection models will be used as sensitivity analyses to determine the range of possible treatment effects under the assumption of not missing at random.[50]

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

Checks will be built into the database to alert the data manager to inconsistent data at the time of data entry. Site personnel will then be prompted to double-check the data. Source documentation will not be verified by an on-site monitor visit during the study. It is the responsibility of the Sponsor Investigator to assure the quality of computerized data for this study.

15. ETHICS AND PROTECTION OF HUMAN PARTICIPANTS

15.1 ICH Guidance E6:

Good Clinical Practice: Consolidating Guideline/ Declaration of Helsinki. The conduct of this study will conform to the International Conference for Harmonization and Good Clinical Practice (ICH-GCP) regulations and guidelines and the current revision of the Declaration of Helsinki.

15.2 Research Ethics Board/ Institutional Review Board

A copy of the protocol (including protocol amendments), all versions of the informed consents, other information to be completed by participants such as questionnaires, and any proposed advertising/ recruitment materials must be reviewed and approved by the REB/IRB prior to implementation of the study. The principal investigator will be responsible for obtaining REB/IRB approval of the annual Continuing Review throughout the duration of the study. The principal investigator will notify the REB/IRB of violations from the protocol and serious adverse events.

15.3 Informed consent process

All participants will be given detailed oral and written information about the study. Consent forms describing in detail the study medications/intervention(s), study procedures, anticipated benefits and potential risks will be given to each participant and written documentation of informed consent is required prior to starting the study. Participants must voluntarily sign and date an informed consent document that has been approved by UHN's REBprior to any procedures being done specifically for the trial. Each participant should have sufficient opportunity to discuss the study and consider the information in the consent

process prior to agreeing to participate. Participants may withdraw consent at any time during the course of the trial. The informed consent will be signed and dated by the participant, the person who conducted the informed consent discussion and the investigator. The original signed informed consent form will be retained in the participant's study files and a copy will be provided to the subject.

15.4 Subject confidentiality

All participant related information including the CRFs, laboratory samples, evaluation forms, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Participants will be identified only by means of a coded number specific to each participant, and a participant letter code. All computerized databases will identify participants by numeric codes only, and will be password protected. Upon request, clinical information may be reviewed by or released to study monitors, auditors, or regulatory agencies.

15.5 Early Termination of the Protocol

The REB/IRB or other government organizations, as part of their duties to ensure that research participants are protected may discontinue the study at any time. Regulatory authorities and the study Sponsor retain the authority to suspend additional enrollment for the entire study as applicable.

15.6 Record Retention

The Investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for 25 years, in accordance with applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and the Sponsor notified. The Investigator should ensure that no destruction of medical records occurs without the written approval of the Sponsor.

Samples collected and sent to the UHN laboratory will be retained for 10 years, after which they will be destroyed.

16.0 PROTOCOL DEVIATIONS

No deviations from this protocol will be permitted without the prior written approval of the Sponsor, except when the modification is needed to eliminate an immediate hazard or hazards to participants. Any deviations that may affect a participant's treatment or informed consent, especially those increasing potential risks, must receive prior approval from the REB unless performed to remove an immediate safety risk to the participants. In this case it will be reported to the REB and the Sponsor immediately thereafter. Any departures from the protocol must be documented.

17.0 STUDY CONDUCT AND MONITORING

Limited monitoring will be done by the Principal Investigator and will include clinical and operational data reviewed for outliers and trends.

18.0 DATA MANAGEMENT RESPONSIBILITIES

It is the responsibility of the Data Management Centre to assure the quality of computerized data for this study. This role extends from protocol development to generation of the final study databases.

19.0 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA DOCUMENTS

Appropriate medical and research records will be maintained for this study and regulatory/ institutional requirements for the protection of confidentiality of study participants. The Principal Investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

Study data will be collected on study specific CRFs. Source documentation should support the data collected on the CRFs. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical trial. Data for CRFs will be collected during participant visits, phone calls with participants and health care providers, completed questionnaires and abstracted from the participant's medical records. It is not acceptable for the CRF to be the only record of participation in the trial.

Clear and detailed instruction explaining CRF completion and where, when and how CRFs are to be sent to the data centre will be included in the study Operations Manual.

20. DISCLOSURE AND PUBLICATION POLICY

Publication of the final study report is planned. The Sponsor-Investigator (Dr. Walmsley) will determine authorship for each manuscript based on contributions to the study design, study execution, and manuscript completion. No author will be included without prior authorization but the intention is to be broadly inclusive of all study investigators who make active contributions as outlined by the ICJME criteria for authorship (Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3).

21. STUDY TEAM ROLES AND RESPONSIBILITIES

Dr. Walmsley, MD is a clinician investigator with a strong and sustained (over 25 year) track record in the conduct of multicentre RCT in clinic HIV management. Her interest and knowledge translation in the field of HIV, aging and women, and her clinical practice which includes HIV infected aging women on therapy will strengthen recruitment and

interest in this study. She directs a clinical research team who will conduct this study at the Immunodeficiency Clinic in Toronto. The team has participated in over 150 HIV related studies and have excellent recruitment and retention records.

Dr. Alice Tseng, PharmD is a specialist consultant at the TGH Immunodeficiency Clinic, co-investigator on several CIHR grants and cofounder of the Canadian HIV/AIDS Pharmacists Network. She will provide pharmaceutical expertise. She will be responsible for reviewing the potential participants for eligibility including the previous ART regimens, resistance profiles, drug interactions etc. She will review the new regimen with each participant and assess any potential adverse drug events. Estimated ½ day per week on the project.

Dr. Melody Ren, MD is a second year infectious diseases fellow under the supervision and mentorship of Dr. Walmsley. She has expressed interest in pursuing a career in HIV related research. She will be involved in the recruitment and follow up of the participants and in assisting in the analysis. This will enable her to expand her knowledge around clinical trials and assist with future career opportunities. She will be responsible for recruiting and following patients. She will write the initial draft of the manuscript. She will commit one day per week to the project.

Dr. Ella Huszti PhD is a Biostatistician at the Biostatistics Research Unit at TGH who has been conducting analyses for HIV research. She will provide biostatistics expertise and oversee the statistician conducting the analysis. She will commit ½ day per week to the project.

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