A5324

A Randomized, Double-Blinded, Placebo-Controlled Trial Comparing Antiretroviral Intensification with Maraviroc and Dolutegravir with No Intensification or Intensification with Dolutegravir Alone for the Treatment of Cognitive Impairment in HIV

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:
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SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

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CONTENTS Page

CONTENTS (Cont'd)

Page

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STUDY MANAGEMENT

All **general** questions concerning this protocol should be sent to actg.teamA5324@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5324@fstrf.org. A response should generally be received within 24 hours (Monday-Friday).

Protocol E-mail Group
Sites should contact the **User** Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5324 e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org

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- Send an e-mail message to **actg.coreA5324@fstrf.org**. Include the protocol number, patient identification number (PID), and a brief relevant history.

Immunology
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Pharmacology
For questions specifically related to pharmacologic laboratory tests, contact the protocol pharmacologists. Send an e-mail message to **actg.coreA5324@fstrf.org** (ATTN: Qing Ma and Gene Morse).

Virology
For questions specifically related to virologic laboratory tests, contact the protocol virologist. Send an e-mail message to **actg.coreA5324@fstrf.org** (ATTN: Robert Coombs).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, case report forms (CRF), the CRF schedule of events, randomization/registration, and other data management issues, contact the data manager. CRFs can be downloaded from the FSTRF website at **www.frontierscience.org**.
- For transfers, reference the **Study Participant** Transfer SOP 119, and contact Dave Rusin (rusin.david@fstrf.org) directly.
- For other questions, send an e-mail message to **actg.coreA5324@fstrf.org** (ATTN: Dave Rusin).
- Include the protocol number, PID, and a detailed question.

Randomization/**Participant** Registration
For randomization/**participant** registration questions or problems and study identification number SID lists.

- Send an e-mail message to rando.support@fstrf.org **or call the** DMC Randomization Desk at 716-834-0900**, extension** 7301.

Computer and Screen Problems
Contact the SDAC/DMC programmers.

- Send an e-mail message to **actg.user.support@fstrf.org** or call 716-834-0900**, extension** 7302.

Protocol Document Questions
For questions concerning the protocol document, contact the clinical trials specialist. Send an e-mail message to **actg.coreA5324@fstrf.org** (ATTN: Jhoanna Roa).

Copies of the Protocol
To request a hard copy of the protocol, send **an email** message to ACTGNCC@s-3.com (ATTN: Diane Delgado). Electronic copies can be downloaded from the ACTG **website at** https://www.actgnetwork.org.

Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
For protocol registration questions, send an e-mail message to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation
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Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call **Nayri Khairalla**, protocol pharmacist, at **301-761-6659**.

Study Drug Orders
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IND (Investigational New Drug) Number or Questions
For any questions related to the IND submission, contact the DAIDS RSC at Regulatory@tech-res.com or call 301-897-1706.

Expedited Adverse Event (EAE) Reporting/Questions
Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Telephone Calls
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Protocol-Specific Web Page

Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

ADL	activities of daily living
ANI	asymptomatic neurocognitive impairment
BDI-II	**Beck Depression Inventory II**
BMI	body mass index
CLIA	Clinical Laboratory Improvement Amendments
CPE	CNS Penetration Effectiveness
CSF	cerebrospinal fluid
DTG	dolutegravir or Tivicay
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorder
HTLV-1	human T-lymphotropic virus type 1
HVLT-R	**Hopkins Verbal Learning Test Revised**
IHDS	**International HIV Dementia Scale**
IP-10	interferon gamma-induced protein 10
LAR	legally authorized representative
LP	lumbar puncture
LPS	lipopolysaccharide
LTR	long terminal repeat sequences
MCP-1	monocyte chemoattractant protein-1
MND	mild neurocognitive disorder
MVC	maraviroc or Selzentry
NFL	neurofilament light chain
PHQ-9	**Patient Health Questionnaire-9**
PML	progressive multifocal leukoencephalopathy
RLS	**resource limited settings**
RPR	rapid plasma reagin
TB	tuberculosis
TBI	traumatic brain injury
VF	virologic failure
VDRL	venereal disease research laboratory
WAT	**Word Accentuation Test**
WRAT-4	**Wide Range Achievement Test 4**

SCHEMA

A5324

A Randomized, Double-Blinded, Placebo-Controlled Trial Comparing Antiretroviral Intensification with Maraviroc and Dolutegravir with No Intensification or Intensification with Dolutegravir Alone for the Treatment of Cognitive Impairment in HIV

DESIGN	This is a phase IV randomized, double-blinded, placebo-controlled study to assess the efficacy of adding maraviroc (MVC) and dolutegravir (DTG) to the current antiretroviral therapy (ART) of HIV-infected individuals with undetectable (<50 copies/mL) plasma HIV-1 RNA, who have mild to moderate neurocognitive impairment, with a primary outcome of improvement in neurocognitive performance.
DURATION	96 weeks
SAMPLE SIZE	186 **participants**
POPULATION	**Participants** will have HIV-associated neurocognitive disorder (HAND) as defined by the Frascati criteria, plasma HIV-1 RNA <50 copies/mL within 90 days prior to entry, and no more than one plasma HIV-1 RNA ≥50 and <200 copies/mL in the past 6 months prior to entry with a subsequent plasma HIV-1 RNA <50 copies/mL, and on stable ART for at least **6** months prior to entry with no plans to change treatment.
STRATIFICATION	**Participants** will be randomized in a stratified manner. Stratification variables will be CD4+ nadir (≤100 vs. >100 cells/mm^3), and HAND severity (asymptomatic neurocognitive impairment [ANI] vs. mild neurocognitive disorder [MND] / HIV-associated dementia [HAD]).
REGIMEN	At entry **participants** will be randomized to one of the following: Arm A: Add to their existing ART: placebo for MVC and placebo for DTG Arm B: Add to their existing ART: DTG and placebo for MVC Arm C: Add to their existing ART: MVC and DTG

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 Primary

In HIV-1-infected **participants** with suppressed plasma viremia and at least mild neurocognitive impairment, improved neurocognition and increased functional capacity over 48 weeks will be seen with addition of maraviroc (MVC) plus dolutegravir (DTG) (Arm C) compared to DTG only (Arm B) and compared to placebos (Arm A). Addition of DTG only (Arm B) compared to placebos (Arm A) will result in improved neurocognition over 48 weeks and increased functional capacity.

1.1.2 Secondary

Changes in **peripheral blood** and cerebrospinal fluid (CSF) biomarkers will parallel improvement in neurocognitive performance following addition of DTG alone or MVC and DTG.

1.2 Primary Objectives

1.2.1 To determine whether intensification with MVC and DTG (Arm C) will improve neurocognitive functioning at week 48 in **participants** who have at least mild neurocognitive impairment, are on a stable antiretroviral therapy (ART) regimen, and have plasma HIV-1 RNA <50 copies/mL, over DTG plus placebo for MVC (Arm B) and over placebo of both drugs (Arm A).

1.2.2 To determine whether DTG with placebo for MVC (Arm B) will improve neurocognitive functioning at week 48 over placebo of both drugs (Arm A).

1.3 Secondary Objectives

1.3.1 To determine the safety and tolerability of MVC and DTG when added to a stable ART regimen. The safety and tolerability measures will include time to discontinuation of any study medication due to adverse events (AEs), proportion of Grade 3 or Grade 4 clinical AEs, proportion of Grade 3 or Grade 4 laboratory abnormalities, and summaries of all treatment-related AEs.

1.3.2 To determine whether intensification with MVC and DTG will improve neurocognitive functioning at weeks 24, 72, and 96.

1.3.3 To determine whether functional status improves at week 48 after intensification with MVC and DTG (Arm C) to a greater extent than when intensified with DTG and placebo for MVC (Arm B) or placebo of both drugs (Arm A).

1.3.4 To assess the effect **of** adding MVC and DTG on biomarkers in **peripheral blood** and CSF.

1.3.5 To assess the association between serum and CSF biomarkers, neuropsychological performance**,** and DTG and MVC pharmacokinetics (PK) throughout the course of the study.

1.3.6 To assess whether the addition of DTG alone (Arm B) or DTG and MVC (Arm C) is associated with maintenance of plasma HIV-1 RNA <50 copies/mL.

1.3.7 To assess changes in blood CD4+/CD8+ counts after intensification with DTG and MVC (Arm C), DTG alone (Arm B) or placebos (Arm A).

1.3.8 To determine associations between **peripheral blood** immunologic markers (s100β, soluble CD14) and changes in neurocognitive function at week 48.

1.3.9 To determine the relationship between changes in CCR5 ligand levels (MIP-1b) and inflammatory marker changes in both **peripheral blood** and CSF.

1.3.10 To determine the effect of DTG intensification on residual viremia, cellular HIV-1 RNA expression, total cellular HIV-1 DNA, and 2 long terminal repeat sequences (LTR) DNA, and to determine whether these virologic changes are associated with week 48 neurocognitive function.

2.0 INTRODUCTION

2.1 Background/Rationale

Despite effective suppression of plasma HIV-1 RNA below levels of detection with highly active antiretroviral therapy (HAART), HIV-infected persons often have cognitive dysfunction (HIV-associated neurocognitive disorder, or HAND), which includes asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD). For example, in the ACTG Longitudinal Linked Randomized Trials (ALLRT) study, 458 (39%) of 1160 individuals receiving HAART had mild and 304 (26%) had mild-to-moderate neurocognitive impairment [1]. Similarly, in the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study, 40% to 52% of the 1555 **participants** were neuropsychologically impaired, including 42% neurocognitive impairment in those without other significant causes for impairment and who had undetectable plasma viral load [2]. The CHARTER study also documented the association between immune system functioning and neurocognitive impairment, with lower CD4+ lymphocyte nadirs predicting increased neurocognitive impairment. A study by Simioni et al**.** [3] found in **participants** who had undetectable plasma HIV-1 RNA (<50 copies/mL) on HAART and no cognitive complaints, 60% had ANI, 4% had MND, and none had HAD. Among those with cognitive complaints, 24% had ANI, 52% had MND and 8% had HAND.

International studies have provided estimates of neurocognitive impairment and examined the effects of ART on neurological and neurocognitive functioning in HIV. Two prior relevant ACTG studies, the international neurological study (A5199,

"International Neurological Study: A Stand Alone Study for Participants of A5175") and the international neurocognitive normative study (A5271, "Collection of Comparison Neurocognitive Data in Resource-Limited Settings") found substantial prevalence of neurocognitive impairment at baseline in HIV+ ART-naïve participants in diverse resource-limited settings (RLS). With ART, there were significant overall reductions in neurocognitive impairment over time [4, 5, 6, 7].

These and other studies demonstrate that neurocognitive impairment is common among HIV-1-infected persons, despite effective ART. There have been several past clinical trials in HAND of potential promising agents, including selegeline, nimodipine, and minocycline, all unsuccessful [**8**, **9**, **10**]. There are no current guidelines for the treatment of HAND.

Cognitive impairment of treated individuals may be due to several, non-mutually exclusive factors including irreversible injury that occurred prior to ART, persistent production of HIV-1 RNA in the central nervous system (CNS) compartment [**11**], toxicities of ART [**12**, **13**], or persistent CNS inflammation [**14**]. In support of the latter hypothesis, several studies have demonstrated elevated markers of immune activation in the CSF of **participants** with undetectable plasma HIV-1 RNA on ART [**15**]. Thus, control of plasma viral replication to <50 copies/mL may not be sufficient to prevent or reverse cognitive impairment. Controversy remains as to whether HAART that better penetrates into the CNS is important in treating or preventing HAND. Such treatment may reduce residual low-level viral replication within the CNS, and potentially reduce consequent pathologic CNS immune activation.

A CNS Penetration Effectiveness (CPE) **method** ranks available antiretroviral (ARV) penetration into the CNS based on several factors [**16**]. The 2010 revision of the CPE scale ranks CNS penetration on a 4**-**point scale**,** where 1 is the lowest and 4 **is** the highest relative CNS penetrance; for example, tenofovir (TDF) is ranked 1 and emtricitabine (FTC) is ranked 3 (Table 1). MVC is ranked at 3. Initial data on CSF penetration of DTG are promising**. The median DTG concentrations in CSF were 18 ng/mL (range, 4-23 ng/mL) at week 2 and 13 ng/mL (4-18 ng/mL) at week 16. Ratios of DTG CSF to total plasma concentration were similar to the unbound fraction of DTG in plasma** [**17**]. Higher CNS penetration of ART is associated with lower CSF HIV-1 RNA in cross-sectional analyses [**18**, **19**] and results in greater decreases in CSF HIV-1 RNA in longitudinal analyses [**13, 20**]**,** but has not conclusively been shown to improve neuropsychological performance in cognitively impaired **individuals**. Although the existing observational data are provocative, a change in clinical practice and treatment guidelines will require randomized controlled trials that carefully evaluate the risk as well as potential benefits of targeting or augmenting the CPE of ART for **indivuduals** with mild cognitive impairment.

