Targeted **A**nti**C**oagulation **T**herapy to reduce **I**nflammation and **C**ellular **A**ctivation in **L**ong-term **HIV** Disease (**TACTICAL-HIV**)

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Protocol Chair: Jason Baker, MD, MS

Lead Statistician: Julian Wolfson, PhD

Protocol Manager: Namo Tetekpor, MPH, MS

Protocol Team Members: Nigel Key, Russell Tracy, Kathleen Brummel-Zeidens, Irini Sereti, Micah Mooberry, Jane Kennedy

NOTE: This protocol was developed consistent with 'Standard Protocol Items: Recommendations for Intervention Trials' (the SPIRIT initiative).[1]

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List of Abbreviations

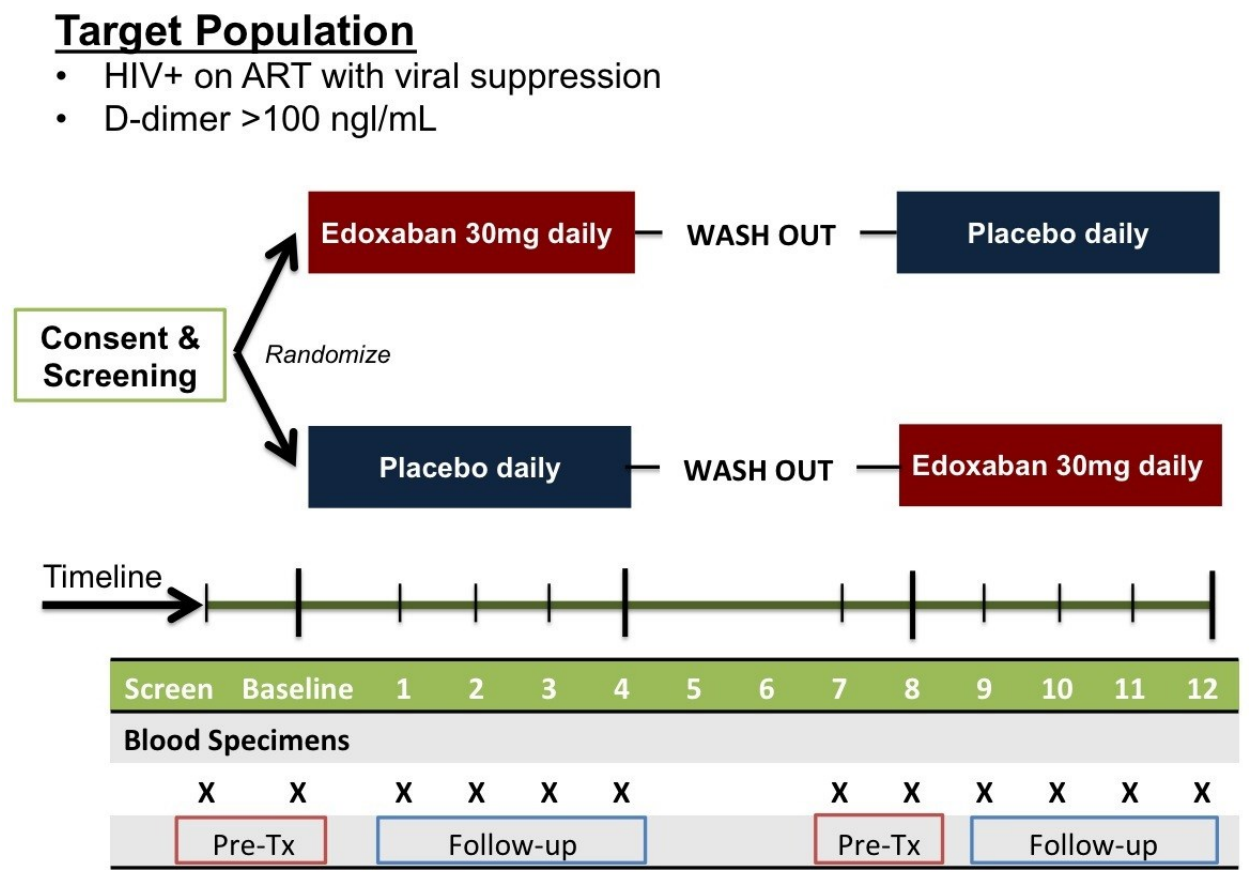
AE	Adverse Event/Adverse Experience
AIDS	Acquired Immune Deficiency Syndrome
ARB	Angiotensin Receptor Blocker
ART	Antiretroviral Therapy
BARC	Bleeding Academic Research Consortium
BMP	Basic Metabolic Panel
BP	Blood Pressure
CCC	Clinical Coordinating Center
CHD	Coronary Heart Disease
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CVD	Cardiovascular Disease
DCC	Data and Coordinating Center
DM	Diabetes Mellitus
DSMB	Data and Safety Monitoring Board
DVT	Deep vein thrombosis
ENGAGE AF-TIMI	Effective anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombylysis in Myocardial Infarction 48
ESPRIT	Evaluation of Subcutaneous Proleukin® in a Randomized International Trial
F	Factor (refering to a coagulation factor, designated by a Roman Numeral; e.g., FX)
FDA	Food and Drug Administration
FXa	Activated Factor X (ten)
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IL-6	Interleukin-6
IND	Investigational New Drug
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IRB	Institutional Review Board
MP	Microparticle
N	Number (typically refers to participants)
NHLBI	National Heart Lung and Blood Institute, NIH
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
PAR	Protease Activated Receptor
PCA	Procoagulant Activity
PD	Pharmacodynamics
PBMC	Peripheral Blood Mononuclear Cells
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QIA	Quantitative Image Analysis
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SD	Standard Deviation
SILCAAT	Subcutaneous, Recombinant, Human Interleukin-2 in HIV-Infected Patients with Low CD4+ Counts Under Active Antiretroviral Therapy
SMART	Strategic Management of AntiRetroviral Therapy
TF	Tissue Factor

List of Abbreviations

VTE Venous thromboembolism

	Protocol Summary
Full Title	Targeted Anticoagulation Therapy to Reduce Inflammation and Cellular Activation in Long-term HIV Disease
Short Title	TACTICAL-HIV
Clinical Trial Phase	Phase 2
IND Sponsor	*NA*
Conducted By	Minneapolis Medical Research Foundation and the University of Minnesota
Principal Investigator	Jason Baker, MD, MS
Lead Statistician	Julian Wolfson, PhD
Sample Size	40 participants
Study Population	HIV positive patients on stable ART with HIV RNA level ≤200 copies/mL, D-dimer level ≥100 mg/L (or ng/mL), and no current/anticipated anti-platelet or anti-coagulation treatment
Accrual Period	Anticipated enrollment 1 year
Study Design	Cross-over placebo-controlled trial, where participants are randomized 1:1 to the sequence they receive edoxaban 30mg or matched placebo daily (double-blind).
Study Duration	12 months; 4 months each of active drug, washout, and placebo
Intervention	Edoxaban 30mg versus matching placebo taken daily
Primary Objective	To evaluate the effects of pharmacologic FXa inhibition (via edoxaban) on inflammation, as reflected in plasma IL-6 levels
Secondary Objectives	Evaluate the effects of edoxaban on monocyte and T-cell activation, coagulation and TF activity, other blood markers of systemic inflammation, and adherence and tolerability

Schematic of Study Design:



Statement of Compliance

This trial will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and the applicable regulatory requirements including U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46 and 21 CFR 50, 56 and 21 CFR 312), directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use as amended by Commission Directive 2005/28/EC and NIAID Clinical Terms of Award. All key personnel (all individuals responsible for the design and conduct of this study) have completed appropriate Human Subjects Protection Training.

1 INTRODUCTION

1.1 Background and Rationale

1.1.1 Premise

Understanding and mitigating persistent inflammation and coagulation activation is central to improving the quality and quantity of life for contemporary HIV-positive persons. HIV treatment with antiretroviral therapy (ART) effectively and durably suppresses viral replication leading to improved survival and profound reductions in risk for AIDS, though excess clinical risk remains from non-AIDS-related end-organ diseases such as cardiovascular disease (CVD). Findings from multiple epidemiologic studies have reported associations between inflammatory (e.g. interleukin-6 [IL-6]) and coagulation (e.g., D-dimer) biomarker levels and risk for CVD and all-cause mortality, independent of traditional risk factors, HIV factors, and other biomarkers. Furthermore, despite effective treatment with ART, IL-6 and D-dimer levels remain elevated when compared to uninfected persons, and predict both short- and long-term mortality over 8 years of follow-up among treated HIV patients. Currently, HIV-related alterations in coagulation biology that account for strong D-dimer clinical risk associations, including strategies to mitigate this risk, remain poorly characterized.

We propose a model where hypercoagulation contributes to disease risk, in part, by amplifying inflammatory pathways, in addition to the direct effects of thrombogenesis. We hypothesize that increased generation of activated factor X (FXa) contributes to a systemic elevation in pro-inflammatory cytokine levels (e.g. interleukin-6 [IL-6]) among HIV positive patients. This occurs, in part, via FXa activation of protease activated receptor 2 (PAR-2) on monocytes and tissue macrophages, which perpetuates innate inflammation. It is well established that inflammation up-regulates coagulation pathways, in part via tissue factor (TF) expression and alterations in key coagulation factors—we have shown that both mechanisms contribute to HIV-related hypercoagulation. However, the notion that coagulation activity can itself amplify inflammatory pathways is a more recent, novel, and testable hypothesis for how low-level hypercoagulation may contribute to excess disease risk among HIV patients.

Expanding our understanding of these complex pathways is critical given somewhat inconsistent observations that: a) a number of hypercoagulable changes are present during chronic HIV disease, while, b) clinically apparent clots do not account for most of the long-term disease risk predicted by elevated D-dimer levels. The TACTICAL-HIV trial is a critical step to advance this field, providing essential information on the underlying mechanisms and on candidate immunologic surrogate markers that will inform larger clinical trials of anticoagulant treatments for HIV positive patients.