Table 1. CNS Penetration-Effectiveness Ranks [**19**]

CLASS	4	3	2	1
NRTIs (nucleoside reverse transcriptase inhibitors)	Zidovudine (ZDV)	Abacavir (ABC) Emtricitabine (FTC)	Didanosine (ddI) Lamivudine (3TC) Stavudine (d4T)	Tenofovir (TDF) Zalcitabine (ddC)
NNRTIs (nonnucleoside reverse transcriptase inhibitors)	Nevirapine (NVP)	Delavirdine (DLV) Efavirenz (EFV)	Etravirine (ETR)	
PIs (protease inhibitors)	Indinavir/ Ritonavir (IDV/r)	Darunavir/ Ritonavir (DRV/r) Fosamprenavir/ Ritonavir (FPV/r) Indinavir (IDV) Lopinavir/ Ritonavir (LPV/r)	Atazanavir (ATV) Atazanavir/ Ritonavir (ATV/r) Fosamprenavir (FPV)	Nelfinavir (NFV) Ritonavir (RTV) Saquinavir (SQV) Saquinavir/ Ritonavir (SQV/r) Tipranavir/ Ritonavir (TPV/r)
Entry Inhibitors		Maraviroc (MVC)		Enfuvirtide (ENF)
Integrase Inhibitors	Dolutegravir (DTG)	Raltegravir (RAL)		

We propose to assess the efficacy of adding the **C-C chemokine receptor type 5 (**CCR5**)** antagonist MVC (Class 3 CPE) and the integrase inhibitor DTG (Class 4 CPE) to the current ART of persons with undetectable (<50 copies/mL) plasma HIV-1 RNA who have mild**-**to**-**moderate neurocognitive impairment with a primary outcome of improvement in neurocognitive performance. We have chosen a three-arm design comparing: (Arm A) placebos for MVC and DTG, (Arm B) DTG active drug and MVC placebo, and (Arm C) MVC and DTG active drugs. This design will allow us to determine the neurocognitive effects of each drug combination (all pairwise comparisons, arm B versus arm A, arm C versus arm A, and arm C versus arm B). MVC was chosen for this study because: 1) its concentrations in CSF consistently exceed the 50% inhibitory concentration for CCR5-using (R5) strains of HIV [**21**, **22**]; 2) the primary target cells for HIV in the nervous system, microglia, express predominantly CCR5 but not C-X-C chemokine receptor type 4 (CXCR4); 3) inhibition of CCR5 may decrease migration of lymphocytes into the CNS thereby diminishing inflammation in the CNS compartment [**23**]; and 4) it is well tolerated. DTG was chosen for this study because: 1) its concentrations in CSF also consistently exceed the 50% inhibitory concentration for wild-type HIV; 2) it is a member of a novel drug class that has reliable antiviral activity in integrase inhibitor-naïve individuals; and 3) it is well tolerated. Since eligible **participants** will have plasma HIV-1 RNA levels <50 copies/mL, performance of tropism and resistance assays will not be possible at the time of study screening; however, this testing can be applied to virological failures during the study, should the need arise. The potential novel properties of MVC on the CNS justify using it in this setting, along with the fact that all intensified **participants** will receive DTG**,** which is an active drug. While it is possible to assess proviral DNA tropism, this will not be done prospectively since the clinical relevance of the findings is unknown. However, depending upon the results of this study, consideration can be given to performing these assays retrospectively on stored peripheral blood mononuclear cells. In designing the intervention, DTG was

chosen as the single additional drug (Arm B) because in addition to having the favorable properties outlined above, it is expected to be an active agent in all enrolled **participants**, which is limited to those who are integrase inhibitor naïve. Because MVC does not have activity against CXCR4-using viruses, and there is one study suggesting that MVC may promote rather than suppress peripheral immune activation, we will not evaluate MVC as a single additional agent.

The study design is also well suited to assess the effects of **intensification with an** integrase **inhibitor** alone or **in combination with an** entry **inhibitor** on residual viremia, cellular HIV-1 RNA expression and 2-LTR circle formation**, using specimens through week 12, as well as the relationship between these indicators of low-level HIV replication** and neurocognitive function at 48 weeks**. The design would allow us to confirm (or refute) the findings of Hatano et al., who performed a randomized, double-blind, placebo-controlled trial of raltegravir intensification** [**24**]. **The trial found that 2 weeks of raltegravir increased the number of 2-LTR circles by more than five-fold, compared with placebo, indicating that low-level HIV replication had been present prior to raltegravir intensification and supporting that intensification with an integrase inhibitor may better suppress it.**

Rationale for 96-Week Follow-up
Including an assessment at 96 weeks in A5324 is important for several reasons:

First, if a neurocognitive benefit is observed, understanding the durability of the improvement and potential long-term toxicities will be important. For this reason, many clinical trials follow **participants** until 96 weeks and sometimes longer to assess both long-term efficacy and safety.

Second, compared with ARV-induced changes in HIV-1 RNA levels and CD4+ T-cell counts, the dynamics of neurocognitive improvement in people with HAND are much slower. For instance, Cysique et al**.** [**20**] showed that neurocognitive functioning continues to improve every 12 weeks after initiating ART. After 48 weeks of ART, the modeled regression line of neurocognitive change still had an upward slope, indicating that functioning was continuing to improve. Importantly, **participants** in this analysis had detectable HIV-1 RNA levels in blood before changing ART. This long-term improvement in neurocognitive scores was also seen in A5199, and persisted to 96 weeks of follow-up. **Participants** in A5324 will have undetectable HIV-1 RNA levels in blood prior to augmenting their ART and may have even slower improvement in neurocognitive functioning.

Third, maximum ARV effectiveness in the CNS does not occur until approximately 18 months of treatment. **Specifically, in** the NIH-funded CHARTER cohort, the proportion of treated **participants** who **had** detectable HIV-1 RNA levels in CSF **declined** over **this time frame**. In this analysis, recursive partitioning identified informative threshold values in the duration of the current ART: <7.2 months: 19.6% detectable HIV-1 RNA in CSF; 7.2 to 18.8 months: 16.6%; 18.8 to 57.4 months: 8.1% (S. Letendre, personal communication, 2014). While multiple factors may explain this finding, evaluating **participants** for longer than 18 months is needed to assess the effects of maximum viral suppression.

MVC (Selzentry)

MVC, in combination with other potent ARV drugs, is approved for suppressing R5 HIV-1 in treatment-naïve and experienced **individuals**. In the MERIT trial, MVC 300 mg once a day (QD) or 300 mg twice a day (BID) was compared to efavirenz (EFV) 600 mg QD, each in combination with Lamivudine (3TC)/zidovudine (ZDV) (300/150 mg BID, Combivir). The MVC 600 mg QD arm failed to meet predefined criteria for non-inferiority to EFV and was prematurely discontinued at week 16. At week 48, MVC 300 mg BID failed to show non-inferiority to EFV for the primary endpoint of plasma HIV-1 RNA <50 copies/mL (65.3% vs. 69.3%), although there was no difference in the proportion who achieved plasma HIV-1 RNA <400 copies/mL [**25**]. In the MERIT-ES study [**26**], data were reanalyzed after Enhanced Sensitivity Tropism Assay (TrofileES) was used to discriminate **participants** with exclusive R5 HIV-1 from those with X4 or dual/mixed strains with improved precision (sensitivity of approximately 0.3%) compared to the **earlier** Trofile assay. This re-analysis, using intent-to-treat (ITT), demonstrated similar suppression of R5 HIV (68% plasma HIV RNA <50 copies/mL) with EFV or MVC. There were fewer instances of rash, neurologic symptoms, and lipid changes in the MVC group. These results were confirmed at week 96 (59% vs. 62% suppressed), although, in general, more **participants** discontinued EFV due to AEs while more discontinued MVC due to virologic failure (VF) [**27**]. There was a greater mean increase in CD4+ T-cell count with MVC compared to EFV. Early failure of MVC appears due to outgrowth of pre-existing X4 or dual/mixed variants under selective drug pressure and later failure due to resistance of R5 variants.

In MOTIVATE, treatment-experienced **individuals** without detectable CXCR4-using virus were randomized to optimized background ARV regimen with or without QD or BID dosing of MVC. In this case, approximately 50% of **participants** in the QD arm and 63% of **participants** in the BID arm had evidence of non-R5 strains at the time of failure with no apparent immunologic consequences [**28**, **29**]. On the other hand, MVC resistance occurred in approximately one-third of **participants** who failed with R5-tropic HIV [**29, 30**]. The mechanisms of MVC resistance are not completely understood, but selection of mutations in the viral envelope gp120 molecule may allow HIV-1 to regain activity despite CCR5 inhibition with MVC [**31**].

DTG (Tivicay)

DTG is an integrase inhibitor approved for use in combination with other antiretrovirals in treatment-naïve and experienced HIV-1**-**infected adults and children aged 12 years and older and weighing at least 40 kg. The recommended dose of DTG in treatment naïve or treatment-experienced, integrase-naïve **individuals** is 50 mg QD, but when coadministered with potent UGT1A/CYP3A inducers such as EFV, fosamprenavir/ritonavir (FPV/r), tipranavir/ritonavir (TPV/r), or rifampin (RIF), a dose adjustment of DTG to 50 mg BID is needed in these **individuals**. The recommended dose of DTG in integrase-experienced **individuals** with certain integrase-associated resistance substitutions (L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R) or clinically suspected integrase resistance is 50 mg BID. Additionally, in these **individuals**, alternative combinations that do not include metabolic inducers should be considered when possible.

DTG is metabolized by the UGT1A1 metabolic pathway with minor CYP3A4, UGT1A3, and UGT1A9 components. DTG has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L/h based on population PK analyses. Following oral administration of DTG, peak plasma concentrations were observed 2 to 3 hours postdose. DTG tablets may be taken with or without food.

In vitro, DTG did not inhibit or induce cytochrome P450 enzymes. DTG is therefore not expected to affect the PK of drugs that are substrates of CYP450. DTG should not be used with etravirine (ETR) without coadministration of atazanavir/ritonavir (ATZ/r), darunavir/ritonavir (DRV/r), or lopinavir/ritonavir (LPV/r, Kaletra). Coadministration with nevirapine (NVP) should be avoided because there are insufficient data to make dosing recommendations. Coadministration with metabolic inducers such as oxcarbazepine, phenytoin, phenobarbital, carbamazepine, and St. John's wort should be avoided because there are insufficient data to make dosing recommendations. DTG should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.

In vitro, DTG inhibited the renal organic cation transporter, OCT2 (IC50 = 1.93 μM). In vivo, DTG inhibits tubular secretion of creatinine by inhibiting OCT2. Thus, coadministration of DTG with dofetilide is contraindicated due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events. In addition, monitoring of glucose levels is recommended when starting or stopping DTG and metformin together**,** as a dose adjustment may be needed for metformin.

DTG is highly protein-bound (approximately 99%) based on in vitro data, and in healthy **individuals**, DTG has a mean unbound fraction of approximately 0.23% [**32**].

The efficacy of DTG in HIV-1**-**infected treatment naïve **individuals** was based on 48-week data from two randomized, international, multicenter, double-blind, active-controlled trials, SPRING 2 (ING113086) and SINGLE (ING114467). In SPRING 2, 822 **participants** were randomized and received either DTG 50 mg QD or raltegravir (RAL) 400 mg BID, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) backbone (either abacavir[ABC]/3TC or TDF/FTC) [**33**]. At 48 weeks, the proportion of **participants** with HIV-1 RNA <50 copies/mL was 88% in the DTG group compared with 85% in the RAL group (adjusted difference 2·5%; 95% confidence interval (CI) –2·2 to 7·1). The median increase from baseline to week 48 in CD4+ cell count was 230 cells/mm^3 in both groups. The most common (≥10%) AEs (all grades) for DTG vs. RAL groups were nausea (14% vs. 13%), headache (12% vs 12%), nasopharyngitis (11% vs 12%), and diarrhea (11% in each group). Few **participants** had drug-related serious AEs (3 [<1%] vs. 5 [1%]), and few discontinued due to AEs (2% in each group). Rates of laboratory abnormalities were similar between treatment groups, and no clinically significant changes in the fasting lipid profile were noted in either group. Nonpathologic inhibition of the organic cation transporter, OCT2, in the proximal renal tubules [**34**] resulted in small, non-progressive increases in serum creatinine early in treatment with DTG (weeks 2**-**4) and then remained stable to week 48, consistent with previous findings [**35**]. No **participants** on the DTG or the RAL arm discontinued ART due to renal AEs. No evidence of treatment-emergent resistance was

observed in **participants** with VF on DTG, whereas among RAL-treated **participants**, one had integrase treatment-emergent resistance and four had NRTI treatment-emergent resistance.

In SINGLE, 833 **participants** were randomized and received either DTG 50 mg QD with fixed-dose ABC/3TC or fixed-dose TDF/FTC/EFV [**36**]. At 48 weeks, the proportion of **participants** with HIV-1 RNA <50 copies/mL was 88% on DTG compared with 81% on TDF/FTC/EFV (adjusted difference 7.4%; 95% confidence interval 2.5% to 12.3%; p=0.003). The adjusted median increase from baseline in CD4+ cell count was 267 cells/mm^3 for DTG+ABC/3TC vs. 208 cells/mm^3 for TDF/FTC/EFV at 48 weeks (adjusted difference 59%; 95% CI**,** 33% to 84%). The most common (≥10%) AEs for DTG+ABC/3TC vs. TDF/FTC/EFV groups were dizziness (7% vs. 32%), nausea (10% vs. 12%), abnormal dreams (6% vs. 15%), and insomnia (10% vs. 5%). The number of **participants** who discontinued study due to AEs for DTG+ABC/3TC was 10 (2%) compared with 41 (10%) on TDF/FTC/EFV groups. Few **participants** had drug-related serious AEs (1 [<1%] vs. 8 [2%]). Renal AEs leading to discontinuation occurred in one **participant** on DTG+ABC/3TC and two **participants** on TDF/FTC/EFV. At 48 weeks, small increases were noted in total, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol in both groups but total cholesterol/HDL ratio remained stable; comparable increases in triglycerides were observed in both groups. No evidence of treatment-emergent resistance was observed in **participants** with VF on DTG, whereas among TDF/FTC/EFV-treated **participants**, four had nonnucleoside reverse transcriptase inhibitor (NNRTI) treatment-emergent resistance and one had major NRTI treatment-emergent resistance.

DTG in CSF

The distribution and antiviral activity of DTG in CSF has been studied in 13 treatment-naïve **participants** on a stable regimen of DTG+ABC/3TC through 16 weeks [**17**]. Median change from baseline to week 16 in CSF (N=11) and plasma (N=12) HIV-1 RNA were -3.42 log_{10} and -3.04 log_{10} copies/mL, respectively. Nine of eleven (82%) **participants** had both plasma and CSF HIV-1 RNA <50 copies/mL and 10/11 (91%) **participants** had CSF HIV-1 RNA <2 copies/mL. At 16 weeks, the median (range) DTG concentration in CSF was 13.2 (3.7**-**18.3) ng/mL with CSF:plasma DTG concentration ratio of 0.41 (0.3-2.04). These data indicate that DTG therapeutic concentrations were achieved in CSF, with DTG CSF concentrations exceeding the in vitro 50% inhibitory concentration for wild-type viruses in peripheral blood mononuclear cells (0.2 ng/mL) [**37**] and decreases in CSF HIV-1 RNA levels were similar to decreases in plasma HIV-1 RNA levels.

Biomarkers

The search for clinically relevant biomarkers for HAND is another important, and largely unmet, need of the field. Many biomarkers have been investigated but an extensive panel is beyond the scope of this project. Instead, the project will measure a concise panel of biomarkers and store fluid to enable more in-depth investigations in the future.

- **Peripheral blood**

  As evaluations for this study will involve neuropsychological testing and classification of **participants** prior to and following randomization, we propose to

additionally investigate the possible correlation between HAND **diagnosis,** neuropsychological **test results,** and biomarkers of CNS injury. S100β is a calcium-binding protein produced by astrocytes that is elevated in the serum in the context of traumatic brain injury, brain ischemia and hemorrhage, active CNS lupus erythematosis, and Human T-lymphotropic virus Type 1 (HTLV-1)**-**associated tropical spastic paraparesis (but not asymptomatic HTLV-1 infection) [**38**, **39**, **40**, **41**]. Glial activation with elevated CSF expression of S100β has been identified in **individuals** infected with HIV-1 [**42**], and higher CSF S100β **is** associated with neurocognitive impairment in people infected with HIV-1 [**43**, **44**]. No studies have investigated the relationship between serum S100β and brain injury in HIV. We propose to use the opportunity afforded by the detailed neuropsychological characterization of enrolled **participants** to assess whether S100β might be a **peripheral blood** biomarker for HIV-associated CNS disease/HAND. In addition to S100β, we will measure the serum concentration of the soluble form of the receptor for bacterial lipopolysaccharide (LPS), CD14, based on the theory of microbial translocation-associated immune activation in HIV disease [**45**]. In vitro and animal model studies suggest that LPS may lead to neurological injury by augmenting trafficking of infected and activated monocytes across the blood**-**brain barrier [**46**]. Human studies have also linked LPS and soluble CD14 to HAND [**47**].

sCD163 is a soluble marker of monocyte/macrophage activation that has been associated with surrogate markers of cardiovascular disease [**48**] and neurocognitive dysfunction in treated HIV infection [**49**]. D-dimer is a coagulation marker that is increased in inflammatory states including treated HIV infection and strongly predicts all-cause mortality in this setting [**50**]. MIP-1b is a natural CCR5 ligand, which has been shown to increase at least 2-fold in plasma during **MVC** intensification [**51**] due to blockade of ligand-receptor complex internalization. The extent of MIP-1b elevation during **MVC** intensification is thus a reasonable surrogate marker for the degree to which **MVC** is preventing natural signaling through CCR5 in vivo.

- CSF

  In the subset of **participants** who agree to undergo an optional lumbar puncture (LP) for CSF collection, we will assess CSF concentrations of selected biomarkers. CSF concentrations of neopterin, monocyte chemoattractant protein-1 (MCP-1), and Interferon gamma-induced protein 10 (IP-10) are increased in people infected with HIV-1 and are indicators of macrophage activation, monocyte-derived macrophage chemotaxis**,** and lymphocyte chemotaxis [**14, 52**, **53**, **54**, **55**, **56**, **57**, **58**]. Neurofilament light chain (NFL) is a sensitive biomarker of axonal injury that can be assayed in CSF **(and peripheral blood)** [**59**, **60**, **61**, **62**, **63**].

While these example biomarkers in plasma and CSF are of current interest, there are often substantial changes over time with the development of new more sensitive and specific biomarkers. As research adds to the knowledgebase in this area, the team will implement and assess the most scientifically rigorous and relevant biomarkers at study conclusion.

3.0 STUDY DESIGN

This is a phase IV randomized, double-blinded, placebo-controlled clinical trial. **Participants** will have at least mild HAND as defined by the Frascati criteria, plasma HIV-1 RNA <50 copies/mL within 90 days prior to entry, no more than one plasma HIV-1 RNA ≥50 and <200 copies/mL in the 6 months prior to entry with a subsequent plasma HIV-1 RNA <50 copies/mL, and on stable ART for at least **6** months prior to entry with no plans to change treatment **except for the allowed changes defined in sections 4.1.2 and 4.1.3**. **Participants** will be randomized to one of three study arms to add to their existing ART, placebo for MVC**,** and placebo for DTG (Arm A), DTG active drug and placebo for MVC (Arm B), or MVC and DTG active drugs (Arm C). Randomization will be stratified by CD4+ nadir (≤100 vs. >100 cells/mm^3) and HAND severity (ANI vs. MND/HAD).

Participants will be assessed at screening and then every 24 weeks for 96 weeks with a neurocognitive battery. The tests in the neurocognitive battery have been implemented successfully in multisite clinical trials, and extensive training materials within the ACTG exist. **Appropriate country- and site-specific normative** data will be used for comparison**,** and the battery is designed to adhere to the recommendations of the Frascati consensus **[7, 64, 65].** These tests can have practice or learning effects upon repeated assessment; however, **alternate versions of the tests will be used at each visit to minimize this effect. In addition,** the placebo group **(Arm A)** will provide an estimate of practice effects and natural history in our analyses. A self-report assessment of functional ability, instrumental activities of daily living (IADLs), and psychological distress will be administered. In addition, an assessment of comorbidities and confounding factors based on the Frascati criteria will be completed at screening then every 24 weeks for 96 weeks and used as a covariate. Refer to the A5324 **Manual of Operations (MOPS)** for details regarding the self-report assessments and the Frascati criteria.

There will be clinical safety evaluation and monitoring at week 2, then clinical and laboratory safety evaluation and monitoring at week 4, week 12**,** and every 24 weeks beginning at week 24.

Blood will be collected for hematology, chemistries, CD4+/CD8+ lymphocytes**,** and quantitative plasma HIV-1 RNA, with plasma and serum collected and stored for single-copy assay (SCA) and assessment of systemic immune and inflammation markers (s100β, soluble CD14 [sCD14], etc.), respectively. PBMC will be cryopreserved at the indicated timepoints for future T-cell and monocyte phenotypic and functional studies as well as HIV reservoir measures (2-LTR circles and total cell-associated HIV-1 RNA and DNA).

A subset of consenting **participants** will undergo LP at entry and 48 weeks.

4.0 SELECTION AND ENROLLMENT OF **PARTICIPANTS**

4.1 Inclusion Criteria

4.1.1 HIV-1 infection, documented by**:**

- **A** licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen or plasma HIV-1 RNA viral load

  NOTE: The term "licensed" refers to a United States **Food and Drug Administration (**FDA**)**-approved kit**, which is required for all IND studies, or for sites located in countries other than the United States, a kit that has been certified or licensed by an oversight body within that country and validated internally. Non-US sites are encouraged to use US FDA-approved methods for IND studies.**

  WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (eg, indirect versus competitive), or a Western blot or a plasma HIV-1 RNA.

  OR

- **Documentation of HIV diagnosis in the medical record by a healthcare provider**

4.1.2 On current ART for at least **6** months prior to study entry with no interruption in treatment of ≥7 **consecutive** days.

Note: The following ART changes are allowed:

- **TDF to tenofovir alafenamide fumarate (TAF)/TAF-containing fixed-dose combination regimens**
- **RTV to cobicistat (COBI)/COBI-containing fixed-dose combination regimens**

4.1.3 No plans to change ART while on study.

Note: The following planned ART changes are allowed:

- **TDF to TAF/TAF-containing fixed-dose combination regimens**
- **RTV to COBI/COBI-containing fixed-dose combination regimens**

4.1.4 HIV-1 plasma RNA <50 copies/mL obtained within 90 days prior to study entry by any FDA-approved assay at any United States laboratory that has a **Clinical Laboratory Improvement Amendments (**CLIA**)** certification or its equivalent**, or at any network-approved non-US laboratory that operates in accordance**

with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

4.1.5 No more than one HIV-1 plasma RNA ≥50 and <200 copies/mL (only one "blip") in the past 6 months with a subsequent HIV-1 plasma RNA <50 copies/mL.

NOTE: There should be no plasma HIV-1 RNA >200 copies/mL within the 6 months prior to study entry.

4.1.6 HAND diagnosis (ANI, MND, or HAD) within **60** days prior to study entry.

HAND is defined as at least mild impairment **on neurocognitive testing** (more than one standard deviation below appropriate normative data in two domains of functioning) and no severely confounding factors.

4.1.7 Screening laboratory values obtained within **60** days prior to study entry **by any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs**:

- Absolute neutrophil count (ANC) ≥500/mm^3
- Hemoglobin ≥7.5 g/dL
- Platelet count ≥40,000/mm^3
- Creatinine ≤2.0 **x** ULN
- Aspartate transaminase (AST) ≤5 x ULN
- Alanine transaminase (ALT) <3 x ULN
- Alkaline phosphatase ≤5 x ULN
- Total bilirubin <1.5 x ULN

  NOTE: If the potential **participant** is taking an indinavir (IDV)- or atazanavir (ATV)-containing regimen at the time of screening, total bilirubin ≤5 x ULN is acceptable.
- Creatinine clearance (CrCl) ≥60 mL/min, either measured or estimated by Cockcroft-Gault equation

  NOTE: A calculator for estimating the CrCl can be found at www.fstrf.org/ACTG/ccc.html

4.1.8 Females of reproductive potential (women who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or women who have not undergone surgical sterilization, hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy or tubal ligation) must have a negative serum or urine pregnancy test **by any US clinic or laboratory that has a CLIA certification or its equivalent, or is using a point of care (POC) / CLIA-waived test, or at any network-approved non-US laboratory or clinic that operates in accordance with GCLP and participates**

in appropriate external quality assurance programs within 48 hours prior to study entry.