1.1.2 Scientific Background

The Changing Spectrum of Morbidity and Mortality Among HIV Positive Patients:
Antiretroviral therapy (ART) effectively and durably suppresses HIV replication, leads to immune recovery (increasing CD4+ T-cell counts) and prolonged life expectancy, and

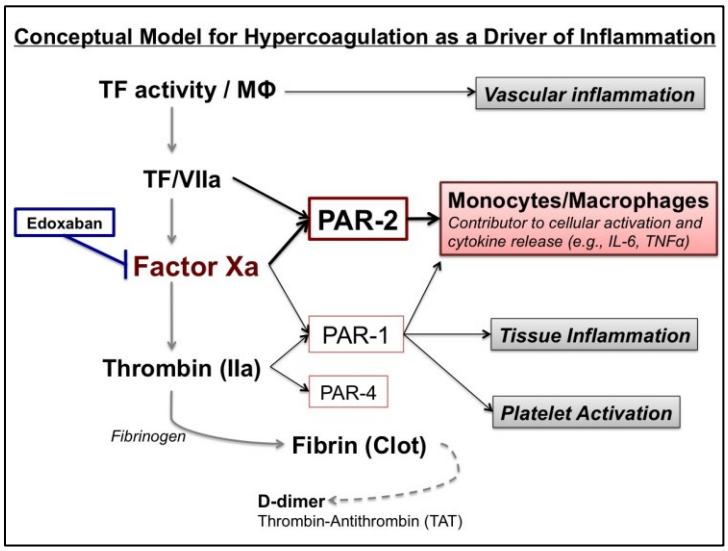
has changed the spectrum of morbidity and mortality among HIV positive persons.[2-8] Among well-treated patients with levels of HIV RNA below the limit of detection, non-AIDS-related conditions are now a more common cause of morbidity and mortality than AIDS.[6, 9-11] The most relevant serious non-AIDS-related diseases in current clinical practice include atherosclerotic cardiovascular disease (CVD), cancer, liver disease, end-stage renal disease, bone disease and subclinical neurocognitive dysfunction. Of these, CVD and cancer constitute the vast majority of clinical events.[5, 10-13]

Reasons for Persistent Inflammation in Persons with ART-treated HIV Infection:
Chronic inflammation in HIV disease arises from high levels of immune activation. HIV treatment with ART reduces activation of the immune response, including levels of inflammatory cytokines, though most immunologic abnormalities persist compared to HIV uninfected persons.[14, 15] HIV infection is classically associated with T-cell activation, reflecting adaptive immunity, but recent data demonstrate that innate immune activation also contributes to chronic inflammation.[16-20] The precise mechanisms driving high level immune activation are not entirely clear, but appear to involve both a persistent anti-HIV response (even with HIV RNA at low levels) and a more generalized immune activation (e.g., cytokine release).[15, 21-23] Specifically, innocent bystander activation—in which the pro-inflammatory aspects of HIV infection non-specifically drive T-cell and monocyte activation—also contributes.[22, 24, 25] Other factors unique to HIV disease that may contribute to excess inflammation include: a) HIV-mediated destruction of gut epithelium, leading to greater translocation of bacterial products, b) dysregulated inflammatory responses to co-pathogens (e.g., CMV), and c) irreversible damage to the adaptive immune system (including lymphatic tissues).[26-31] Treatments that reduce persistent inflammation among ART-treated HIV positive patients are lacking, and represents an area of extensive research.[32]

Potential Pathologic Consequences of HIV-related Hypercoagulation:
We have demonstrated that hypercoagulation in HIV disease arises, in part, from increases in tissue factor (TF) procoagulant activity and alterations in the composition of coagulation factors.[33, 34] Potential mechanisms driving these changes include: a) non-specific innate inflammation,[35, 36] b) non-specific response to viral infections (e.g., interferon gamma release),[37, 38] and c) HIV specific damage, e.g., loss of mucosal integrity with microbial translocation and TF activation.[39] The net-result is hypercoagulation; this concept is supported by data from our group and others showing that D-dimer levels remain elevated in treated HIV disease.[14, 39-41]

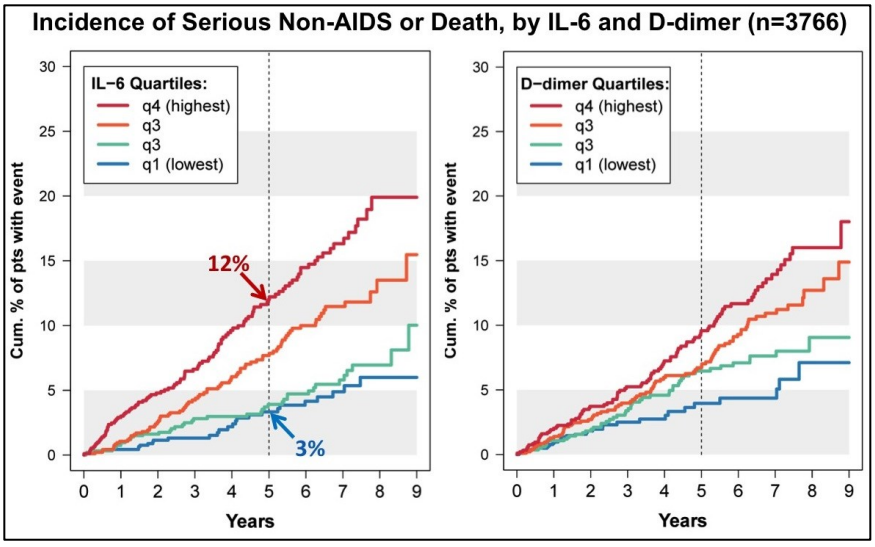
Although HIV is associated with increased risk for venous thromboembolic disease, very few clinical events predicted by D-dimer levels include large vessel thrombosis.[42] One explanation provided by non-human primate data suggests that hypercoagulation may manifest in end-organ damage via microvascular clotting resulting in thrombotic microangiopathy.[43] This hypothesis is supported by the well-recognized association between HIV and thrombotic thrombocytopenic purpura (TTP).[44] Another novel explanation entails our innovative aim 1 hypothesis, namely that hypercoagulation contributes to clinical risk in treated HIV disease by up-regulating systemic inflammation, in part, via TF/VIIa and FXa activation of PAR-2 pathways (**Figure**).

Recent data have established the interplay between coagulation and inflammation, including bi-directional feedback.[36] Protease activated receptors (PARs) play a central role in mediating this cross-talk, as established in conditions like acute lung injury, sepsis and myocardial infarction.[45, 46] PAR-1 is activated by various proteases, including FXa and thrombin, whereas PAR-2 is activated by the TF:FVIIa complex, FXa, as well as other proteases[47-50] In this proposal we use an experimental approach to test this hypothesis by blocking FXa with low-dose edoxaban.



Outcomes: IL-6 (and D-dimer) Predict Risk for Non-AIDS Defining Clinical Events:

Excess risk for non-AIDS conditions is due to multiple factors, including a higher burden of traditional risk factors, but persistent inflammation despite ART is a key HIV-related risk factor. Recent data from a number of epidemiologic studies have shown that inflammatory biomarkers well validated in the aging and cardiovascular fields[19, 51-54] are elevated with untreated and (to a lesser degree) treated HIV infection,[14, 40, 55] and predict risk for CVD, cancer, and non-AIDS mortality.[42, 56-61] Our group conducted a series of nested case-control and cohort studies in collaboration with INSIGHT investigators, using data from 3 large HIV trials (SMART, ESPRIT, and SILCAAT), and determined that associations for risk of CVD, cancer, a composite of serious non-AIDS events, and all-cause mortality was most robust for levels of interleukin-6 (IL-6), as well as D-dimer (**Figure**).[62-64] These associations are not attenuated by adjusting for HIV or traditional CVD risk factors, are several-fold higher than reported in HIV-negative studies, and persist over a median of 5.5 years of follow-up. Importantly, these IL-6 and D-dimer associations are independent of each other, making them ideal candidate surrogate clinical risk markers reflecting the potential harm from systemic inflammation and coagulation.[42, 63, 65, 66] An important implication is that any treatment candidate that down regulates both pathways (e.g., edoxaban) has significant potential for corresponding clinical benefit.



1.2 Hypothesis and Objectives

We hypothesize that increased generation of activated factor X (FXa) contributes to a systemic elevation in pro-inflammatory cytokine levels (e.g. IL-6) among HIV positive patients. This occurs, in part, via FXa activation of protease activated receptor 2 (PAR-2) on monocytes and tissue macrophages, which perpetuates innate inflammation. We will test our hypothesis with an oral antagonist to FXa (edoxaban), and quantify the immunologic effects of PAR-2 inhibition on systemic inflammation and monocyte activation. We will address the following specific objectives:

- **Primary Objective:** Evaluate the treatment effects of edoxaban on systemic inflammation

- **Main Secondary Objectives:** Evaluate the treatment effects of edoxaban on monocyte activation, tissue factor activity and coagulation.

2 METHODOLOGY

2.1 Trial Design

The potential benefits of pharmacologic inhibition of FXa will be studied among HIV positive participants receiving ART with suppressed HIV viral load and a D-dimer >100 ng/mL. The study design is a cross-over placebo controlled randomized trial of edoxaban 30mg daily versus matched placebo (n=40 total participants). After screening and baseline visits, participants will be randomized to the sequence of drug administration (i.e., edoxaban vs. placebo). The full visit sequence is listed below in **Table 1**. After randomization, participants will start study medication #1 and follow-up for visits at months 1, 2, 3 and 4. They will then stop study medication for 3 months, return for visits at months 7 and 8 (analogous to screening and baseline, respectively), then start study medication #2 and follow-up for visits at months 9, 10, 11, and 12.

Table 1: Study Visit Timing and Measures	Screening	Baseline	Month 1	Month 2	Month 3	Month 4	Washout	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Study Medication #1 (e.g., edoxaban)		X	X	X	X	X							
Study Medication #2 (e.g., placebo)									X	X	X	X	X
Blood measurements	X	X	X	X	X	X		X	X	X	X	X	X

This cross-over design will efficiently study short-term treatment effects among a smaller sample. The half-life of edoxaban is approximately 6-10 hours and treatment related changes in biomarkers such as IL-6 and D-dimer is typically present within 1-2 months. Thus, the washout period of 3 months extends beyond potential post-treatment effects, prior to starting study medication #2.

The treatment effect (i.e., changes from pre-treatment levels) over 4 months will be assessed in measures of inflammation, immune activation, tissue factor (TF) activity

and coagulation. For comparisons with placebo, each participant will then serve as his or her own control in this cross-over design.

2.2 Study Population

The target population is HIV positive patients receiving effective ART treatment with viral suppression. These participants are at low risk for AIDS progression, and low clinical event risk over the short term. Health consequences in this population are largely due to non-AIDS defining complications over the longer term, related to persistent inflammation and coagulation activity (e.g., CVD). Participants must also not have co-morbid diseases known to be pro-inflammatory, or have current use of immune-modulatory or anti-coagulant drugs. Participants will be recruited from the HCMC HIV clinic, in Minneapolis, which provides care for 2000 HIV positive participants (>80% of whom are receiving ART with suppressed viral load).

A D-dimer threshold of ≥100 ng/mL is used to improve the potential risk-benefit balance, by excluding those at the lowest clinical risk with little to no evidence of coagulation activation. This threshold corresponds approximately to the separation between the 1st (lowest) and 2nd quartile of D-dimer levels among ART-treated participants (n=3766) in our preliminary data (see Figure of Kaplan Meier plots within scientific rationale above). Participants with D-dimer levels in the 1st quartile had very low rates of clinical events during follow-up. This D-dimer threshold enriches the target population with participants most likely to benefit while still studying the treatment effects over a wide range of coagulation activity. Clinical lab measures of D-dimer will be used for screening only; outcome analyses will use D-dimer measures from the central core lab.

2.2.1 Inclusion Criteria

- HIV infection (verified by previous positive antibody or detectable HIV RNA level)
- Age ≥18 years
- Receiving continuous ART for ≥2 years (regimen changes >3 months prior to enrollment are acceptable)
- HIV RNA level ≤200 copies/mL for ≥1 year (1 measure ≥200 allowed if also <500 and preceded and followed by one or more values ≤200 copies/mL)
- D-dimer level ≥100 ng/mL in FEU, or ≥50 ng/mL in DDU, measured within 60 days of randomization
- Estimated creatinine clearance ≥50 mL/min
- Body weight ≥60kg
- Do not anticipate starting (or stopping) statin or aspirin therapy during the study
- For women of child bearing potential, agrees to use a reliable form of birth control

2.2.2 Exclusion Criteria

- Pregnancy or breast feeding
- A contra-indication to taking edoxaban
- A clinical indication for anticoagulation therapy (e.g., atrial fibrillation or DVT/PE)

- Treatment with anti-platelet or anti-coagulation therapy; prior treatment with aspirin is not itself an exclusion.
- Daily NSAID use; periodic use (i.e., ≤3 days per week) is not itself an exclusion.
- Treatment with systemic immune-modulatory therapy within the past 3 months.
- Grade ≥1 hematology lab abnormality for INR (>1.1 x ULN), hemoglobin (<10.0 g/L), platelets (<100,000 cells/μL), or WBC (<2,500 cells/mm^3)
- Grade ≥2 lab abnormality for chemistries (i.e., BMP) or liver panel
- No alcohol or illicit drug abuse/dependency currently, or anticipation of ongoing use during study
- History of prior myocardial infarction or unstable atherosclerotic disease
- History of prior stroke or transient ischemic attack (TIA)
- History of active gastrointestinal ulcer or bleeding disorder within the prior year
- Intent to have surgery during the study period (12 months)
- Hepatitis C treatments (e.g., interferon, ribavirin, protease inhibitors) within the past 3 months
- Cirrhosis or hepatic impairment (e.g., Child-Pugh class B or C).
- Seizure disorder
- Previous/current CNS space occupying lesion (e.g., Toxoplasmosis, mTB) with persistent abnormalities on CNS imaging after completion of treatment.
- Surgical or invasive procedure anticipated during study period.
- Invasive cancer in the prior year or receiving cancer treatment (not including carcinoma-in-situ or basal cell cancer of the skin)
- Rheumatologic or inflammatory disease, systemic in nature (e.g., systemic lupus erythematosus, rheumatoid arthritis, vasculitis, sarcoidosis, Crohn's disease)
- Assessment by the clinical investigator that enrollment into the study could entail excess risk to the participant, beyond what is intended or expected.