4.1.9 Females of reproductive potential must agree not to participate in the conception process (ie, active attempt to become pregnant, in vitro fertilization), and if participating in sexual activity that could lead to pregnancy, must use at least one reliable form of **contraception**. Female **participants** must use contraceptives while receiving study treatment and for 6 weeks after stopping study treatment.

Acceptable forms of **contraception** include:

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormonal contraceptive

Females who are not of reproductive potential or whose male partner(s) has documented azoospermia are not required to use contraceptives. Any statement of self-reported sterility or that of her partner's must be entered in the source documents.

NOTE: Acceptable documentation of lack of reproductive potential is oral or written documentation from the **participant**.

4.1.10 Men and women age ≥18 years who are able to complete the neuropsychological tests.

4.1.11 Ability and willingness of **participant** or a legally authorized representative (LAR; see section 4.3.1.1) to provide informed consent.

4.1.12 Ability and willingness to take oral study medications.

4.2 Exclusion Criteria

4.2.1 Current or past medical condition(s) that**,** in the opinion of the investigator**,** prevents attribution of the cause of cognitive impairment to HIV. For example:

4.2.1.1 Major depressive disorder with psychotic features

4.2.1.2 Traumatic Brain Injury (TBI) with a clear impact on activities of daily living

4.2.1.3 **Developmetal delay, intellectual deficit,** and/or severe educational disability resulting in some dependence for activities of daily living

4.2.1.4 Ongoing substance use with significant impact on activities of daily living. Difficult or impossible to determine whether cognitive or functional decline is due to substance use or HIV, or both

4.2.1.5 Evidence of intoxication or withdrawal during the screening evaluation

4.2.1.6 CNS infections or opportunistic conditions: Brain abscess (bacterial, mycobacterial, fungal**,** or Toxoplasma), meningitis with persistent neurologic impairment, primary CNS lymphoma, progressive multifocal leukoencephalopathy (PML), or another structural brain lesion with neurological sequelae

4.2.1.7 Other CNS conditions: Non-opportunistic primary or metastatic brain tumors, uncontrolled seizure disorder, progressive multiple sclerosis, stroke with neurological sequelae, or dementia due to causes other than HIV (eg, Alzheimer's disease)

4.2.1.8 Constitutional illness (eg, persistent unexplained fever, diarrhea, significant weight loss, disabling weakness) within 30 days of screening

4.2.1.9 Known untreated B12 deficiency or malnutrition (body mass index [BMI] <18) at screening

4.2.2 Evidence of current hepatitis C virus infection (HCV) (ie, HCV antibody **[Ab]** positive within 90 days prior to study entry unless also shown to be **plasma** HCV RNA negative within the same time period).

4.2.3 Unstable and advanced liver disease (as defined by the presence of **at least one of the following:** ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice).

4.2.4 Prior or current use of any **CCR5 antagonist (such as MVC and cenicriviroc [CVC]) and integrase inhibitor (such as RAL, DTG, and elvitegravir [EVG])**.

4.2.5 Current use of any medication, including antiretrovirals, prohibited in the study (refer to **the A5324 protocol-specific web page [PSWP]** for the prohibited medications).

4.2.6 Breastfeeding.

4.2.7 Presence of an AIDS-defining opportunistic infection within **6 months** prior to entry.

Note: Refer to the A5324 MOPS for the list of AIDS-defining opportunistic infections.

4.2.8 Active syphilis or treatment for syphilis within 90 days prior to study entry.

NOTE: Active syphilis is defined as four-fold increase in serum rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) tests in **an individual** with past syphilis, or newly reactive serum RPR or VDRL with a reactive confirmatory test (enzyme immunoassays [EIA] **or chemiluminescent assay [CIA]**, *T. pallidum* particle agglutination [TP-PA], or fluorescent treponemal antibody absorbed [FTA-ABS]).

4.2.9 Known allergy/sensitivity or any hypersensitivity to components of study drugs or their formulation.

4.3 Study Enrollment Procedures

4.3.1 Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) will be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement **the** amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific ICF(s) will not be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

Sites that are registering for the first time with Version 2.0 should follow the protocol registration procedure for an initial registration.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for study entry has been identified, details will be carefully discussed with **him or her**. The **participant** (or, when necessary, the LAR [see section 4.3.1.1]) will be asked to read and sign the approved protocol consent form.

For **participants** from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the Data Management Center (DMC) Subject Enrollment System.

4.3.1.1 Surrogate Consent by a Legally Authorized Representative (LAR)

A potential **participant** who lacks the capacity to provide informed consent due to cognitive impairment may be considered if the **participant** has a designated surrogate who can consent on his/her behalf. The designated surrogate is a LAR who has the ability to provide consent for the **participant's** participation in this research protocol as defined in the state and/or local laws.

4.3.2 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.3.3 Randomization

At the entry visit, **participants** will be randomized according to standard ACTG data management procedures.

For **participants** from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the protocol, an ACTG Screening Failure Results form must be completed and keyed into the database.

4.4 Coenrollment Guidelines

- Sites are encouraged to coenroll **participants** in A5128, "Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses." Coenrollment in A5128 does not require permission from the A5324 protocol chairs.

- **Non-US sites are encouraged to co-enroll participants in A5243, "Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses." Co-enrollment in A5243 does not require permission from the A5324 protocol chairs.**

- Sites that have been selected to participate in the "Imaging and Inflammatory Biomarkers in Anti-Retroviral NeuroIntensification (SPIRIT)" study are encouraged to coenroll **participants** who are eligible. Coenrollment in the SPIRIT study does not require approval of the A5324 protocol chairs.

- For specific questions and approval for coenrollment in other studies, sites should first check the PSWP or contact the protocol chairs via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment is defined as maraviroc (MVC) or placebo for maraviroc, and dolutegravir (DTG) or placebo for dolutegravir.

The study treatment will be added to the current non-study-provided ART.

5.1 Regimens, Administration, and Duration

5.1.1 Regimens

Participants will be randomized (1:1:1) to one of the three (3) following regimens:

- ARM (A): Placebo for maraviroc + Placebo for dolutegravir
- ARM (B): **DTG** + Placebo for maraviroc
- ARM (C): **MVC** + **DTG**

NOTE: **Participants** will receive the following regimen, based on their existing **ART** therapy (see Tables A and B):

- DTG OR placebo for dolutegravir

  AND
- MVC OR placebo for maraviroc

Table A.

Background Regimen	ARM A	ARM B	ARM C
EFV + NRTI	Placebo for dolutegravir One **(50 mg Placebo)** tablet BID	DTG One (50 mg) tablet BID	DTG One (50 mg) tablet BID
	Placebo for maraviroc Two (300 mg Placebo) tablets BID	Placebo for maraviroc Two (300 mg Placebo) tablets BID	MVC Two (300 mg) tablets BID
RPV + NRTI	Placebo for dolutegravir One **(50 mg Placebo)** tablet QD	DTG One (50 mg) tablet QD	DTG One (50 mg) tablet QD
	Placebo for maraviroc One (300 mg Placebo) tablet BID	Placebo for maraviroc One (300 mg Placebo) tablet BID	MVC One (300 mg) tablet BID

Table B.

Background Regimen	ARM A	ARM B	ARM C
PI/r + NRTIs OR PI/r + NNRTI +/- NRTI	Placebo for dolutegravir One **(50 mg Placebo)** tablet QD	DTG One (50 mg) tablet QD	DTG One (50 mg) tablet QD
	Placebo for maraviroc One (150 mg Placebo) tablet BID	Placebo for maraviroc One (150 mg Placebo) tablet BID	MVC One (150 mg) tablet BID

Any changes to the ART regimen, other than the allowed changes in section 7.6, should be discussed with the A5324 core team in advance (actg.corea5324@fstrf.org).

5.1.2 Administration and Dispensing

All of the study products in the regimen should be taken with or without food. See section 10.2.1 for holding doses prior to the week 12 PK visit.

5.1.2.1 MVC or placebo for maraviroc will be administered orally as one 150 mg tablet BID OR two **(**300 mg**) tablets** BID OR one 300 mg tablet BID depending upon background ARV regimen.

5.1.2.2 DTG or placebo for dolutegravir will be administered orally as one 50 mg tablet BID OR one 50 mg tablet QD depending upon background ARV regimen.

5.2 Study Product Formulation and Preparation

5.2.1 **MVC** 150 mg tablets; 300 mg tablets. Store at room temperature 25°C (77°F); excursions permitted to 15°C-30°C (59°-86°F) [see USP Controlled Room Temperature].

5.2.2 DTG 50 mg tablets. Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°-86°F) [see USP Controlled Room Temperature].

5.2.3 Placebo for maraviroc 150 mg tablets and Placebo for maraviroc 300 mg tablets. Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

5.2.4 Placebo for dolutegravir tablets. Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

MVC and placebo for maraviroc will be supplied by ViiV Healthcare Ltd.

DTG and placebo for dolutegravir will be supplied ViiV Healthcare Ltd.

Study products will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain the study products for this protocol by following the instructions in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks in the section Study Product Management Responsibilities.

No other ARV therapy will be provided through the study.

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. **At US clinical research sites (CRSs), all** unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks. **At non-US CRSs, the site pharmacist must follow the instructions in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for the destruction of unused study products.**

5.4 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medications' and study agents' most recent package inserts, Investigator's Brochures, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the updated ACTG Drug Interactions Database located at **http://tprc.pharm.buffalo.edu/home/di_search/**.

5.4.1 Prohibited Medications

For a list of prohibited medications, refer to the PSWP.

5.4.2 Precautionary Medications

For a list of precautionary medications, refer to the PSWP.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of **Evaluations**

Evaluation	Screening	Pre-Entry	Entry	Post-Entry Evaluations (Weeks)										Confirmation of VF	Premature Study/Treatment Discontinuation
				2	4	12	24	**36**	48	**60**	72	**84**	96		
Visit Windows				± 1 wk		± 2 wks		- 4 wks, + 8 wks							
Documentation of HIV-1	X														
Medical History	X		X												
Medication History	X		X												
Nadir CD4+			**X**												
Clinical Assessment	X		X	X	X	X	X		X		X		X		X
Neurological Exam			X						X						
Frascati HAND Rating Scale	X						X		X		X		X		X
Neuropsychological Baseline Data	X														
Neurocognitive Batteries	X						X		X		X		X		X
Questionnaires	**X**						**X**		**X**		**X**		**X**		**X**
Adherence Assessment			**X**		**X**	**X**	**X**		**X**		**X**		**X**	**X**	**X**
Study Medication Dispensing			**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**			
Hematology	X		X			X	X		X		X		X		
Liver Function Tests	X		X		**X**	X	X		X		X		X		
Chemistry	X		X		**X**	X	X		X		X		X		
Urinalysis	X												**X**		X
Pregnancy Testing	X		X	Whenever pregnancy is suspected											If pregnancy is suspected

Evaluation	Screening	Pre-Entry	Entry	Post-Entry Evaluations (Weeks)										Confirmation of VF	Premature Study/Treatment Discontinuation
				2	4	12	24	**36**	48	**60**	72	**84**	96		
Visit Windows				± 1 wk		± 2 wks		- 4 wks, + 8 wks							
HCV Ab	X														
Syphilis Screening	X														
CD4+/CD8+			X			X	X		X		X		X		X
Plasma HIV-1 RNA	X		X			X	X		X		**X**		X	X	X
Stored Plasma		X	X	X	X	X	X		X		X		X	X	X
Stored Serum			X				X		X				X		X
Stored Viable PBMCs		X	X	X	X	X			X				X		
CSF supernatant and pellets (only in **participants** who undergo LP)			X						X						
PK Studies						X	X		X						
LP Safety Laboratory Tests **(only in participants who will be undergoing LP)**			**X**						X						
LP (Optional)			X						X						
Resistance Testing														X	
Tropism Testing														X	

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening
Screening evaluations to determine eligibility must be completed within **60** days prior to study entry unless otherwise specified. In addition to data being collected on **participants** who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

Pre-Entry
The screening and pre-entry visits can occur on the same day. Sites have the option to complete the screening and pre-entry evaluations in stages (such as conducting the neurocognitive battery one day then the laboratory **and clinical** evaluations on another day) if it will be easier for the site and the **participant**.

Results of the screening and pre-entry evaluations must be received at least 24 hours prior to entry.

6.2.2 Entry Evaluations

Entry evaluations must occur at least 24 hours after pre-entry unless otherwise specified. **Participant** must begin treatment within 3 days after randomization.