2.3 Study Medication Intervention

At baseline, participants will start blinded study medication, either edoxaban or matching placebo at 30mg daily. After 4 months they will stop study medication. Participants will remain off study drug between month 4 and month 8. At the month 8 visit, participants will again begin blinded study medication, corresponding to the comparison drug for that which was taken between baseline and month 4. Thus, participants are randomized to either: a) active study drug x4 months, washout (no drug), matched placebo x4 months, or b) matched placebo x4 months, washout (no drug), active study drug x4 months. Double blinding is maintained.

Clinical labs, including HIV staging labs and coagulation measures, will be monitored prior to initiating each study medication and at 1 and 4 months after starting each study medication (see **Table 2** of study outcomes and visit schedule below)

2.3.1 Edoxaban

Edoxaban is a competitive direct inhibitor of FXa, and will be used to test our central hypothesis that FXa activity (via PAR-2) contributes monocyte activation and systemic

inflammation. Edoxaban exhibits >10,000-fold selectivity for FXa relative to thrombin, which exhibits immunologic cross-talk via activation of PAR-1. Edoxaban is currently FDA-approved for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) and as treatment for deep vein thrombosis (DVT) or pulmonary embolism (PE). The recommended dose is 60mg orally once daily for both indications (NVAF and DVT/PE). The dose should be reduced to 30mg once daily for patients with an estimated creatinine clearance of 30-50 mL/min. Finally, for the NVAF indication the FDA recommended not using edoxaban among patients with a creatinine clearance >95 mL/min due to decreased efficacy in the prevention of ischemic stroke; given this was not due to an increase risk for bleeding complications, there is no upper limit in creatinine clearance as part of the inclusion/exclusion criteria for TACTICAL-HIV.

In the TACTICAL-HIV study, study drug will be taken as one 30mg dose of edoxaban (or matching placebo) daily in the morning (AM), and only participants with a creatinine clearance >50 mL/min will be enrolled.

Pharmacokinetic properties of edoxaban include rapid absorption with attainment of peak plasma concentration within 1-2 hours, and a half-life of approximately 6-10 hours.[67] Metabolites are formed largely via hydrolysis with only minor contribution from cytochrome P450 (CYP) 3A. There is little systemic accumulation of edoxaban at 10 days after administration.[67] Edoxaban can be administered with or without food, with little effect on bioavailability. Edoxaban is a substrate for the efflux transporter P-glycoprotein (P-gp), and as a consequence serum levels may increase with concomitant administration of strong P-gp inhibitors (e.g., verapamil, quinidine). Renal clearance likely involves active secretion.

Risks associated with edoxaban use include bleeding. Phase-3 clinical trial safety data arises from the ENGAGE AF-TIMI and Hokusai-VTE trials.[68, 69] Major bleeding event, defined by the International Society on Thrombosis and Haemostasis, was 1.6% with edoxaban 30mg daily among those with atrial fibrillation in ENGAGE AF-TIMI, and also 1.6% among those receiving a higher dose of edoxaban at 60mg for clinical VTE.[68-70] In addition, in Hokusai-VTE study populations the rate of any clinically relevant bleeding was 8.5% for edoxaban (compared to 10.3% for warfarin). The most common side effects overall in these studies were bleeding, rash, abnormal liver tests, and anemia.

The greatest potential for drug interactions entails the potential need for dose reduction with concomitant use of P-gp inhibitors. Concomitant administration of platelet-inhibitors or NSAIDs may also increase bleeding risk. Edoxaban is not safe for use during pregnancy.

Routine clinical lab monitoring of coagulation tests are not indicated during edoxaban use. Anti-factor Xa assay increases proportionally to serum levels of edoxaban. INR/PT and aPTT increase with edoxaban use, but to a highly variable degree. Episodes of bleeding from direct FXa inhibitors such as edoxaban are managed clinically with supportive care and potential use of Prothrombin Concentrate Complex (PCC).

2.3.2 Randomization and Blinding

Eligible participants who consent to study procedures will be randomized 1:1 to the sequence that they receive edoxaban or matching placebo. Treatment assignments will be generated using a permuted block randomization scheme. Sites will use a secure, on-line program to obtain treatment assignments. The program will also verify eligibility and the existence of key baseline data. Treatment assignments will be verified and recorded in a dataset blinded to view by site staff.

A bottle ID number (BID) unique to each bottle will be assigned to participants, and used by study staff to obtain the correct blinded study drug (active or placebo). Site staff will not have access to the treatment assignment linked to each bottle number, and bottle numbers will not be assigned in sequence.

Blinding will occur at 3 levels: 1) treatment assignment will be blinded, 2) interim data summaries will blinded to all but the unblinded statistician and 3) core laboratory staff will be blinded to treatment group. In the rare event that the blind must be broken, every effort will be made to minimize the extent of the unblinding (for staff and participants) and an assessment of blinding will occur at the end of the study.

The blind may be broken in cases of a clinical bleeding event, where reversal of anti-coagulation is being considered—e.g., with prothrombin concentrate complex (PCC). Procedures will be established for the study coordinator to obtain the key/blind for a given participant from the dispensing pharmacy.

2.3.3 Study Drug Production and Distribution

Active edoxaban 30mg tablets and matching placebo will be provided and distributed by Daiichi Sankyo, Inc. Study drug will be provided in prepackaged bottles that include a one-month supply plus additional drug to facilitate a visit window of +/- 2 weeks (n=42). Each bottle will have a unique bottle ID number, along with appropriate packaging, license and content information per regulations. Clinical site pharmacy will receive and store study drug until dispensing to participants or site staff (who then dispense to participants) in the context of study visits. One bottle will be dispensed at baseline, and one additional bottle at the 1, 2, and 3-month study visits. No study drug will be dispensed or taken between month 4 and 8, but one bottle will again be dispensed at the 8, 9, 10 and 11-month study visit.

The clinical site will communicate directly with the Daiichi Sankyo study team representative to ship drug to sites. Daiichi-Sankyo will provide the DCC with the key linking the BID (unique to each bottle) with whether the contents are active edoxaban or matching placebo. The DCC will then instruct sites which bottle(s) to dispense to patients based on the BID.

2.4 Outcomes

Primary Outcome

- IL-6 plasma levels: the difference between treatment and control conditions in change from pre-treatment to on-treatment values

Secondary Outcomes

- Adherence
- Tolerability and side effects
- Bleeding episodes: Major bleeding and those defined as BARC Type 2, 3, 4, 5
- Monocyte activation: cellular phenotypes (e.g., CD14+/CD16+), monocyte microparticles (MMPs), and plasma biomarkers (e.g., sCD14, sCD163, TNF-α, sTNFr-1)
- Functional TF pro-coagulant activity: TF-positive microparticle (MPTF), cell-associated TF, and whole blood TF pro-coagulant activity
- Coagulation activity (e.g., D-dimer levels, thrombin-antithrombin complex [TAT], and functional thrombin potential assay)
- Endothelial activation: endothelial cell microparticles (EMPs)
- T-cell activation and senescence phenotypes in blood
- Explore the potential impact of edoxaban co-administered with ART on viral suppression and the anti-inflammatory treatment effect (via subgroup analyses defined by type/class of antiretroviral use)

Important Exploratory Analyses

- Determine if the treatment effect from Edoxapan differs depending on pre-treatment FXa activity (estimated from computational modeling)
- Estimate the potential effect of Edoxaban treatment on clinical event risk (e.g., serious non-AIDS events, CVD, mortality, etc.), as predicted by IL-6 and D-dimer associations with clinical risk.

2.4.1 Study Visit Schedule

Participants will be screened and, if eligibility criteria are met, will be randomized at the baseline visit to start active study drug or matched placebo (blinded). Randomization will occur within 60 days of screening.

After screening and baseline visits, participants will start edoxaban 30mg once every morning (or matched placebo). They will return for study visits at months 1, 2, 3 and 4, after which they will stop study medication. At month 7 and 8 they will return for repeat laboratory and study visit procedures. After the month 8 study visit is completed, participants will resume blinded study medication (either edoxaban 30mg or placebo, whichever was not given from baseline to month 4), and then follow-up for study visit procedures at months 9, 10, 11 and 12. The visit schedule is outlined in the table below. Patients will be fasting for all blood draws (except screening).

Toxicity labs and a clinical assessment will be ascertained as part of follow-up study visits. If clinical labs (e.g., HIV RNA level, CD4 count, BMP, hepatic panel, and CBC) are available as part of routine clinical monitoring during the study visit window, these results may be used in place of repeating clinic labs at the study visit. If new symptoms develop that may be related to study medications, the site study investigator is to be

notified within 24 hours and a clinical determination is to be made whether additional toxicity labs and/or adherence requires assessing.

TABLE 2: Visit Timeline	Screening	Baseline	Month 1	Month 2	Month 3	Month 4	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
ON STUDY DRUG AT VISIT	--	--	+	+	+	+	--	--	+	+	+	+
Informed consent and eligibility criteria	X	--	--	--	--	--	--	--	--	--	--	--
Randomization	--	X	--	--	--	--	--	--	--	--	--	--
Clinical Assessments												
Adherence	--	--	X	X	X	X	X	X	X	X	X	X
Side Effect Screen/Assessment	--	X	X	X	X	X	X	X	X	X	X	X
Bleeding & Adverse Events	--	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	--	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Measures												
D-dimer screen	X*	--	--	--	--	--	--	--	--	--	--	--
HIV viral load	X*	X	X	X	X	X	--	X	X	X	X	X
CD4 count	--	X	--	--	--	X	--	X	--	--	--	X
CBC, INR, aPTT	X*	X	X	X	X	X	--	X	X	X	X	X
Anti-Xa		X				X		X				X
BMP, LFTs	X*	X	X	--	--	X	--	X	X	--	--	X
Hep Bs Ag & Hep C Ab	--	X*	--	--	--	--	--	X*	--	--	--	--
Lipid Panel	--	X	--	--	--	--	--	--	--	--	--	--
Pregnancy test (for women)	X	--	X	X	X	X	--	X	X	X	X	X
Study Outcomes												
Stored plasma	X	X	X	X	X	X	X	X	X	X	X	X
Stored PBMCs	--	X	X	--	--	X	--	X	X	--	--	X

**Lab values from anytime within 30 days of visit can be used; previously positive hepatitis labs (i.e., HBsAg or HCV Ab) do not need to be repeated.*

2.4.2 Power and Sample Size Considerations

The study employs a cross-over design, with participants serving as their own comparison. To reduce variability in the primary outcome (log IL-6), we will average the 2 pre-treatment measures (i.e., screening and baseline or months 7 and 8) as well as the 4 follow-up measures (i.e., months 1, 2, 3, and 4, or months 9, 10, 11, and 12).

2.4.2.1 Primary outcome (IL-6) power and sample size

We estimate that this cross-over design with n=40 participants will have 80% power at level alpha=0.05 to detect a treatment effect of 0.35 SD on log IL-6, corresponding to a 23% relative difference in (non-log transformed) IL-6 levels between treatment conditions. In addition to the study and analysis structure described above, our simulation-based power calculation assumes a study attrition rate of 10% (i.e., 90% of subjects provide valid follow-up data). Measurements were simulated from the following random effects model: $Y_{ijk} = \beta_0 + b_{0i} + \beta_1 trt_{ij} * fu_{ij} + \epsilon_{ijk}$, where trt_{ij} is the treatment indicator and fu_{ij} is the indicator that the measurement is a follow-up

measurement. b_{0i} is an individual-specific random effect, and ϵ_{ijk} is the residual, assumed independent of b_{0i}. b_{0i} and ϵ_{ijk} are assumed to be normally distributed with zero mean and variances chosen to simultaneously satisfy $Var(Y_{ijk}) = Var(b_{0i}) + Var(\epsilon_{ijk}) = 0.55$, and $\rho(Y_{ijk}, Y_{ijl}) = \frac{Var(b_{0i})}{Var(b_{0i})+Var(\epsilon_{ijk})}$ = 0.4, respectively the cross-sectional variance and longitudinal correlation of log IL-6 observed in data from the SMART study.

2.4.2.2 Power for secondary objectives and exploratory analyses

Few pilot data are available to characterize the correlation between multiple measurements of monocyte activation and monocyte TF-activity. However, preliminary data provide variance estimates for some of these markers.[71] We conducted a simulation similar to that described for the primary outcome above, varying the between-time correlation of markers from 0.1 (low) to 0.7 (high). Across all cases, the given sample size gave at least 80% power to detect a 0.35 SD effect size, which corresponds to 22%, 32%, 24%, and 10% relative reductions in CD14+/CD16+, TF+, sCD163, and sCD14, respectively. For D-dimer, our study will have approximately 80% power to detect a 26% difference in (non-log transformed) levels of this marker between treatment conditions. Though data are unavailable on TAT, it is anticipated that the between-measurement correlation is likely to be the same and hence a 0.35 SD effect will correspond to a difference of approximately 20-30% on this marker.

Our analysis is also well-powered to detect a difference in treatment effect by degree of continuous pre-treatment FXa activity: we estimate >80% power to detect a 0.25 SD log IL-6 difference in treatment effect (~22% relative difference on original IL-6 scale) between groups differing by 1 SD in FXa activity.

The effects on IL-6 and D-dimer that we are well-powered to detect with our given sample size (i.e., ~25% reductions) correspond to estimated reductions of ~37% in the risk for the composite outcome of serious non-AIDS event (CVD, cancer, liver or renal event) or death (see **Scientific Background 1.1.2**), when using a joint model and assuming both biomarkers are reduced by the same amount. If one marker changes more than the other, e.g., a 30% reduction in D-dimer levels with a minimal 5-10% reduction in IL-6 levels, this would correspond to a predicted 20% reduction in event risk (again, see IL-6 and D-dimer data in **Scientific Background 1.1.2**).

3 CLINICAL MANAGEMENT

3.1 Administration of Study Procedures

Study site coordinators will be trained prior to study implementation and will perform all study visit procedures during the conduct of the study. The lead physician investigator will conduct clinical and drug toxicity assessments as indicated during the study.

3.2 Categorization of Bleeding Events

All bleeding events will be categorized using the Bleeding Academic Research Consortium (BARC) definitions outlined below and in **appendix B**. In addition a 'major bleeding' event will be defined based on definitions established by the International Society on Thrombosis and Haemostasis (ISTH).

3.2.1 ISTH Definition of Major Bleeding

Major bleeding in non-surgical patients are defined by the following criteria:

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of ≥2 g/dL, or leading to transfusion of ≥2 units of whole blood or red cells.

3.2.2 Bleeding Academic Research Consortium (BARC) Definitions

BARC definitions are reviewed in detail in Appendix B, but briefly entail:

- Type 0 – No bleeding
- Type 1 – Bleeding that is not actionable or requiring healthcare evaluation
- Type 2 – Overt bleeding beyond what would be expected for a clinical circumstance that requires healthcare evaluation but does not meet criteria for type 3, 4, or 5.
- Type 3 – Overt bleeding with hemoglobin drop >3 g/dL, bleeding requiring transfusion, intracranial hemorrhage, or bleeding into other designated body compartments (e.g., cardiac tamponade)
- Type 4 – Bleeding related to cardiac surgery
- Type 5 – Fatal bleeding

3.3 Study Management of Bleeding Events

The site investigator will review all bleeding events, of any grade or severity, as soon as the study team becomes aware of the event. At that time, the event will be categorized in terms of BARC or ISTH classification and a corresponding decision will be made with respect to continuation of study drug.

Participants with BARC Type 1 and 2 adverse bleeding episodes will continue with the study drug, unless assessment by the study investigator or medical care provider indicates that continuing on study drug would be associated with escalation of the bleeding event or other excess risk in the clinical context.

Participants with BARC Type 3 or a 'major bleeding' event will have the study medication permanently discontinued. Participants must be followed regularly (e.g., weekly) until resolution of the adverse event.

Any participant planning to undergo a surgical procedure during the follow-up period should not be enrolled into the study. If there is a need for a surgical procedure during the follow-up period, the study drug should be discontinued permanently. It is important that the treating physician be made aware the participant may have been taking edoxaban (and oral FXa inhibitor).

If any participant suffers a fatal bleed the blind for that participant will be broken. If the participant were taking edoxaban at the time of the event, the study will be temporarily stopped while the DSMB can review the event in the context of other clinical and safety information.

Participants should be referred for acute medical evaluation with any overt clinical bleeding, bleeding consistent with BARC Type 2 or above, or a major bleeding event. Study team investigators should immediately make the clinical treatment team aware that the study participant is potentially taking edoxaban, a factor Xa inhibitor; this should include a direct phone call as well as documentation in the electronic health record. Clinical management will include standard of care along with cessation of study medication. See **APPENDIX C** for an approach to bleeding complications related to Factor Xa-inhibition with edoxaban. **NOTE:** *Prothrombin concentrate complex (PCC), such as K-Centra (i.e., replacement of factors II, VII, IX, and X), may be effective in management of bleeding in the context of FXa inhibition, but there is no current antidote and dialysis is not effective.*

3.4 Study Drug Cessation

At baseline, participants will start blinded study medication consisting of edoxaban or matching placebo at 30mg every morning. **No dose adjustment can be made during the study.** Tolerability, side effects, adverse events and clinical laboratory monitoring will be assessed at each study visit (via participant report and clinical labs), and at anytime during the study per the discretion of the clinical site investigator.

If an adverse event of grade ≥3 is assessed as related to study drug, study medication should be stopped. If a grade 2 rash is persistent, study medication may also be stopped at the discretion of the site investigator. Medication may also be stopped for grade <3 adverse events if the study investigator determines that the participant may be at risk for an escalation of the adverse event, persistent toxicity, or at risk in excess of what would be expected due to other contextual circumstances. If study medication was discontinued due to an adverse event of grade <3 that is not expected to recur, the study investigator may recommend re-initiating study medication.

Any of the following will also result in stopping study medication (see section 3.1.2):

i. Major bleeding event
ii. BARC Type 3 bleeding event
iii. Any surgical procedure with bleeding risk
iv. Investigator or participant wishes to stop study medication

3.5 Adherence and Tolerability

Adherence will be assessed via participant self-report and pill count (by study coordinators) during each follow-up visit. Tolerability will also be assessed via self-report, with additional laboratory assessments performed for toxicity.

3.6 Concomitant Medications and Antiretroviral Therapy

Any antiretroviral medication and ART regimen may be used that is recommended as a potential option in the US DHHS guidelines on use of ART for adults with HIV infection.[72]

Concomitant medications will be assessed at every study visit. Medications contraindicated for this study include those that may increase risk of bleeding and/or substantially increase the effective exposure or serum drug levels of edoxaban (e.g., substrates for P-gp). **NOTE:** There are numerous medications that are substrates for P-glycoprotein (P-gp), and therefore have potential to influence edoxaban levels (and vice-a-versa). Concomitant medications associated with potential drug-drug interactions that are anticipated to be modest/minimal will not necessarily be contra-indicated for this short-term study (e.g., atorvastatin, digoxin).

3.6.1 Contraindicated concomitant medications for this study include:

i. Aspirin (daily use >3 days)
ii. Platelet inhibitor (e.g., clopidogrel)
iii. NSAIDs (daily use >3 days)
iv. Fibrinolytic therapy (within 1 month)
v. Verapamil
vi. Quinidine
vii. Amiodarone
viii. Dronedarone
ix. Ketaconazole and other azoles
x. Erythromycin and other macrolides
xi. Illicit drug use (e.g., cocaine)
xii. Medications or drugs that may be associated with unacceptable increase risk to participants, as determined by the study investigator.

3.7 Data Collection

All data will be entered into web-based case report forms and transferred to servers at the data coordinating center (DCC) at University of Minnesota School of Public Health using REDCap software. Paper source documentation will also be kept in a secure, locked location at each clinical site. Study coordinators and/or other qualified research technicians will perform all blood draws and blood specimen processing.

3.8 Blood Specimen Processing

The blood specimen collection tubes and processing protocols are outlined in the study laboratory manual. Participants will be fasting for all study visit blood draws (optional for screening visit). Plasma and serum specimens will need to be processed from whole blood within 1 hour of collection. Peripheral blood mononuclear cell (PBMC) specimens will be processed locally at the University of Minnesota and stored until analyzed by core immunology laboratory at the end of follow-up.

3.9 Clinical Labs

All clinical labs will be measured on fresh blood specimens the day of the study visit, at the HCMC clinical lab using CLIA approved standards. D-dimer levels at screening will be assessed at HCMC using HemosIL D-Dimer HS, a latex-enhanced turbidimetric immunoassay, on the ACL TOP automated analyzer (from Instrumentation Laboratory). Normal range for D-dimer levels using these methods are 0-229 ng/mL. Plasma HIV RNA level will be estimated using COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0.

The following clinical labs will be assessed to monitor for toxicity per Table 2 above:

i. Complete Blood Count (CBC, with platelet count and differential)
ii. Basic Metabolic Panel (BMP)
iii. Coagulation panel (INR/PT, aPTT, anti-FXa)
iv. Hepatic Function panel (ALT, AST, Total bilirubin)

4 SAFETY AND ADVERSE EVENTS

4.1 Measures to reduce risk for adverse events

Risks related to edoxaban are principally related to bleeding events. To reduce this risk, participants will be counseled to avoid concomitant medications that may increase risk for bleeding and be made aware of potential signs/symptoms that may be associated with occult bleeding (e.g., dyspepsia, black stools, weakness, fatigue).

4.2 Adverse Event Definitions

4.2.1 Adverse Event (AE):

Any untoward medical occurrence in a clinical research participant administered an investigational product, which may or may not have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

If a preexisting condition worsens post-enrollment (frequency increases and/or severity grade increases), it should be reported as an adverse event.

A symptom check-list will be included in the CRF (detailed in the protocol implementation manual) that includes common symptoms or side effects typically related to edoxaban therapy.