6.2.3 Post-Entry Evaluations

On-Treatment Evaluations
Post-entry evaluations should occur following the visit windows in the Schedule of **Evaluations** (SOE), section 6.1.

NOTE: The week 96 evaluations should be peformed as close to the week 96 schedule as possible.

Confirmation of VF
For **participants** who have suspected VF, a confirmatory plasma HIV-1 RNA test and adherence assessment as per section 6.1 are to be performed within 30 days after receipt by the site of the results of the initial HIV-1 RNA sample indicating suspected VF. **Participants** who have their first plasma HIV-1 RNA >200 copies/mL at their final study visit should be asked to return to the clinic for a confirmatory visit within 30 days of receipt of the result from their final visit.

NOTE: VF is defined as confirmed HIV-1 RNA levels >200 copies/mL after study entry.

If the confirmation of VF visit coincides with a regularly scheduled visit, the evaluations should be combined.

Participants who have confirmed VF will discontinue the study medications but will continue on study and followed through week 96. See sections 6.1 and 6.2.4 for the procedures at premature treatment discontinuation.

Samples drawn for resistance and tropism testing at the confirmation of VF visit should be stored. The samples should be sent to the testing laboratory following the guidelines in sections **6.3.19** (Resistance Testing) and **6.3.20** (Tropism Testing).

6.2.4 Discontinuation Evaluations

Evaluations for Randomized **Participants** Who Do Not Start Study Treatment
All case report forms (CRFs) must be completed and keyed for the period up to and including the entry visit. No further follow**-**up is required. **Participants** must be taken off study.

Premature Treatment Discontinuation Evaluations
Participants who discontinue the study medications before the end of the study should have the premature treatment discontinuation evaluations done within 14 days after stopping study medications. **Participants** will be followed off study treatment/on study. They should be encouraged to continue to attend all study visits and receive study evaluations as per section 6.1, with the exception of the adherence questionnaires**,** and optional lumbar puncture, through completion of the study.

Premature Study Discontinuation Evaluations
All **participants** who prematurely discontinue participation in the study should have the premature study discontinuation evaluations done as per section 6.1. **Participants** who prematurely discontinue participation in the study should report to the clinic to have the premature study discontinuation evaluations performed as soon as possible.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS **website** for information about what must be included in the source document: **https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf.**

All stated evaluations are to be recorded on the CRF and keyed into the database unless otherwise specified. This includes events that meet the International Conference on Harmonisation (ICH) definitions for a serious adverse event:

- Results in death
- Life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other important medical event (may not be immediately life-threatening or result in death or hospitalization) but may jeopardize the patient or may require intervention to prevent one of the events listed above.

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric AEs (DAIDS AE Grading Table), **Version 2.1, March 2017**, which can be found on the DAIDS RSC Web site: **http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables**.

6.3.1 Documentation of HIV-1

Section 4.1.1 specifies assay requirements **and medical notes** for HIV-1 documentation. HIV-1 documentation is not recorded on the CRF.

6.3.2 Medical History

The medical history must include all diagnoses identified by the ACTG criteria for clinical events and other diagnoses. In addition to reporting all diagnoses within the past 30 days prior to study entry, the following diagnoses should be reported regardless of when the diagnosis was made**:**

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B
- Any neurologic disease

Any allergies to any medications and their formulations must also be documented.

6.3.3 Medication History

A medication history must be present, including start and stop dates (except as otherwise indicated on the CRF). If only estimated start and stop dates are

available, these are acceptable. The table below lists the medications that must be included in the history and recorded on the CRFs.

Medication Category	Complete History or Timeframe
ART	Complete
Immune-based therapy	30 days prior to study entry
Blinded study treatment	30 days prior to study entry
HIV-1-related vaccines	30 days prior to study entry
Prescription drugs for treatment of opportunistic infections	30 days prior to study entry
Prescription drugs for prophylaxis of opportunistic infections	30 days prior to study entry
Prescription drugs (other)	30 days prior to study entry
Alternative therapies	30 days prior to study entry
Dietary supplements	30 days prior to study entry

6.3.4 Nadir CD4+

The **participant's** prior nadir CD4+ cell count (absolute value and date) should be documented when possible with a copy of the nadir CD4+ cell count report **or participant report**. If this documentation is not available **or the participant is unable to recall**, **either the best available information should be used or recorded as missing data in the CRF**.

6.3.5 Clinical Assessments

Complete Physical Exam
A complete physical examination at screening is to include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; and examination of the lower extremities for edema. The complete physical exam will also include height, weight, signs and symptoms, diagnoses, and vital signs (temperature, pulse, and blood pressure).

Targeted Physical Exam
After screening, a targeted physical examination, including height (at entry and week 12 only), weight**,** and vital signs (temperature, pulse, and blood pressure) should be per section 6.1**,** along with additional assessments based upon previously identified findings, diagnoses, or new signs or symptoms since the last visit.

Height
Height in centimeters (cm) will be recorded on the CRF at the entry visit only.

Weight
Weight in kilograms (kg) will be measured and recorded in the CRF at entry **and** weeks 12, 24, and 48.

Signs and Symptoms
At entry, record on the CRFs all signs/symptoms occurring within 30 days prior to entry.

After entry, all Grade ≥3 signs/symptoms, any signs/symptoms regardless of grade that lead to a change in treatment, that meet EAE, SAE, or ICH guidelines, or are defined by the protocol as reportable events that require detailed event reporting.

Diagnoses
At screening, record diagnoses in the medical history per section 6.3.2. At study entry and thereafter, record all new diagnoses since the last study visit identified **in** the **appropriate diagnoses appendix specified in the CRF**.

Concomitant Medications
All current prescription medications (with start and stop dates) are to be recorded on the CRF. Current non-prescription medications are recorded in the source documents only. Alternative and traditional medications are reported as Yes/No on the CRF and keyed into the database.

Post-entry, new and discontinued prescription concomitant medications must be recorded on the CRFs.

Study Treatment Modifications
At entry and weeks 4 to 96, record all study medication modifications, including initial doses, **participant**-initiated and/or protocol-mandated modifications, and inadvertent and deliberate interruptions **of ≥3 days**. Record any permanent discontinuation of treatment.

6.3.6 Neurological Exam

The neurological exam will be performed only in **participants** who consent to undergo the lumbar puncture procedure for collection of CSF. The exam will be performed as scheduled in section 6.1. Refer to the A5324 **MOPS** and the PSWP for specific details.

6.3.7 Neuropsychological Baseline Demographic Data

At screening, baseline demographic data, including age, educational level, and primary language will be collected.

6.3.8 Neurocognitive Batteries

Neurocognitive testing will be performed as scheduled per section 6.1. This testing will take about an hour to complete. Refer to section 3.0 (Study Design), the A5324 **MOPS,** and the PSWP for additional information.

Frascati HAND Rating
Eligibility **of the participant for the study** will be based on the Frascati criteria for neurocognitive impairment. **An assessment of relevant confounding factors based on medical history and participant report are recorded on the CRF, and are a necessary part of the HAND diagnostic criteria.** Refer to the A5324 **MOPS** for description and instructions **for** HAND diagnoses based on the Frascati criteria**, which is determined by the A5324 Protocol Chair**.

Refer to the A5324 MOPS for the Frascati HAND rating procedure for the post-entry visits.

A5324 Neurocognitive Battery
Based on the A5324 Neurocognitive battery administered at screening, **participant** impairment will be determined according to the Frascati criteria for HAND diagnoses. The tests will be administered **based on CRS location as described below.**

Neurocognitive Test Battery for CRSs in the United States:

- Attention/Working Memory (Symbol Search**, Trail Making A**)
- Speed of Information Processing (Stroop Word, Stroop Color, Digit Symbol)
- Executive Function (Trail Making B, Stroop Color/Word, Letter and Category Fluency)
- Verbal Learning (Hopkins Verbal Learning Test Revised **[HVLT-R]**)
- Verbal Memory (Delayed Recall – HVLT-R)
- Fine Motor Skills/Complex Perceptual (Grooved Pegboard Bilateral)
- Language/Premorbid Skills (**Wide Range Achievement Test 4 [**WRAT-4**]** Reading **OR Word Accentuation Test [WAT] for participants with Spanish as their primary language**)

Neurocognitive Test Battery for CRSs outside the United States:

- **Attention/Working Memory (Color Trails 1)**
- **Speed of Information Processing (Digit Symbol)**
- **Executive Function (Color Trails 2, Category Fluency)**
- **Verbal Learning (HVLT-R)**

- **Verbal Memory (Delayed Recall – HVLT-R)**
- **Fine Motor Skills/Complex Perceptual (Grooved Pegboard Bilateral, Fingertapping Bilateral); Gross Motor (Timed Gait)**
- **International HIV Dementia Scale (IHDS)**

6.3.9 Questionnaires

Activities of daily living (ADLs), psychological distress, and substance abuse will be assessed using self-report questionnaires as scheduled in section 6.1. The following questionnaires will be administered:

- **Revised Lawton and Brody Activities of Daily Living Scale**
- **Beck Depression Inventory II (BDI-II) (CRSs in the US only)**
- **Patient Health Questionnaire (PHQ)-9 (CRSs outside the US only)**
- **ACTG Substance Abuse questionnaire**

Refer to the A5324 MOPS and PSWP for the specific information and instructions for completing the questionnaires.

6.3.10 Adherence Assessment

Adherence to all study-provided and background ART medications will be assessed by self-report and completed as scheduled in section 6.1.

Sites will provide adherence reinforcement, according to standard practice, throughout the study. Participants with poor adherence (ie, less than 95%) will be provided counseling by the site.

6.3.11 Study Medication Dispensing

At study entry and thereafter, study medications will be dispensed every 12 weeks. At weeks 36, 60, and 84, participants will return for study medication dispensing only. No other study evaluations will be performed.

6.3.12 Laboratory Evaluations

Record all protocol-required laboratory values, regardless of grade, obtained at screening and entry on the CRFs.

After entry, record:

- all creatinine and liver function test (LFT) values,

  AND

- Grade ≥3 for all other laboratory values.

All laboratory values that lead to a change in study treatment, regardless of grade, must be recorded.

Hematology
Hemoglobin, hematocrit, white blood cell count (WBC), with differential **including** Absolute Neutrophil Count (ANC), and platelet count.

Liver Function Tests (LFTs)
Total bilirubin, AST, ALT, alkaline phosphatase.

Blood Chemistries
Electrolytes (Na+, K+, Cl-, HCO_3/CO_2), glucose, creatinine, phosphate, and blood urea nitrogen.

Urinalysis
Dipstick urinalysis with microscopic examination if dipstick urinalysis is abnormal or when thought necessary by the investigator. Results will be recorded on the CRFs.

Pregnancy Test
For women with reproductive potential: serum or urine β-HCG (urine test must have a sensitivity of ≤25 mIU/mL).

Negative pregnancy test must be obtained within 48 hours prior to study entry for females of reproductive potential as defined in section 4.1.8. After entry, perform a pregnancy test when pregnancy is suspected. **Refer to section 7.3 for pregnancy and pregnancy outcome reporting requirements.**

Serologies
HCV Ab must be performed at the screening visit in **participants** without an HCV Ab test result within 90 days prior to study entry.

Syphilis
Screening for active syphilis will be done using nontreponemal tests (RPR or VDRL) with reflex confirmation with treponemal test. If screening with a treponemal test (EIA, **CIA,** TP-PA**,** or FTA-ABS), a nontreponemal test must also be performed if the treponemal test is reactive.

6.3.13 Immunologic Studies

CD4+/CD8+
During the study, CD4+/CD8+ assays must be performed as indicated in section 6.1**. For entry and post-entry evaluations, all laboratories must possess** a CLIA certification or equivalent and **must be** certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program.

The same assay must be used across all study visits. Due to diurnal variations in CD4+/CD8+ counts, determinations for individual **participants** should be obtained consistently in either the morning or the afternoon throughout the study, if possible.

NOTE: If the lab is using dual platform technology to obtain the results, each time a measurement is obtained, the local lab must perform a WBC and differential from the sample collected at the same time.

6.3.14 Virologic Studies

Plasma HIV-1 RNA
Screening HIV-1 RNA must be performed within 90 days prior to study entry by a laboratory that possesses a CLIA certification or equivalent using any FDA-approved assay. Eligibility will be determined based on the screening value.

HIV-1 RNA on study will be performed as scheduled in section 6.1. The samples will be processed and shipped to the designated testing laboratory **associated with each non-US CTU/CRS or to Quest Diagnostics for each US CTU/CRS;** plasma HIV-1 RNA will be performed in real-time using the current approved assay selected by the ACTG. See the A5324 laboratory processing chart (LPC) for directions.