Appendix E provides a table of adverse events, with grading criteria, adopted from the DAIDS 2009 Table for Grading the Severity of Adult and Pediatric Adverse Events

4.2.2 Serious Adverse Event (SAE):

Any adverse event occurring at any dose that results in any of the following outcomes:

i. Death,
ii. A life-threatening condition,
iii. A congenital anomaly/birth defect,
iv. Inpatient hospitalization or prolongation of existing hospitalization,
v. Persistent or significant disability/incapacity,
vi. An important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require intervention to prevent one of the outcomes listed above.

4.2.3 Unanticipated Problem (UP):

Any event that is:
i. Unexpected, AND
ii. Related to study participation in this study, AND
iii. Increase the risk of harm to the participant or others (or be an SAE)

4.3 Documenting Adverse Events and Unanticipated Problems

All serious adverse events (SAE) and unanticipated problems (UP), regardless of the assessed relationship with study drug, will be ascertained and recorded on study visit CRFs (through the online REDCAP interface).

All new non-serious adverse events of grade ≥3 or deemed related to study drug will be ascertained and recorded on study visit CRFs (through the online REDCAP interface). Criteria for assigning a grade of severity of adverse events are summarized in **Appendix E.**

NOTE: adverse events based on laboratory criteria will only be ascertained/recorded if ≥ grade 3, and no adverse events will be ascertained/recorded based on CD4+ T-cell count criteria.

There are five severity grades that can be assigned to adverse events, which are defined as follows:

i. Grade 1 = Mild
ii. Grade 2 = Moderate
iii. Grade 3 = Severe
iv. Grade 4 = Potentially life-threatening
v. Grade 5 = Death

Additional information ascertained for each adverse event includes: a) date of onset, b) relationship to study drug (see section 4.3.1 below), c) any action taken on study drug, and d) whether the adverse event qualifies as an SAE (including the criteria fulfilled).

Source documentation (in addition to the CRF variables for AEs) will be collected by research coordinators at the clinical site for all AEs of grade ≤3, SAEs or UPs.

4.3.1 Adverse Event Relationship to Study Drug

For all adverse events grade ≥3, SAEs or UPs that occur after randomization, study investigator(s) will assess the potential relationship of the event to the study medication. One of the following designations will be used:

i. Related: There is a reasonable possibility that the AE may be related to the study agent(s).

ii. Not related: There is not a reasonable possibility that the AE may be related to the study agent(s). Alternative etiology, diagnosis or, explanation for the AE should be provided.

4.4 Reporting Serious Adverse Events and Unanticipated Problems

The IRB (or Human Subjects Committee) and the Data Safety Monitoring Board (DSMB, see section 5 below) will receive notification of all **SAE**s that are deemed protocol related, or a **UP**. ***NOTE:*** *an adverse event (of any grade) that is unexpected, is reasonably believed to be related to study participation, and involves risk to the participant or others should be captured as a* ***UP*** *(per definitions above 4.2).*

The site will enter information about the SAE/UP event into the appropriate case report form (via REDCap reporting). The data center can generate a summary of individual, or a series of, AE events upon request from the site.

Daiichi Sankyo will receive notification of all SAEs and/or UPs within 5 business days of learning of the event. Reporting of all SAE/UP events will be made to Daiichi Sankyo, the FDA (voluntary submission) and the NHLBI Program Official using the same reporting information (FDA Form 3500 per below). Specifically, sites must:

a) Inform local IRB per institutional guidelines and timelines
b) fill out an SAE/UP case report form, via REDCap online reporting

c) fill out an SAE/UP Form provided by Daiichi Sankyo (APPENDIX F)
d) email the completed to Daiichi Sankyo representative
e) voluntary reporting to FDA, via either submitting MedWatch Form FDA 3500 or complete voluntary reporting online via FDA MedWatch (see below for link)

FDA MedWatch reporting forms may be found at:
http://www.fda.gov/safety/medwatch/howtoreport/downloadforms/default.htm

FDA MedWatch online voluntary reporting process can be performed at:
https://www.accessdata.fda.gov/scripts/medwatch/

The table below summarizes SAE and UP reporting timelines that will be implemented.

Table 3: NHLBI SAE and UP reporting Timelines

What event is reported	When is Event reported	By whom is event reported	To whom is Event reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within **7 calendar days** of initial receipt of information	Investigator	Local IRB NHLBI and/or Data Coordinating Center DSMB DSI
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within **15 calendar days** of initial receipt of information	Investigator	Local IRB NHLBI and/or DCC DSMB DSI
Unanticipated Problem that is not an SAE	Within **14 days** of the investigator becoming aware of the problem	Investigator	Local IRB NHLBI and/or DCC DSMB
All Unanticipated Problems[1] Related or Unrelated to study	Within **30 days** of the IRB's receipt of the report of the UP from the investigator.	IRB	OHRP[2] NHLBI

1. Per OHRP guidance: only when a particular AE or series of AEs is determined to meet the criteria for an UP should a report of the AE(s) be submitted to the IRB at each institution under the HHS regulations at 45 CFR part 46. Such reports to the IRB will be submitted by the investigator.
2. Office for Human Research Protections

4.5 Participant Withdrawal

Participants may withdraw from the study at any time at their request, as described in the consent. All randomized participants will be encouraged to complete a final study visit, including all visit procedures.

5 Data and Safety Monitoring Plan

The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis. A Data and Safety Monitoring Board (DSMB) will be formed with Dr. Wolfson as the un-blinded statistician; other members will not be part of the study team. Committee members will have experience with HIV/AIDS clinical research and thrombosis and anticoagulation therapy.

5.1 Interim Analysis

Most of the primary blood and tissue outcomes will not be available until after visits are completed, as samples will be batch processed at our participating laboratory site. Hence, there will be no formal interim analyses for efficacy or futility related to the main study outcomes.

5.2 Frequency and Content of Data and Safety Monitoring

To ensure compliance and data are reported correctly and completely, CRF data will be monitored monthly for completeness and compliance with the study protocol. Queries for clarification or data completion will be communicated from the data center to the clinical site.

Prior to enrollment the DSMB will review the protocol and data analysis plan. During the study the DSMB will meet at every 6 months, and on an ad-hoc bases as necessitated for adverse events. An initial DSMB meeting will be scheduled as soon as any of the following occurs:

i. Six months have elapsed since enrollment of the first patient
ii. 50% of goal enrollment is achieved
iii. 15 participants have completed 1st study drug period (i.e., 4 months)

The data and safety monitoring report will include data on: enrollment (including progress), visit attendance, completeness of data, completeness and quality of specimen collection, baseline characteristics, adherence and discontinuation of medication, and side effects and adverse events.

5.2.1 Safety Monitoring by DSMB Officers

The PI will be informed of all **SAEs** deemed protocol related, **UPs,** or significant bleeding events as soon as they occur and will notify the DSMB for review within 7 business days of notification. The two clinicians (one HIV/Medicine and one Hematology) on the DSMB will also serve as medical officers and will perform independent safety monitoring for the study. **Independent safety monitoring will occur for any of the following:**

- **SAE or UP deemed related to protocol/study drug**
- **Major bleeding event (ISTH definition in 3.2)**
- **Bleeding event of BARC type ≥3 (definition in 3.2 and appendix B)**

Independent safety monitoring will entail a review of a summary report of (de-identified) clinical data via email. The DSMB will then determine whether the study should:
a) continue and conduct the next scheduled DSMB meeting as planned, or
b) continue but conduct an additional DSMB call to re-evaluate study safety, or
c) temporarily stop enrollment, but continue follow-up of randomized participants, until an additional DSMB meeting can be performed, or
d) provide more clinical information on the adverse event to properly inform a decision.

As a result of this review a determination will then be made whether: a) continuing the study without change and without additional DSMB review (beyond scheduled meetings as planned), b) continue the study but conduct an additional DSMB meeting/call to re-evaluate study safety, c) temporarily stop enrollment in the study, but continue follow-up of randomized participants, until an additional DSMB meeting can be performed to re-evaluate study safety and appropriateness to continue, d) more clinical information is needed on the adverse event to properly inform a decision.

5.3 DSMB (Data and Safety Monitoring Board)

The following individual(s) has/have accepted position(s) as part of the DSMB. Should there be any questions regarding the independence of the DSMB, it will be addressed and corrected if necessary at that time. Julian Wolfson (lead statistician) will produce data reports and represent the protocol team as part of both open and closed sessions for the DSMB.

- Biostatistician: Holly Janes, PhD (hjanes@fhcrc.org)
- HIV/General Medicine: Matthew Freiberg, MD (matthew.s.freiberg@vanderbilt.edu)
- Hematology Medicine: Sam Schulman, MD (schulms@mcmaster.ca)
- Hematology Medicine: David Garcia, MD (davidg99@uw.edu)

The DSMB will monitor progress of the study and safety of the intervention while the study is still blinded to the investigators. **The frequency of the DSMB monitoring is listed above in 5.2.** As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. The DSMB will also assess the performance of the overall study operations and any other relevant issues as necessary.

5.3.1 DSMB Conflict of Interest and Protection of Confidentiality

DSMB members should have no direct involvement with the study investigators or intervention. Each DSMB member will sign a Conflict of Interest Statement which includes current affiliations, if any, with pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and / or associated with commercial interests pertinent to study objectives.

Data will be presented in a blinded manner during the open sessions of the DSMB that include the study PI. At DSMB meetings, data and discussion are confidential. Participant identities will not be known to the DSMB members.

5.3.2 DSMB Responsibilities

The DSMB Charter provides a detailed list of the DSMB responsibilities. They include:

- Review the research protocol, informed consent documents and plans for data safety and monitoring;
- Recommend subject recruitment be initiated after receipt of a satisfactory protocol;
- Evaluate the progress of the trial, accrual and retention, periodic assessments of data quality and timeliness, participant risk versus benefit, and other factors that can affect study outcome;
- Evaluation of all SAE/UPs, bleeding events of BARC type ≥3, and/or major bleeding Event (ISTH definition), will be reviewed by the designed medical officers on the DSMB within 1 week of report. An assessment will be made at that time if a full DSMB meeting is required before then next schedule meeting;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- Protect the safety of the study participants.

6 ANALYSIS PLAN

The primary analyses involving the main effect of treatment will be performed in an intent-to-treat framework using a random effects model with random subject-specific intercepts and fixed effects for treatment period and pre-treatment IL-6 (average of two measures, from screening and baseline). Separate models with an interaction term between treatment and pre-treatment FXa activity will used to test whether the effect of treatment differs by the degree of FXa activity (as estimated from computational modeling). The coefficients of the period indicator will be tested to check for evidence of treatment sequencing and/or carry-over effects. The characteristics of any patients who drop out of the study will be compared to the characteristics of those who do not to ascertain whether drop-out was informative. Secondary outcomes will be analyzed in a similar fashion to analysis of changes in IL-6. In secondary exploratory analyses, we will also perform per-protocol (‘on treatment’) analyses, as well as imputation and (if

necessary) sensitivity analyses to account for missing data. If medication adherence is sub-optimal, we will also consider compliance-adjusted analyses.

We will also use the IL-6 and D-dimer associations with clinical risk (Scientific Background in 1.1.2.),[63] to estimate the predicted risk reductions for both a composite outcome (serious non-AIDS events) as well as individual events such as cardiovascular disease (CVD) events. Statistical tests will include a significance level of alpha=0.05.

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APPENDIX A: BLOOD SPECIMEN COLLECTION AND STORAGE

Updated: April 2015

	CLINICAL	Blood Collection Tube	Blood Volume	S	B	M1	M2	M3	M4	M7	M8	M9	M10	M11	M12
HCMC Labs Processing	HIV RNA	(1) 4ml EDTA Lavender	2-3mL	X*	X	X	X	X	X		X	X	X	X	X
	CD4 Count + CBC	(1) 4ml EDTA Lavender	4mL		X				X		X				X
	CBC		2-3mL	X*		X	X	X				X	X	X	
	BMP, Hepatic Panel	(1) 5mL Green	4mL	X*	X	X			X		X	X			X
	Lipid Panel				X										
	INR, aPTT	(1) 5mL NaCitrate Blue	4mL	X*	X	X	X	X	X		X	X	X	X	X
	D-Dimer			X*											
	Anti-Xa				X				X		X				X
	HBsAg & HCV Ab	(1) 5mL SST Red	4mL		X*						X*	X	X	X	X
	Pregnancy, Urine			X		X	X	X	X		X	X	X	X	X

	Core Labs	BLOOD FOR STORAGE		Blood Vol	Cryo Vials **	S	B	M1	M2	M3	M4	M7	M8	M9	M10	M11	M12
Study Lab Processing	NIH	PBMC (Processing at UMN)	(4) 10mL CPT Tiger Top	36mL	3		X	X			X		X	X			X
	UNC	Platelet Free Plasma	(3) 5mL NaCitrate Blue	15mL	4	X						X					
				15mL	8		X	X	X	X	X		X	X	X	X	X
		Whole blood storage	[5mL Na-Citrate Blue]	5mL	4	X	X	X	X	X	X	X	X	X	X	X	X
	UVT	Serum	5mL SST Red	5mL	1	X						X					
				5mL	3		X	X	X	X	X		X	X	X	X	X
		Platelet Poor Plasma	10mL EDTA Lavender	10mL	3	X						X					
				10mL	7		X	X	X	X	X		X	X	X	X	X

*Labs values from anytime within 30days of screening can be used; previously positive hepatitis labs (i.e., HBsAg or HCV Ab) do not need to be repeated

**Vials are to be 500µl Full

[ ] Aliquot prior to plasma processing

APPENDIX B: BLEEDING ACADEMIC RESEARCH CONSORTIUM (BARC) DEFINITIONS

Type 0	no bleeding
Type 1	bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3	Type 3a • Overt bleeding plus hemoglobin drop of 3-<5 g/dL (provided hemoglobin drop is related to bleed) • Any transfusion with overt bleeding Type 3b • Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) • Bleeding requiring intravenous vasoactive agents Type 3c • Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) • Subcategories confirmed by autopsy or imaging or lumbar puncture • Intraocular bleed compromising vision
Type 4	CABG-related bleeding (cardiac surgery) • Perioperative intracranial bleeding within 48 hours • Reoperation after closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period • Chest tube output ≥2 L within a 24 hour period

APPENDIX C: CLINICAL MANAGEMENT OF FACTOR X INHIBITOR BLEEDING EVENTS

NOTE: *TACTICAL-HIV participants the present with acute or active bleeding complication during the course of the study should be referred for clinical evaluation at the appropriate or nearby health care facility. Management of clinical bleeding complications will not be directed by the TACTICAL-HIV study team, and will be supported by the participant's health insurance or third-party payer.*

There is no specific reversal agent or pharmacologic antidote to edoxaban-related bleeding, thus management of hemorrhagic complications is primarily supportive. Edoxaban is moderately protein bound (e.g., 50-60%) and is not dialyzable. If patients require pharmacologic therapy to manage hemorrhagic complications, a Hematology/Coagulation consult is advised.

A FXa-activity level can is available by most clinical labs (and at HCMC), which can provide information quickly on the degree of FXa inhibition. The table below summarizes one approach to management of Factor Xa inhibitor-related bleeding events, adapted from University of North Carolina Anticoagulation Reversal Guidelines:
www.med.unc.edu/emergmed/files/emergent-anticoagulation-reversal-in-the-ed

Bleeding Severity	Management Approach
Mild	Delay next dose or discontinue Factor Xa inhibitor
Moderate	Consider any of the following based on bleeding severity: • Symptomatic treatment • Mechanical compression • Surgical intervention • Fluid replacement and hemodynamic support • Blood product transfusion • Oral activated charcoal (if previous dose ingested within 2 hours) Dose: Liquid charcoal with sorbitol 50 g PO x 1 dose *If hemostasis is not achieved with the strategies outlined above, proceed to the steps below and obtain a Hematology/Coagulation consult for further recommendations*
Severe or Life-Threatening	Consider any of the strategies outlined above based on bleeding severity. No agent currently available in the US has been shown to successfully reverse the anticoagulant effects of Factor Xa inhibitor-related bleeding events. However, the strategy below may be considered based on the currently available evidence. Therefore, the pharmacologic interventions below may be considered, but are not required in the management of Factor Xa inhibitor-related bleeding. A Hematology/Coagulation consult should be obtained after the following: 1) Administer KCentra (4-factor PCC) 50 units/kg IV x 1 (max 5000 units) 2) For persistent refractory bleeding, pursue formal Heme/Coag consult. 3) To investigate potential causes of the bleeding event, obtain the following: serum creatinine, PT, aPTT, anti-Xa activity (send-out lab), CBC (platelets). 4) If PT prolonged, administer vitamin K 10mg IV x one dose (as there may be vitamin K deficiency present).
Table adapted from Eerenberg, Circulation 2011 (Oct 4);124(14):1573-1579	

APPENDIX D: DEFINITION AND CRITERIA FOR AIDS EVENT

The following list encompass the CDC's 1993 surveillance case definition of AIDS (without the CD4+ criterion), with the addition of several diagnoses increasingly felt to be associated with severe immunosuppression in participants infected with HIV.

Modified CDC Category C 1993 Definition

- Candidiasis of bronchi, trachea or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- CMV disease (other than liver, spleen, or nodes)
- CMV retinitis (with loss of vision)
- Encephalopathy, HIV-related (including AIDS Dementia Complex)
- *Herpes simplex*, chronic ulcers (> 1 mo); or bronchitis, pneumonitis or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi's sarcoma (mucocutaneous or visceral)
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
- *M. tuberculosis*, any site (pulmonary or extrapulmonary)
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia (*pneumocystic jiroveci*)
- Pneumonia, recurrent bacterial (2 episodes within 1 yr of each other, after randomization)
- Progressive multifocal leukoencephalopathy
- *Salmonella* sepsis, recurrent (2 episodes within 1 year of each other, after randomization)
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

Additions to CDC Definition

- Aspergillosis, invasive
- Bartonellosis
- Chagas disease (American trypanosomiasis) of the CNS
- *Herpes zoster*, multi-dermatomal (≥10 lesions in a non-contiguous site)
- Leishmaniasis, visceral (kala-azar)
- Lymphoma, Hodgkin's
- Lymphoma, non-Hodgkin's, all cell types
- Microsporidiosis (> 1 month's duration)
- Nocardiosis
- *Penicillium marneffii*, disseminated
- *Pneumocystis carinii*, extrapulmonary
- *Rhodococcus equi* disease

APPENDIX E: ADVERSE EVENTS GRADING TABLES (FROM NIH/DAIDS)

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Version 2.0
November 2014

MODIFIED FOR TACTICAL-HIV STUDY (PCC008)

Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
US Department of Health and Human Services

Table of Contents

Glossary and Acronyms

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: <u>Adult</u> Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. <u>Young Children</u> Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

Introduction

The Division of AIDS (DAIDS) oversees clinical trials throughout the world which it sponsors and supports. The clinical trials evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

The DAIDS AE grading table is a shared tool for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in clinical trials. Over the years as scientific knowledge and experience have expanded, revisions to the DAIDS AE grading table have become necessary.

This document is for use in PCC008 (TACTICAL-HIV). Instructions and information related to pediatric events and microbicide studies have been removed from the 2014 clarification of the DAIDS Table for Grading AE's. Thus, all definitions pertain to adults (≥ß18 years old)

Instructions for Use

General Considerations

The *Division of AIDS* (*DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS AE grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS AE grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use parameters defined by age and sex values as applicable.
- Male and female sex are defined as sex at birth.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

Instructions for Use

When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric AEs
When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes
In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades
If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Laboratory Values
General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the CRFs.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory

value. For example, “Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory’s normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant’s magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Estimating Severity Grade for Parameters Not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1]				
Hypertension *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalizati	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A delivery of a live-born neonate occurring at ≥ 20 to < 37 weeks gestational age.
[8] Definition: A clinically recognized pregnancy occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medicamylasal intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[9]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[10] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[11]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)

[9] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[10] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).
[11] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Underweight[12] *> 5 to 19 years of age*	NA	WHO BMI z-score < -2 to ≤ -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[12] WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[13] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[13] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Laboratory Values
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[14], High*** *> 28 days of age*	NA	NA	> ULN	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*

[14] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*) *≥ 7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10 x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Creatinine Clearance[15] or eGFR, Low *Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR ≥ 30 to < 50% decrease from baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Glucose, Low (mg/dL; *mmol/L*) *≥ 1 month of age*	55 to 64 *3.05 to 3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences

[15] Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High				
≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High				
≥ 18 years of age	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[16], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.81 to < LLN*	1.4 to < 2.0 *0.65 to < 0.81*	1.0 to < 1.4 *0.32 to < 0.65*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 135*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

[16] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[17], Low (g/dL; *mmol/L*)[18] *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[17] Male and female sex are defined as sex at birth.
[18] The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

APPENDIX F: ADVERSE EVENT REPORTING FORM (FOR DSI)

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM

Protocol #: _____	**Site #:** _____	**Subject Initials:** _____

When completed, send to <<CRO>>.

Supplemental pages used *(Mark all that apply)*: ☐ SAE ☐ Lab Results ☐ Concomitant Medications

Report Type: ☐ Initial ☐ Follow-up #

1. Source

Investigator Name: _____ **Country:** _____

Address: _____

Phone #: _____ **Fax #:** _____

2. Subject and Study Information

Screening #/Subject #: _____ **Randomization #:** _____ **Subject Initials:** _____

Birth Date: *(dd Mmm yyyy)* _____ **Gender:** ☐ Male ☐ Female

Weight: ☐ kg ☐ lb _____ **Height:** ☐ cm ☐ in _____

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino

Race: ☐ Asian ☐ Black ☐ Caucasian ☐ American Indian/Alaskan Native ☐ Native Hawaiian/Pacific Islander ☐ Other _____

Phase of Study at time of SAE: ☐ Screening ☐ Washout ☐ Placebo/Run-in ☐ Randomized ☐ Post Study ☐ Open-label

Date of Informed Consent: *(dd Mmm yyyy)* _____

3. Primary Serious Adverse Event

(Use appropriate medical terminology, symptoms should be grouped together as syndromes and diagnosis.)