6.3.15 Stored Samples

EDTA blood for plasma and PBMC will be collected at the visits indicated on the SOE, section 6.1. Samples will be batch-tested at the end of the study. See the A5324 LPC for processing, storage, and shipping directions.

Plasma
Plasma will be collected and stored for single copy assay (SCA).

Plasma collected at the confirmation of VF visit will be stored for resistance and tropism testing if VF is confirmed (see sections **6.3.19** and **6.3.20**).

Serum
Serum will be collected and stored for assessment of the correlation of systemic immune and inflammation markers (s100β, sCD14, etc.) and **neuropsychological test performance**.

Viable Peripheral Blood Mononuclear Cells (PBMCs)
Viably cryopreserved PBMCs from whole blood collected at visits indicated on the SOE, section 6.1, will be stored for future T cell and monocyte phenotypic and functional studies, HIV reservoir measures (2-LTR circles and total cell-associated HIV-1 RNA and DNA) and future studies. HIV reservoir measures will be performed on samples collected at pre-entry, entry**,** and weeks 2, 4**,** and 12.

CSF
See section **6.3.18** for CSF, CSF Supernatant**,** and CSF Pellets storage.

6.3.16 PK Studies (refer to section 10; see the A5324 LPC for processing, storage, and shipping directions)

At week 12, samples for MVC and DTG levels will be collected pre-dose and at 2 and 4 hours post-dose. At weeks 24 and 48, samples will be collected pre-dose.

6.3.17 Lumbar Puncture Safety Laboratory Tests

Participants who agree to undergo an optional LP will need to have platelets and PT/INR measured within 1 week prior to the LP **only** if there is a known history of abnormalities of bleeding and coagulation, including at time of entry, or if the investigator has any concerns that the **participant** may have a heightened bleeding risk. For these **participants** that **require** LP safety laboratory tests to be performed, the following safety criteria must be met prior to the LP:
Platelet count ≥100,000 cells/mm^3
INR ≤1.4

6.3.18 Lumbar Puncture (optional)

In **participants** who agree to undergo an optional LP, CSF will be collected at entry and week 48.

At week 48, the CSF sample will be collected either after the observed morning dose or 1 hour after the trough (pre-dose) sampling.

The LP will not be performed in **participants** with known pregnancy due to risks of increased discomfort or difficulty with the procedure with advanced pregnancy.

CSF Storage
CSF will be stored at week 48 to measure concentrations of MVC, DTG and selected biomarkers.

CSF Supernatant and CSF Pellets
The CSF supernatant will be stored at entry and week 48 for studies of soluble markers already noted in the protocol, as well as potential studies of additional soluble markers of immune activation, neural biomarkers, and intensive virologic assays (for example, single copy assay HIV RNA quantitation) in the future, as allowed by new collaborations and funding support.

The CSF pellets will be stored for future potential studies**,** which may include assays such as CSF immune cellular phenotyping and quantitation and sequencing of CSF cell-associated HIV-1 DNA and RNA.

6.3.19 Resistance Testing

Perform only in **participants** who prematurely **discontinue** study medications due to confirmed VF. The test will be performed in the designated laboratory. See the A5324 LPC for processing, storage, and shipping directions.

If the HIV-1 RNA obtained at the confirmation of VF visit is ≥1,000 copies/mL, a sample should be submitted for HIV-1 **resistance** testing and protease and integrase genotype testing.

6.3.20 Tropism Testing

Perform only in **participants** who prematurely **discontinue** study medications due to confirmed VF. The test will be performed in the designated laboratory. See the A5324 LPC for processing, storage, and shipping directions.

If the HIV-1 RNA obtained at the confirmation of VF visit is ≥1000 copies/mL, then a sample should be submitted for HIV-1 coreceptor tropism with reflex to ultradeep sequencing. If the HIV-1 RNA is <1000 copies/mL, then a sample should be submitted for HIV-1 coreceptor tropism, proviral DNA.

7.0 CLINICAL MANAGEMENT ISSUES

7.1 Toxicity Management

Only toxicities related to study medications provided through this study (MVC, DTG, placebo for MVC, placebo for DTG) will be considered in the toxicity management section. The grading system is located in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version **2.1**, **March 2017**.

For toxicities potentially attributed to one or more of the study medications, one or both of the study medications (or the matching placebo) may be held **or permanently discontinued**.

Participants who have switched to any non-study ARV medication should be monitored for toxicity for that medication per standard of care and the site investigator should assure that no dose adjustments are needed for the study medications. Any changes to the **participant's** background ARV regimen must be discussed with the core team (actg.coreA5324@fstrf.org).

7.1.1 Grade 1 or 2

Participants who develop a Grade 1 or 2 AE or toxicity may continue study medications without alteration of the dosage **at the discretion of the investigator**. **Participants** experiencing Grade 1 or 2 AEs who choose to

discontinue all study medications should complete the premature treatment discontinuation evaluations. The site investigator should contact the core team (actg.coreA5324@fstrf.org), and the **participant** should be encouraged to complete follow-up protocol study evaluations.

NOTE: If **participants** discontinue study medications due to Grade 1 or 2 AEs, this should be noted on the premature treatment discontinuation CRF as the reason for discontinuation.

7.1.2 Grade 3

If the investigator has evidence that the AE was NOT caused by study medications, dosing may continue. Grade 3 AE or toxicity must be evaluated and managed by the site investigator according to the standard of care. Discontinuation of one or both study medications may be necessary. Consultation with the core team is encouraged. The core team (actg.corea5324@fstrf.org) must be notified by e-mail regarding toxicities that result in a change in regimen. If study medication(s) are **suspended** the **participant** should be reevaluated weekly until the AE returns to ≤ Grade 2 or baseline, at which time the study medications may be reintroduced, at the discretion of the site investigator or according to standard practice.

If the same Grade 3 AE, excluding those AEs noted in the following sections, recurs within 4 weeks of restarting treatment, the suspected study medication must be permanently discontinued. However, if the same Grade 3 AE recurs after 4 weeks, the management scheme outlined above may be repeated.

Participants experiencing Grade 3 AEs requiring permanent discontinuation of one or both of the study medications should be followed weekly until resolution of the AE and should be encouraged to complete the premature treatment discontinuation evaluations and continue other study evaluations according to the protocol. The core team (actg.corea5324@fstrf.org) must be notified.

7.1.3 Grade 4

Participants who develop a Grade 4 symptomatic AE or toxicity will have all study medications permanently discontinued except as indicated below. **Participants** experiencing Grade 4 AEs requiring permanent discontinuation of all study medications should be followed weekly until resolution of the AE and encouraged to continue other study evaluations according to the protocol. Premature treatment discontinuation evaluations should be completed and recorded on the CRF and the core team (actg.corea5324@fstrf.org) must be notified.

Asymptomatic Grade 4 abnormalities must be evaluated and managed by the site investigator according to the standard of care. Discontinuation of all study medications may be necessary. Consultation with the core team is encouraged.

The core team (actg.corea5324@fstrf.org) must be notified by e-mail regarding toxicities that result in a change in regimen.

7.1.4 AST or ALT Elevations

All study medications may be continued for asymptomatic ≤ Grade 3 AST/ALT elevations, at the discretion of the site investigator. Careful assessments should be done to rule out the use of alcohol, non-study medication-related toxicity, or viral hepatitis (including viral hepatitis complicated by immune reconstitution inflammatory syndrome) as the cause of Grade 3 elevations.

For symptomatic Grade 3 (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia) or any Grade 4 elevations in AST or ALT, all study medications should be held and the core team should be consulted (actg.corea5324@fstrf.org). In addition, for ALT ≥3 x ULN and bilirubin ≥1.5 x ULN (attempts should be made to fractionate the bilirubin), the study medications should be held and the core team consulted as this will likely result in permanent study medication discontinuation.

Participants who develop symptomatic Grade 3 or any Grade 4 AST or ALT elevation should be followed weekly until resolution to ≤ Grade 2. **Participants** will be followed off study treatment, on study after study medication discontinuation. **Refer to section 11.4.2 for the EAE reporting criteria for AST or ALT elevations.**

Participants with Grade 3 or 4 AST or ALT elevation with fever, rash or eosinophilia should stop all study medications and not be re-challenged. These individuals should be followed weekly until resolution to ≤ Grade 2 elevation and should be followed off study treatment, on study.

In consultation with the core team, careful assessments should be done to rule out the use of alcohol, non-study medication-related toxicity, or viral hepatitis (including viral hepatitis complicated by immune reconstitution inflammatory syndrome) as the cause of Grade 3 or 4 AST/ ALT elevations. Evaluations to be considered (but are not required) include:

- Viral hepatitis serology including: Hepatitis A IgM antibody; Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Hepatitis E IgM antibody;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening;
- Drugs of abuse screen including alcohol;
- Serum acetaminophen test (APAP adduct test);

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;
- Liver imaging to evaluate liver disease.

7.1.5 Calculated Creatinine Clearance (CrCl) Decline

Non-study medications should be adjusted for decline in CrCl at the discretion of the primary provider per the standard of care. **CrCl should be calculated, using the Cockcroft-Gault Equation, at each post-entry visit when serum creatinine is measured. Refer to section 4.1.7 for the Cockcroft-Gault Equation calculator.**

MVC use is not allowed for CrCl <30 mL/min. MVC or placebo for **MVC** should be discontinued in this setting and then restarted if CrCl increases to 30 mL/min or above.

7.1.6 Postural Hypotension

If a **participant** develops postural hypotension of any grade, the investigator should contact the core team (actg.corea5324@fstrf.org).

7.1.7 Allergic Reaction

Participants may continue study medication for Grade 1 or 2 allergic reactions at the discretion of the site investigator. The **participant** should be advised to contact the site investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with ≥ Grade 3 allergic reactions that are considered to be possibly or probably related to the study medications should permanently discontinue the putative study medication or medications and continue to be followed off study treatment, on study. The **participant** should not be re-challenged. The **participant** should be treated as clinically appropriate and followed until resolution of the AE.

Allergic reactions that include but are not limited to severe rash or any rash with fever, general malaise, fatigue, muscle or joint aches, oral lesions, conjunctivitis, facial edema or eosinophilia should result in all study medications being stopped and the **participant** should not be re-challenged. The **participant** should be followed off study treatment, on study.

7.1.8 Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first **10** weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks. A single case of hypersensitivity with DTG involved a profuse, purpuric and coalescing leukocytoclastic vasculitis as well as clinically significant liver chemistry elevations. Other than this case, no other instances of serious skin reaction, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and erythema multiforme, have been reported for DTG in clinical trials.

Hepatotoxicity accompanied by severe rash or systemic allergic reaction, including potentially life-threatening events, have been reported in **individuals** taking MVC. Severe skin and hypersensitivity reactions including SJS and TEN have also been reported in **individuals** taking MVC.

Participants with an isolated Grade 1 rash may continue study medications at the site investigator's discretion. The **participant** should be advised to contact the site investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.

Participants may continue study medications for an isolated Grade 2 rash. However, study medications (and all other concurrent medication(s) suspected in the site investigator's causality assessment) should be permanently discontinued for any ≥ Grade 2 rash that is associated with an increase in ALT. The **participant** should be advised to contact the site investigator immediately if rash fails to resolve (after more than **2** weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

If the etiology of the rash can be definitely diagnosed as being unrelated to study medications and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

Participants should permanently discontinue study medications (and all other concurrent medication(s) suspected in the site investigators causality assessment) for an isolated Grade 3 or 4 rash, and the **participant** will be followed off study treatment, on study. **Participants** should be treated as clinically appropriate and followed until resolution of the AE.

7.1.9 Suicidal Ideation

Participants with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behavior). In addition, there have been some reports of depression and/or suicidal ideation and behavior (particularly in patients with a pre-existing history of depression

or psychiatric illness) in some patients being treated with integrase inhibitors, including DTG. Therefore, it is appropriate to monitor participants for suicidality before and during treatment.

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. It is recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior.

If the **participant** expresses suicidal ideation or intent, the data will be captured as AEs. Any suicide thought or attempts that qualifies as an EAE will be reported using the standard EAE mechanism **(see section 11.4.2)**.

7.2 Additional Considerations for **Participants** Infected with Hepatitis B Virus (HBV)

Particular diligence should be applied in initiating or maintaining effective anti-HBV therapy (referring to treatment guidelines such as IAS) when starting DTG-based therapy in HBV co-infected **individuals**. Liver chemistry elevations consistent with immune reconstitution syndrome have been observed in some HBV co-infected **individuals** at the start of DTG therapy, particularly in the setting where anti-hepatitis therapy was withdrawn.