If additional events are reported, use supplemental page. If supplemental SAE pages were used, mark here: ☐

SAE (Event/Diagnosis): _____

Date Event Became Serious: *(dd Mmm yyyy)* _____ **Date Event Stopped → or →:** *(dd Mmm yyyy)* _____

Continuing	Severity	Outcome	Seriousness Criteria *(see protocol for SAE definitions)*
☐ Yes ☐ No	☐ Mild ☐ Moderate ☐ Severe	☐ Recovered/Resolved ☐ Recovered/Resolved with sequelae ☐ Not Recovered/Not Resolved ☐ Fatal ☐ Unknown	☐ Death ☐ Life-threatening ☐ Hospitalization-initial or prolonged ☐ Disability or Permanent Damage ☐ Congenital anomaly/Birth Defect ☐ Important Medical Event

	Not Applicable	Related	Not Related
Study Procedure (eg, Biopsy, CT scan, MRI scan, other protocol specified procedures; Separate from study drug administration)	☐	☐	☐

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM

Protocol #: _____	**Site #:** _____	**Subject Initials:** _____

Is the event related to a study procedure?			
Study Drug Causality *(Complete one line for each study drug)*			
Drug Name		**Related**	**Not Related**
		☐	☐
		☐	☐
		☐	☐
		☐	☐

4. In Case of Death

Date: *(dd Mmm yyyy)* _____ **Autopsy:** ☐ Yes ☐ No

Certificate: ☐ Yes ☐ No **Cause:** _____

5. Study Drug Dosing

*Record only dose given to subject **at time of SAE**. Complete all previous dosing regimes including placebo run-in Section 6.*

Study Drug Dosing						**Study Drug Action Taken**				
Study Drug	**Unit Dose**	**Frequency**	**Route**	**Start Date** *(dd Mmm yyyy)*	**Stop Date** *(dd Mmm yyyy)*	**None**	**Discontinued**	**Reduced**	**Interrupted**	**Increased**
						☐	☐	☐		☐
						☐	☐	☐		☐
						☐	☐	☐		☐

Was the subject withdrawn due to SAE? ☐ Yes ☐ No

Was Study Drug Code broken due to SAE? ☐ Yes ☐ No If Yes, Date: *(dd Mmm yyyy)* _____

Who: _____ Drug: _____ Dosing: _____

6. Previous Study Drug Dosing Regimens per Protocol, including placebo run-in.

Study drug dosing at the time of SAEs is captured in Section 5. ***Do NOT complete with "See Attached".***

If not applicable mark here: ☐

Drug Name	**Unit Dose**	**Frequency**	**Route**	**Start Date** *(dd Mmm yyyy)*	**Stop Date** *(dd Mmm yyyy)*

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM

Protocol #: _____	**Site #:** _____	**Subject Initials:** _____

7. Relevant Concomitant Medications

(Include those taken before the onset of the event, not taken as a treatment for the event.) ***Do NOT complete with "See Attached".*** If Supplemental Concomitant Medication page is used, mark here: ☐

Generic/Brand Name	Dose	Frequency	Route	Start Date *(dd Mmm yyyy)*	Stop Date *(dd Mmm yyyy)*	Indication	Continuing ?
							☐
							☐
							☐
							☐
							☐
							☐

8. Relevant Lab Results

Do NOT complete with "See Attached." If supplemental Lab Results pages were used, mark here: ☐

Lab Test	Date *(dd Mmm yyyy)*	Results	Reference Normal Range (Units)

9. Relevant Medical History Including Allergies

Do NOT complete with "See Attached."

Date of Onset *(dd Mmm yyyy)*	Current *(Mark one only)*	Past *(Mark one only)*	Description
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	

10. Narrative

Record a detailed description of the event including the course of the event, evaluation, assessment and treatment.

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM

Protocol #:	**Site #:**	**Subject Initials:**

11. Person Completing This Form

Name	**Signature**	**Date**
Title	**Phone Number**	

Investigator Name	**Signature**	**Date**

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM
(Supplemental SAE)

Protocol #: _____ **Site #:** _____ **Subject Initials:** _____

SAE (Event/Diagnosis) #: 2 _____

Date Event Became Serious: *(dd Mmm yyyy)* _____ **Date Event Stopped → or →:** *(dd Mmm yyyy)* _____

Continuing	Severity	Outcome	Seriousness Criteria *(see protocol for SAE definitions)*
☐ Yes ☐ No	☐ Mild ☐ Moderate ☐ Severe	☐ Recovered/Resolved ☐ Recovered/Resolved with sequelae ☐ Not Recovered/Not Resolved ☐ Fatal ☐ Unknown	☐ Death ☐ Life-threatening ☐ Hospitalization-initial or prolonged ☐ Disability or Permanent Damage ☐ Congenital anomaly/Birth Defect ☐ Important Medical Event

	Not Applicable	Related	Not Related
Study Procedure (eg, Biopsy, CT scan, MRI scan, other protocol specified procedures; Separate from study drug administration) **Is the event related to a study procedure?**	☐	☐	☐

Study Drug Causality *(Complete one line for each study drug)*

Drug Name	Related	Not Related
	☐	☐
	☐	☐
	☐	☐
	☐	☐

SAE (Event/Diagnosis) #: 3 _____

Date Event Became Serious: *(dd Mmm yyyy)* _____ **Date Event Stopped → or →:** *(dd Mmm yyyy)* _____

Continuing	Severity	Outcome	Seriousness Criteria *(see protocol for SAE definitions)*
☐ Yes ☐ No	☐ Mild ☐ Moderate ☐ Severe	☐ Recovered/Resolved ☐ Recovered/Resolved with sequelae ☐ Not Recovered/Not Resolved ☐ Fatal ☐ Unknown	☐ Death ☐ Life-threatening ☐ Hospitalization-initial or prolonged ☐ Disability or Permanent Damage ☐ Congenital anomaly/Birth Defect ☐ Important Medical Event

	Not Applicable	Related	Not Related
Study Procedure (eg, Biopsy, CT scan, MRI scan, other protocol specified procedures; Separate from study drug administration) **Is the event related to a study procedure?**	☐	☐	☐

Study Drug Causality *(Complete one line for each study drug)*

Drug Name	Related	Not Related
	☐	☐
	☐	☐
	☐	☐
	☐	☐

SAE (Event/Diagnosis) #: 4 _____

Date Event Became Serious: *(dd Mmm yyyy)* _____ **Date Event Stopped → or →:** *(dd Mmm yyyy)* _____

Continuing	Severity	Outcome	Seriousness Criteria *(see protocol for SAE definitions)*
☐ Yes ☐ No	☐ Mild ☐ Moderate ☐ Severe	☐ Recovered/Resolved ☐ Recovered/Resolved with sequelae ☐ Not Recovered/Not Resolved	☐ Death ☐ Life-threatening ☐ Hospitalization-initial or prolonged

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM
(Supplemental SAE)

Protocol #: _____ **Site #:** _____ **Subject Initials:** _____

		☐ Fatal ☐ Unknown	☐ Disability or Permanent Damage ☐ Congenital anomaly/Birth Defect ☐ Important Medical Event

	Not Applicable	Related	Not Related
Study Procedure (eg, Biopsy, CT scan, MRI scan, other protocol specified procedures; Separate from study drug administration) **Is the event related to a study procedure?**	☐	☐	☐

Study Drug Causality *(Complete one line for each study drug)*

Drug Name	Related	Not Related
	☐	☐
	☐	☐
	☐	☐
	☐	☐

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM
(Supplemental Concomitant Medications)

Protocol #: _____ **Site #:** _____ **Subject Initials:** _____

7. Relevant Concomitant Medications (Continued)

(Include those taken before the onset of the event, not taken as a treatment for the event.) ***Do NOT complete with "See Attached".***

Generic/Brand Name	Dose	Frequency	Route	Start Date *(dd Mmm yyyy)*	Stop Date *(dd Mmm yyyy)*	Indication	Continuing?
							☐
							☐
							☐
							☐
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							☐

SERIOUS ADVERSE EVENT REPORT (SAVER) FORM
(Supplemental Lab Results)

Protocol #: _____	**Site #:** _____	**Subject Initials:** _____

8. Relevant Lab Results (Continued)

Do NOT complete with "See Attached."

Lab Test	Date *(dd Mmm yyyy)*	Results	Reference Normal Range (Units)

APPENDIX G: SAMPLE INFORMED CONSENT FORM (ICF)

SUBJECT INFORMATION AND INFORMED CONSENT FORM (ICF)

Protocol:	**Targeted AntiCoagulation Therapy to Reduce Inflammation and Cellular Activation in Long-Term HIV Disease**
Short Title:	**TACTICAL-HIV**
Funding:	**National Heart Lung and Blood Institute /National Institutes of Health** **Daiichi-Sankyo (study drug)**
Site:	**Hennepin County Medical Center (HCMC)**
Investigator:	**Jason Baker, MD, MS**

CONSENT FOR PARTICIPATING IN AN NHLBI/NIH-FUNDED RESEARCH TRIAL

INTRODUCTION AND PURPOSE: WHY IS THIS STUDY BEING DONE?

You are invited to be in a research study that looks at the use of a medication that may improve the health of HIV positive people who are already on HIV medicines. The medication (edoxaban) is approved by the Food and Drug Administration (FDA), but not for treatment of HIV infection; it is commonly used to treat or prevent blood clots. However, this medication may help address some of the damage that HIV causes in the body. Forty HIV positive patients will be enrolled in this study at HCMC in Minneapolis.

Damage caused by HIV infection results in problems with the immune system and other organs in the body. One of these problems involves the coagulation system, which is how our bodies form blood clots to prevent bleeding. HIV 'activates' or turns on the coagulation system. Over time this increases risk for having blood clots and also results in 'inflammation' that can damage the body. Inflammation occurs when the body's immune system is responding to injury or infection. Inflammation can be helpful in the short term, but when it is persistent it can also cause more damage to the body over time. These problems impair normal health over many years and cannot be fully corrected, even with effective HIV treatment using antiretroviral medications.

Problems with clotting and ongoing inflammation with damage to the body contribute to risk for diseases like heart disease among HIV positive persons. This study will determine if a low dose of edoxaban, which reduces blood clotting, will reduce inflammation. If

successful, edoxaban may then be studied as an approach to achieve normal health outcomes for persons with HIV infection.

YOUR PARTICIPATION IS VOLUNTARY
This consent form gives you information about the clinical research study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign this consent form. You will be given a copy to keep.

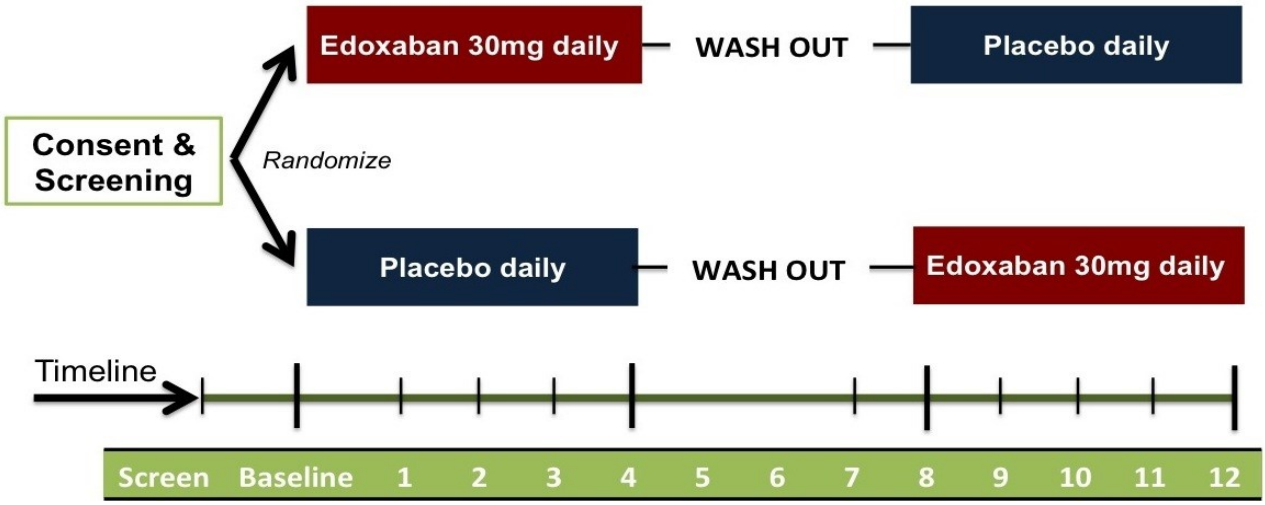
Before you learn about the study, it is important that you know the following:
Your participation is entirely voluntary.

You may decide not to take part or to withdraw from the study at any time without losing the benefits of your routine medical care.

Eligibility: Who is being asked to be part of this research study?
You may be eligible for this study if you have HIV infection, you are taking your antiretroviral medications, you have evidence of increased coagulation ('risk for clotting') based on a blood test, and you do not have contraindications to study procedures. Your HIV 'viral load' must be undetectable. If your doctor or the study investigators feel that it would not be safe to take the study medication then you will not be eligible to participate. Some factors that could make you ineligible for this study include using other anti-clotting medications ('blood thinners') or having other inflammatory, liver or kidney disease.

HOW LONG WILL YOU BE IN THE STUDY?
The study will last approximately 12 months and consists of 12 visits. After the screening visit, if you qualify, you will come in for a 'baseline' study visit, and then follow-up visits at 1, 2, 3, 4, 7, 8, 9, 10, 11 and 12 months.

HOW WILL THE STUDY WORK?
If you agree to participate in this study, you will be asked to take 30mg of edoxaban and a matching placebo pill once daily, but you would only be taking one medication at any given time during the study (i.e., you would not be taking edoxaban and placebo at the same time). At the beginning of the study you will be randomly assigned to start one study medication, which will either be edoxaban or a matching placebo. At month 4 you will stop taking study medications. At month 8 you will be asked to start the second study medication. The second medication will be placebo if your first medication was edoxaban, and will be edoxaban if your first medication was placebo. Neither you, nor the study investigators, will know which study medication you take first or second. A picture of this process is then shown below.



PROCEDURES: WHAT DO YOU HAVE TO DO IF YOU ARE IN THIS STUDY?

Screening visit:
You will be asked to come in for a screening visit, where your study investigators will review the study procedures and this consent form. If you agree to participate, you will have your blood drawn (approximately 2 tablespoons) and medical history reviewed (similar to a routine clinic visit) to determine if you are eligible to participate. If you meet study criteria, you will then return within 1 month to begin the study.

Baseline and follow-up (month 1, 2, 3, 4, 7, 8, 9, 10, 11, 12) clinic study visits:
The baseline and follow-up clinical visit will last approximately 1-2 hours, and will consist of:

Medical History: You will be interviewed to review your medical history and assess your risk for developing heart disease. We will also access your medical chart to obtain the results of recent lab tests and medications you are taking.

Blood Draw: We will obtain a blood sample (up to 8 tablespoons) from a vein in your arm. The total blood draw volumes per visit will be less than 100 mL. <u>You must be fasting for at least 6 hours</u> prior to having your blood drawn at study visits. Blood samples will be used to measure markers in the blood related to inflammation, coagulation ('clotting') and other markers that may contribute to heart disease and other complications of HIV infection. These samples may be stored for up to 20 years.

At the baseline visit, you will start taking edoxaban (or placebo). You will take 1 tablet (30 mg) every day in the morning. The nurses will give you the study medicine during your clinic visits. At follow-up visits you will be asked to bring in all of your study medication, and adherence and tolerability to the treatment will be assessed.

STORED SAMPLES
During your participation in this study, blood will be collected by standard blood drawing techniques.

Samples will be used to evaluate the potential benefits of edoxaban. Additional samples will be stored up to 20 years for future research. These samples can help us learn more about HIV, AIDS, immune function, inflammation, coagulation (blood 'clotting'), or other related diseases that affect patients with HIV infection. In general, the research tests we perform are not like routine medical tests and may not relate directly to your medical care. For this reason, we may not put future research test results in your medical record or share these test results with your medical provider. We will communicate any clinical labs obtained during the study to your primary medical provider.

Genetic Testing
Future research on stored samples might involve genetic testing. Genetic testing may tell researchers something about how health or illness is passed on to you by your parents or from you to your children. Some genetic information, such as the ability to make certain proteins in the body, has been associated with an increased risk of certain diseases like arthritis.

Any genetic information collected or discovered about you or your family will be confidential. Genetic information about you will not be revealed to others, including your relatives, without your permission. We will not release any information about you or your family to any insurance company or employer unless you sign a document allowing release of information.

HOW WILL YOU GET MEDICINES FOR THE STUDY?
Study medications will be provided to you by the study and will be distributed by study nurses during study visits. You will be provided with sufficient supply to last the duration of the study. You will be asked to return any unused study medication, including empty containers.

WHAT ARE THE RISKS AND/OR DISCOMFORTS OF THIS STUDY?

You will be monitored for side effects at each visit, and your lab tests will include an evaluation for signs of medication toxicity.

Risks of Study Procedures
You will have your blood drawn at each study visit. This is identical to having your blood drawn at a medical clinic, and can involve discomfort, light-headedness and/or minor bruising. Discussion of past medical history or risk factors for HIV infection may be stressful and cause anxiety. You may decline to answer any questions that you do not feel comfortable answering.

<u>Study Medication: Edoxaban</u>
This medication is approved by the FDA. Edoxaban is used to prevent and treat blood clots. The most significant possible side effects of edoxaban is bleeding. This may be mild, like a bloody nose, or more significant and require medical evaluation. Examples of serious or major bleeding from edoxaban include bleeding in the stomach or intestines, or bleeding in the brain. Major bleeding events were rare, occurring between 1-2% of the time, in prior clinical studies of edoxaban. We will ask you about signs or symptoms of bleeding during each of your visits, such as abdominal pain, black stools, dizziness, lightheadedness, fatigue, or headache. We will also monitor your blood

results for signs of bleeding at each visit. We do not expect that edoxaban will interact with any of your HIV medicines.

This medication should not be used during pregnancy. If a developing fetus is exposed to edoxaban, injury or even death may result. For this reason, if you are a woman of childbearing potential, you will be asked what type of birth control you use. You must be willing to use a reliable form of birth control for the duration of the study period, such as a barrier method or spermicide. Condoms cannot be the only form of birth control you use. If you become pregnant during the study or think you may be pregnant, you should inform either the site investigator or a study nurse immediately. We will ask that you return any study medication. We will ask permission to contact you at the end of the pregnancy to check on the health of you and the baby.

WHAT ABOUT PREGNANCY AND BREASTFEEDING?
If you are pregnant, breastfeeding or planning to become pregnant, you will not be eligible for this study. If you become pregnant during the study, you will be asked to stop study medications and withdraw. Therefore, if it is possible that you could become pregnant, we ask that you use a reliable form of birth control for the duration of the study (listed above in 'Study Medication').

WHAT ARE THE BENEFITS OF THIS STUDY?
If you take part in this study, there are no anticipated benefits directly to your health. The research has the potential to benefit people with HIV infection, after the study is completed and the findings have been analyzed.

COMPENSATION
You will be paid $25 for each study visit you attend after the screening visit. You may receive a total of $275 for participating in the study. Study investigators may ask for your social security number as part of the monitoring process for this compensation.

WHAT IF THERE ARE NEW FINDINGS?
We will not be analyzing data during the study. However, if during the course of this research study, there are significant new findings discovered which might influence your willingness to continue, the researchers will inform you of those developments. You may request your own results after the study by contacting the research investigators.

WHAT IF YOU DON'T WANT TO BE IN THE STUDY ANY LONGER?
If you enroll in this study, you may decide to stop participating at any time. Withdrawing from this study will not affect the benefits of your regular medical care.

CAN YOUR STUDY PARTICIPATION BE STOPPED WITHOUT YOUR CONSENT?
You may be taken off of study medicines before the end of the study if investigators or your doctor recommend this. You may be taken off the entire study without your consent if:

- Your study doctor decides that continuing in the study would harm you;
- Your lab results indicate that you are experiencing toxicity from study medications;

WHAT OTHER CHOICES DO YOU HAVE BESIDES THIS STUDY?
You may discuss other strategies for improving your health with your doctor.

WHAT ARE THE COSTS TO YOU?
The medications that are part of this study will be provided free-of-cost to you, and will be distributed during study visits. During the study, you, your insurance company, or some other third-party payer must pay for all other medicines, including HIV medicines not paid by the study and medicines needed to prevent or treat other illnesses. We will provide all clinical and professional services, lab work, and other tests that are part of this study and not part of your regular care at no cost to you.

HOW IS YOUR PRIVACY PROTECTED?
Any information that could be used to identify you will be treated in strict confidence to the extent allowed by law. Nevertheless, some uses and disclosures of your information are necessary to conduct the study. If you agree to be part of this study, you will also be allowing the uses and disclosures of your private health information as needed for the purposes of this study as described in this consent.

"Private health information" means information that identifies you and is collected:
- during this study;
- from your past and current medical records maintained by your regular health care providers, to the extent the information is relevant to this study or to your eligibility for this study; or
- from any payment records relating to items or services furnished to you during this study.

By signing this consent, you are agreeing that your private health information may be disclosed to and used by:
- the doctors and other health care providers involved in this study;
- their staff;
- the research center;
- members of this institution's Human Subjects Research Committee/Institutional Review Board;
- Daiichi-Sankyo;
- the sponsor of this study and its agents; and
- monitors from the United States Government and/or Food and Drug Administration (FDA).

The findings of this study may be used for scientific meetings, written reports, and publications, but no information that could be used to identify you will be disclosed for these purposes.

Once your private health information has been disclosed to a third party, federal privacy laws may no longer protect it from re-disclosure. However, anyone obtaining access to your private health information under this consent must agree to protect your information as required by this consent.

This consent to use your private health information as described above does not expire. However, if you later change your mind, you can revoke this consent by writing to Dr. Jason Baker [701 Park Avenue; Mail Code G5; Minneapolis, MN 55415; phone 612-873-

2705] saying that you no longer wish to allow your private health information to be used for this study. If you revoke your consent, you may no longer be able to participate in the study. Moreover, we cannot undo uses or disclosures of your private health information that have already taken place in reliance on your prior consent.

PLEASE NOTE:
A) In the event of a positive result for Hepatitis B or C, we may be required to report these results to the local state Department of Health.

B) Lab results from this study that are also part of clinical care may be entered into the electronic medical record (EPIC) at Hennepin County Medical Center. These lab results may then be viewed by your medical provider(s) and other allied health professionals.

WHAT IF YOU ARE INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment. The cost for treatment will be charged to you or your insurance company. There is no program through this institution to compensate participants who have research related injuries. You will not be giving up any of your legal rights by signing this consent.

WHAT IF YOU HAVE PROBLEMS OR QUESTIONS?
If you ever have questions or in the case of research-related injuries, you should contact:

Hennepin County Medical Center
Minneapolis, Minnesota, United States 55417
Principal Investigator: Jason Baker, MD, MS
Phone: 612-873-2700 Email: baker@umn.edu

Contact: Andrea Dolan, BS
Phone: 612-873-7678 Email:andrea.nolan@hcmed.org

If you have questions about research subject's rights you can contact**:**

Human Subjects Research Committee
Hennepin County Medical Center
Contact: Karen Heim-Duthoy
Phone: 612-873-6882 Email: heimd001@umn.edu

RESEARCH STUDY REGISTRY
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at anytime.

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE TACTICAL-HIV STUDY

As part of our ongoing research studies to better understand disease and improve health we often contact patients about clinical studies for which they may be eligible to participant. By signing this consent, you would also authorize us to contact you about future studies. If you would prefer we not contact you directly about future studies, please indicate this by placing a check after 'do not contact me' and then initialing.

Do not contact me for future studies: _____ Initial: _____

I have read this consent form, had the opportunity to ask questions and have received answers to any questions I have asked. I willingly give my consent to participate in this study, and authorize the use and disclosure of my health information as described in this form. By signing this consent form I do not give up any of my legal rights. Upon signing this form I will be given a signed copy of the form for my records.

If you have read the consent (or if you have had it explained to you) and understand the information, and you voluntarily agree to join this study, please sign your name below.

_____	_____	_____
Participant's name (typed or printed)	Participant's signature	Date
_____	_____	
Person obtaining consent	Date	