Clinical trial and marketed use of 3TC, FTC and TDF have shown that some **individuals** with chronic HBV disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of 3TC, FTC or TDF, which may have more severe consequences in **individuals** with decompensated liver disease. If 3TC, FTC**,** or TDF is discontinued in **participants** co-infected with HBV, periodic monitoring of both liver chemistry tests and markers of HBV replication should be considered.

7.3 Pregnancy

Pregnancy and pregnancy outcome will be recorded on the CRFs. Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Phone: 800-258-4263; Fax: 800-800-1052. For studies conducted at sites outside the United States, report to The Antiretroviral Pregnancy Registry—Telephone: 910-679-1598; Fax: 44-1628-789-666 or 910-256-0637.

Pregnancy Outcomes and Reporting

The core team (actg.corea5324@fstrf.org) should be notified immediately if a **participant** becomes pregnant after study entry. Study medications must be discontinued and the underlying ART regimen continued at the discretion of the site investigator. **Participants** will come in for a premature treatment discontinuation evaluation visit within 14 days after stopping study medications. **Participants** who choose to stay on study will continue to be followed on study/off study treatment, but will

not have blood drawn for PK studies and stored plasma/PBMCs. They also will not have to complete the adherence questionnaire.

If a woman has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should request permission to contact her regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on a CRF at the end of the pregnancy.

7.4 Breastfeeding

Breastfeeding is not allowed during the study.

7.5 Unblinding

Unblinding can be requested in the following settings:

- At any time that virologic failure occurs if the primary provider is considering switching therapy and believes that the unblinded study medication information will assist in choosing the next regimen.
- For an adverse event that leads to permanent discontinuation of one or both study medications only if the unblinded study medication information will affect patient management.

Site should send requests for unblinding to the core team (actg.corea5324@fstrf.org). Unblinding procedures will follow the ACTG Standard Operating Procedure for Unblinding **Participants**, which is located on the ACTG website. At the time of the request, all data relevant to the medication substitution or virologic failure should have been entered into the ACTG database. All discussion of unblinding should be limited to the actg.corea5324@fstrf.org email and should be carefully worded to prevent unblinding the team, if possible.

7.6 Antiretroviral Therapy Changes

Study participants should enter the study with the intention to continue on the same ART regimen. Any changes to the ART regimen, other than TDF to TAF-based regimens and RTV to COBI-based regimens, should be discussed with the A5324 core team in advance (actg.corea5324@fstrf.org). New regimens should not include ARVs on the prohibited medications list.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Premature Treatment Discontinuation

- Pregnancy **or breastfeeding**
- Drug-related toxicity (see section 7.1)

- Requirement for prohibited concomitant medications (see section 5.4)
- Request by **participant** to terminate treatment
- Clinical reasons believed life-threatening by the physician, even if not addressed in the toxicity section of the protocol

8.2 Premature Study Discontinuation

- **Participant** missed both week 24 and week 48 visits
- Request by the **participant** to withdraw
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the **participant**
- **Participant** judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results
- At the discretion of the IRB/EC, **FDA,** NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

A5324 is a randomized, placebo-controlled, double-blinded, phase IV clinical trial designed to compare changes in neurocognitive functioning at week 48 in Arm C (MVC and DTG) to Arm B (placebo for MVC and DTG) and Arm A (placebo for MVC and placebo for DTG) in **participants** who have at least mild neurocognitive impairment, are on a stable ART, and have plasma HIV-1 RNA <50 copies/mL. In addition, a comparison of the (Arm B: placebo for MVC and DTG) and (Arm A: placebo for MVC and placebo for DTG) arms will be conducted. A comparison of the safety and tolerability will be conducted as well. Eligible **participants** will be randomized to add one of the following to their existing ARV regimen:

- Arm A: Placebo for MVC and Placebo for DTG
- Arm B: DTG active drug and Placebo for MVC
- Arm C: MVC and DTG active drugs

All **participants** will be assessed at pre-entry, and then every 24 weeks for 96 weeks with a neurocognitive battery.

Limitations of the design include the fact that changes over time will be a function of both intervention effects, natural history, and practice effects that are common in neuropsychological studies. However, randomized treatment comparisons will be valid.

9.2 **Outcome Measures**

9.2.1 Primary **Outcome Measures**

The primary **outcome** is the change in normalized composite neurocognitive test score at week 48 from pre-entry. The normalized neurocognitive test score is defined as the average of z-scores on the following tests:

Neurocognitive Test Battery for CRSs in the United States:

a) Attention/Working Memory (Symbol Search **Trail Making A**)

b) Speed of Information Processing (Stroop Word, Stroop Color, Digit Symbol)

c) Executive Function (Trail Making B, Stroop Color/Word, Letter and Category Fluency)

d) Verbal Learning (**HVLT-R**)

e) Verbal Memory (Delayed Recall – HVLT-R)

f) Fine Motor Skills/Complex Perceptual (Grooved Pegboard Bilateral)

g) Language/Premorbid Skills (WRAT-4 Reading **OR WAT for participants with Spanish as their primary language**)

Neurocognitive Test Battery for CRSs outside the United States:

a) Attention/Working Memory (Color Trails 1)

b) Speed of Information Processing (Digit Symbol)

c) Executive Function (Color Trails 2, Category Fluency)

d) Verbal Learning (HVLT-R)

e) Verbal Memory (Delayed Recall – HVLT-R)

f) Fine Motor Skills/Complex Perceptual (Grooved Pegboard Bilateral, Fingertapping Bilateral); Gross Motor (Timed Gait)

g) IHDS

For **the assessment of neurocognitive impairment at baseline, weeks 24, 48, 72, and 96**, z-scores will be calculated by subtracting a demographically appropriate (adjusted for age, race, sex, and years of education) norm and dividing by a demographically appropriate standard deviation. Normative data will be available from Heaton et al**.** [**65, 66**] **and A5271**, and the best available normative data will be utilized. Functional change will be defined as a change on the IADL instrument: Best minus Now, summed across items 1-16, where positive changes or increments reflect better functional capacity and negative changes or decrements reflect poorer functional capacity. **Items with a**

response of 8 (not applicable) or that are missing will be excluded from the summation in both Best and Now.

For assessment of change over time **in neurocognitive impairment**, z-scores will be calculated by subtracting the **z-scores of the two time points of interest**.

In addition, based on the z-scores, Global Deficit Scores (GDS) will be computed for the domains, and the total battery. The GDS emphasizes impairment, reduces minimal learning/practice and has the advantage of reducing 'sum to zero' effects seen with counterbalancing positive and negative scores in a **participant's** assessment. However, this approach does minimize the ability to observe subtle changes as scores are grouped into larger categories [**67**].

9.2.2 Secondary **Outcome Measures**

9.2.2.1 Treatment related AEs.

9.2.2.2 Change of normalized composite neurocognitive test score at weeks 24, 72, and 96. Change of normalized component neurocognitive test scores at weeks 24, 48, 72, and 96 will also be examined.

9.2.2.3 Change in functional status scores based on the IADLs form at weeks 24, 48, 72, and 96.

9.2.2.4 Change from baseline of **peripheral blood and CSF biomarkers** at week 48.

9.2.2.5 Plasma HIV-1 RNA less than 50 copies/mL at weeks 24, 48, and 96.

9.2.2.6 CD4+ T-cell counts and changes from baseline to weeks 24, 48, and 96.

9.2.2.7 CD8+ T-cell counts and changes from baseline to weeks 24, 48, and 96.

9.2.2.8 Changes from baseline to week 48: residual viremia, cell-associated HIV-1 RNA/DNA/2-LTR circles and SCA, T cell and monocyte activation.

9.3 Randomization and Stratification

Eligible **participants** will be randomized with equal probability to add to their existing ART either Arm A: placebo for **MVC** and placebo for DTG, or Arm B: DTG active drug and placebo for MVC, or Arm C: MVC and DTG active drugs. Randomization will be stratified by CD4+ nadir (≤100 vs. >100 cells/mm^3) and HAND severity (ANI vs. MND/HAD). Since it is difficult to enroll **participants** with MND and HAD, strict balance

among the HAND stratification factors is not required. However, the distribution of HAND stratification factors will be closely monitored to ensure successful enrollment of **participants** with MND and HAD (≥25%).

The CPE score of the current ART (before intensification) will not be used as a stratification factor at randomization. Instead, it will be used as a continuous covariate in regression models to account for CNS penetrations of different ARTs.

9.4 Sample Size and Accrual

The primary **outcome** of this study is the 48-week change in normalized composite neuropsychological test score. For the primary analyses, all pairwise comparisons (ie, Arm B versus Arm A, Arm C versus Arm A, and Arm C versus Arm B) will be conducted to test for difference in the primary **outcome**. Based on previous results from A5235, we assume a standard deviation (SD) of 0.7 in the 48-week change in normalized neurocognitive test score.

Standard Deviation	Number of Primary Comparisons	Nominal Power	Sample Size per Group	Adjusted Sample Size per Group	Total Sample Size	Adjusted Total Sample Size
0.6	2	0.80	28	33	84	99
		0.85	32	38	96	114
		0.90	36	42	108	126
0.6	3	0.80	31	36	93	108
		0.85	34	40	102	120
		0.90	39	46	117	138
0.7	2	0.80	38	45	114	135
		0.85	43	51	129	153
		0.90	49	58	147	174
0.7	3	0.80	41	48	123	144
		0.85	46	54	138	162
		0.90	53	62	159	186
0.8	2	0.80	49	58	147	174
		0.85	56	66	168	198
		0.90	64	75	192	225
0.8	3	0.80	54	64	162	192
		0.85	61	72	183	216
		0.90	69	81	207	243

In the sample size calculation, the null hypothesis is that there is no difference in changes of neurocognitive functioning from baseline to week 48 across the treatment arms, while the alternative hypothesis is that the change of neurocognitive functioning is at least 0.5 higher for the (MVC and DTG) arm. The Bonferroni correction has been applied to account for multiple comparisons between treatments. One interim analysis of

efficacy is planned in the middle of the study and the adjusted sample sizes assume a 15% loss to follow-up. To achieve a power of 90%, we would expect a sample size of 62 **participants** per group for a total 186 **participants** on study. The team anticipates that the targeted sample size can be reached in around one year.

A secondary objective of this study is to compare the changes in CSF biomarkers (eg, neopterin) between arms. Since CSF biomarkers are measured through *optional* LP procedures, data on CSF biomarkers will not be available for all participants in this study. Thus, it is of importance to provide power and sample size justification for this secondary objective as well. Using neopterin as an example and assuming a SD of 1.0 from prior studies, we will need 17 participants per group to detect a mean difference of 1.0 nmol/L with 80% power (based on a two-sample t-test). In HIV-infected **individuals** on suppressive HAART, CSF neopterin remains persistently elevated to a median 6.3 nmol/L, while normal levels in HIV uninfected **individuals** are between 4.3 and 5.3 nmol/L. Reducing the CSF neopterin by 1.0 nmol/L would lower this marker of macrophage immune activation to levels close to levels in HIV negative **individuals**. The figure below also shows the power curves under more conservative SD assumptions (ie, 1.5 and 2.0).

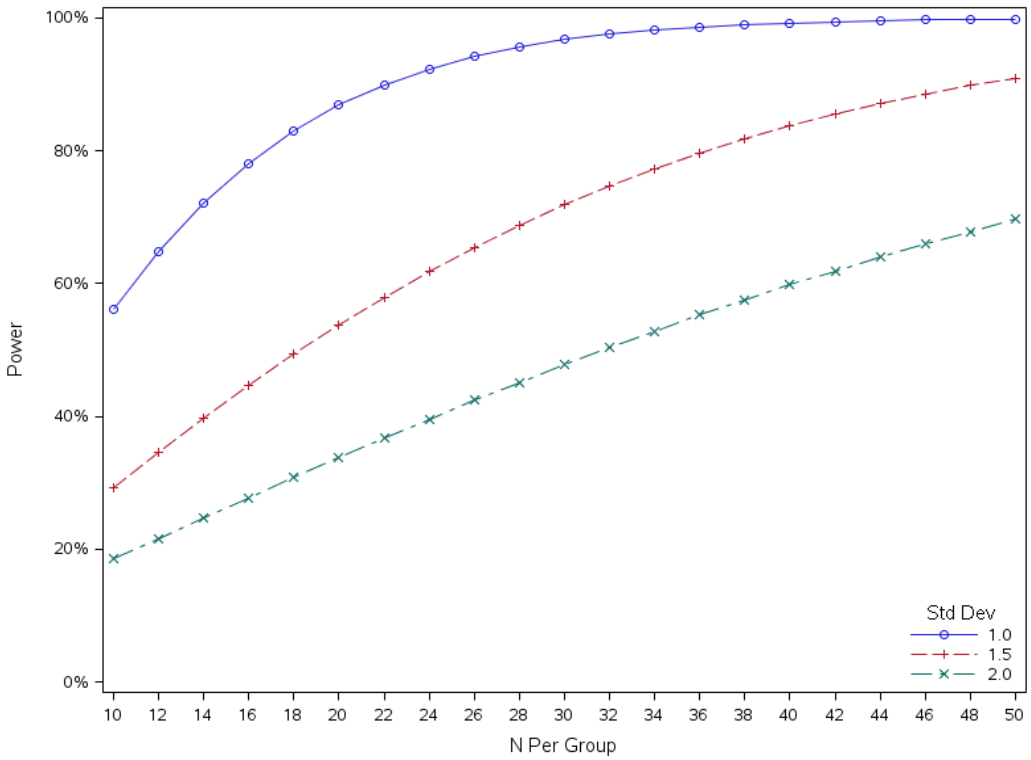

Figure: Power Plots for Comparing CSF Neopterin Levels at Week 48

9.5 Monitoring

Three types of monitoring reviews will be conducted based on reports prepared by study statisticians and/or data manager and/or lab data managers. They are routine monitoring reviews, data quality reviews, and reviews by Study Monitoring Committee (SMC) of the Neurology Collaborative Science Group.

Routine monitoring reviews **will** monitor proper execution of the protocol. The study core team will receive monthly reports on accrual, study status, screening failures, **and** missing forms and outcomes. The accrual report will also be distributed to the whole protocol team. **Quarterly toxicity reports and biannual data availability reports will be sent to the core team.**

The DAIDS clinical representative will review and assess EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs as applicable. Additionally, the DAIDS clinical representative will review aggregated adverse event summaries by blinded treatment arm prepared every 6 months by the Statistical and Data Analysis Center (SDAC).

In addition, the team anticipates **enrollment of** 8 **participants** in each arm **who consent to voluntary** LP when the study has accrued half the required **participants**. If this is not reached, the team will focus **on** recruitment/enrollment efforts at the sites that have experience performing LPs.

Data quality reviews **will** ensure all required samples are collected and tracked, and corresponding outcomes are entered in the study database. Eligibility verification will be checked monthly. HIV-1 RNA virology data and pregnancy will be checked every three months.

There are three types of Neurology Collaborative Science Group SMC reviews: one interim analysis review, routine SMC reviews, and unexpected safety events reviews. The purpose of the interim analysis review is to re-evaluate sample size and to assess efficacy of treatment arms. This happens in the middle of the study when about 50% **of participants are enrolled and followed-up for 48 weeks**.

Observed SD for the primary endpoint will be compared to the assumed value (SD=0.7) to determine the necessity of sample size adjustment. Also two steps will be conducted for monitoring efficacy.

- Step 1: Pairwise comparisons will be conducted for three blinded treatment arms. Based on the repeated confidence intervals (RCIs) method and Bonferroni correction, we will use threshold p-value 0.0007 for each comparison, which correspond to a 99.93% CI.
- Step 2: If none of the pairwise comparisons shows significance, then we will continue with all three arms; If any pairwise comparison is significant, then we

predicted interval plots (PIPS) method [68, 69] will be used to see if we can stop the arm/study early and claim efficacy.

Routine SMC reviews **will** assess the study progress via reviewing accrual, study status, screening failures, toxicity, etc. This will happen at least annually **after enrolling the first participant** as required by NIH guidelines. Unexpected safety event reviews **will** report any unexpected safety events to the Neurology Collaborative Science Group SMC when safety concerns are raised by the core team.

NOTE: Please refer to the A5324 study monitoring plan for details of the monitoring process or any updates.

9.6 Analyses

9.6.1 Primary Analysis

The ITT principle (ie, all randomized **participants** will be included in the primary analyses) will be used for the primary analysis to compare the changes of neurocognitive functioning from baseline to week 48. Multiple imputation methods will be used to handle missing values. Sensitivity analyses will be conducted under different assumptions to assess the impact and informativeness of missing data. In addition, a per-protocol analysis will also be conducted by restricting the analysis to **participants** who adhere perfectly to the instructions in the study protocol. The Kolmogrov-Smirnov test will be employed to check whether the primary **outcome** is normally distributed. If the normality assumption is not rejected, the two-sample t-test will be used for pairwise comparisons between any two arms. Otherwise, the nonparametric analogue of the two-sample t-test (ie, Wilcoxon rank-sum test) will be used as an alternative. The test will be stratified by CD4+ nadir (≤100 vs. >100 cells/mm^3) and HAND severity (ANI vs. MND/HAD). All pairwise comparisons will be conducted among the three study arms.

9.6.2 Secondary Analyses

9.6.2.1 The Cox proportional hazards model will be applied to compare the time to discontinuation of medication due to AEs. Logistic regression models will be used to characterize the proportion of **participants** with Grade 3 or Grade 4 clinical AEs or laboratory abnormalities.

9.6.2.2 The Kruskal-Wallis test will be employed to compare changes in neurocognitive functioning across the three treatment arms at weeks 24, 72, and 96. All pairwise comparisons between two treatment arms will be conducted based on the Wilcoxon rank-sum test.

9.6.2.3 Similar to the analyses for neurocognitive functioning, changes in functional status scores at weeks 24, 48, 72, and 96 will also be compared among treatment arms using the Kruskal-Wallis test (for

overall comparisons across the three treatment arms) and the Wilcoxon rank-sum test (for pairwise comparisons between two treatment arms).

9.6.2.4 Wilcoxon signed-rank test will be used to assess the changes from baseline of **peripheral blood** biomarkers and CSF biomarkers at week 48. Comparisons of changes in these biomarkers between any two treatment arms will be conducted through Wilcoxon rank-sum test.

9.6.2.5 Association between **peripheral blood** and CSF biomarkers and neuropsychological performance will be estimated at each visit using the Spearman correlation.

9.6.2.6 For each treatment arm, the proportions of **participants** with HIV-1 RNA less than 50 copies/mL and their associated 95% CIs will be plotted over time. Logistic regression models will be used to compare the odds corresponding to the proportions across the treatment arms at weeks 24, 48, and 96.

9.6.2.7 Average CD4+/CD8+ counts and their associated 95% CIs will be plotted over time for each treatment arm. Changes in CD4+/CD8+ counts from baseline to weeks 24, 48, and 96 will be compared across treatments arms through Wilcoxon rank-sum test.

9.6.2.8 Spearman correlation will be used to determine the association between changes in blood immunologic markers and changes in neurocognitive function from baseline to week 48.

9.6.2.9 Spearman correlation will be used to explore the relationship between changes in CCR5 ligand levels (MIP-1β) and inflammatory markers changes from baseline to week 48. Scatterplots will display relationships.

9.6.2.10 Wilcoxon rank-sum test will be used to compare Arm A and Arm B to assess the effect of DTG intensification on virologic changes. Association between the vriologic changes and changes in neurocognitive function from baseline to week 48 will be examined using the Spearman correlation.

9.6.2.11 Similar to the primary analysis, the ITT principle will be used to compare the changes of GDS scores from baseline to week 48. All pairwise comparisons will be conducted among the three study arms.

9.6.2.12 Subgroup analyses will be performed for the primary outcome in each participating country. In presence of significantly different results by country, the changes of neurocognitive functioning will be compared by adjusting for country effects.

10.0 PHARMACOLOGY PLAN

MVC is a CCR5 co-receptor antagonist that is given twice daily. In phase II and III studies (MOTIVATE-1 and MOTIVATE-2)**,** MVC demonstrated potent ARV activity and good tolerability in treatment-experienced **participants** [**28, 29**]. Importantly, it was noted, and confirmed in the phase II and III studies that MVC in combination with other ARV agents resulted with a significant reduction in viral load in adult **participants** with no detectable CXCR4-using plasma HIV-1 who were experiencing virologic failure on their current ARV regimen with multi-resistant virus. In addition, the CD4+ cell count was increased to a significantly greater extent with MVC compared with placebo in these studies. The most frequently seen AEs in the phase II and III studies are diarrhea (8-10%), nausea (6%), headache (2-5%), fatigue (3-4%), upper respiratory tract infection (4-5%), and fever (2-6%). The other common AEs (>8% incidence) include cough, pyrexia, rash**,** and dizziness. Hepatotoxicity accompanied by severe rash or systemic allergic reaction including potentially life-threatening events has been reported.

MVC is a substrate of CYP3A and P-gp, inhibitors and inducers of these enzymes/transporters influence MVC pharmacokinetics (PK). A dosage of 150 mg BID is recommended when given with potent CYP3A inhibitors, including HIV-1 protease inhibitors, such as LPV/r, DRV/r, saquinavir/ritonavir (SQV/r), and ATV/r, as well as ketoconazole that significantly increase the C_{max} and AUC of MVC, whereas 300 mg BID of MVC is recommended with concurrent use of NRTIs, TPV/r, NVP, DTG**,** and other drugs that are not potent CYP3A inhibitors or inducers. When MVC is coadministered with potent CYP3A inducers, eg, RIF, ETR and EFV, there is a significant reduction in MVC C_{max}, AUC, and C_{min}. As a result, it is recommended that when used with these agents, 600 mg of MVC should be given BID.

Data from several studies with a small sample size, which evaluated MVC concentrations in CSF, suggest that MVC achieves therapeutic concentrations (EC_{50}-EC_{90}) in the CSF even though MVC plasma concentrations and physiochemical characteristics are poor predictors of its CNS distribution [**21, 70**, **71**, **72**]. While the trough MVC plasma concentration ranged from 94.9 to 337 ng/mL, the mean CSF concentration ranged from 2.4 to 7.5 ng/mL. The mean CSF:plasma ratio was ~0.02. Small increases in cerebral metabolite markers of neuronal integrity were reported in 12 **participants** treated with MVC, and these changes associated with MVC plasma trough concentrations [**71**].

10.1 Pharmacology Objectives

10.1.1 Investigate DTG and MVC plasma concentrations and determine PK parameters including area-under-the curve and clearance.

10.1.2 Investigate the relationship between plasma PK and CSF concentrations for DTG and MVC including CSF:plasma ratio.

10.1.3 Investigate associations between DTG and/or MVC plasma and CSF concentrations in a multivariate analysis including:

a) Changes in neurocognitive testing scores.

b) Self-reported adherence.

c) Changes in **peripheral blood** and CSF biomarkers.

10.2 Pharmacology Study Design

Only DTG and MVC will be measured based on the assumption that the neurocognitive benefits of intensification are directly related to DTG and/or MVC.

10.2.1 A single abbreviated plasma PK study at week 12 in all **participants** including a pre-dose sample and observed dose. Two additional samples at 2 and 4 hours after the dose at week 12.

If DTG/placebo for **DTG** is taken once daily in the evening:

- At least 3 days prior to the week 12 PK visit, the evening DTG/placebo for **DTG** dose should be converted to a morning dose. **Participants** should be reminded at least 5 days prior to the week 12 PK visit to convert the evening DTG/placebo for **DTG** dose to a morning dose at least 3 days prior to the visit. **Participants** should be instructed to hold their morning doses of DTG/placebo for **DTG** and MVC/placebo for **MVC** on the day of the week 12 PK visit and the doses will be given in the clinic after the pre-dose sample has been obtained.
- If the **participant** does not convert DTG/placebo for **DTG** to morning dosing, there will be no observed dose of DTG/placebo for **DTG**. The **participant** should still hold the morning dose of MVC/placebo for **MVC** and the dose will be given in the clinic after the pre-dose sample is obtained. The PK sampling will remain the same.

If DTG/placebo for **DTG** is taken twice daily:

- **Participants** should be instructed to hold their morning doses of DTG/placebo for **DTG** and MVC/placebo for **MVC** on the day of the week 12 PK visit. The doses will be given in the clinic after the pre-dose sample has been obtained.

10.2.2 Repeated trough samples at weeks 24 and 48.

Participants taking DTG/placebo for **DTG** once daily in the evening should be instructed to convert to morning dosing as described in section 10.2.1. **Participants** should also be instructed to hold their morning doses of DTG/placebo for **DTG** and MVC/placebo for **MVC** as described in section 10.2.1. The doses will be given in the clinic after the PK sample has been obtained.

10.2.3 CSF concentrations of MVC and DTG in **participants** who consent to LP (see section **6.3.18**).

10.3 Primary and Secondary Data, Modeling, and Data Analysis

Using PK models derived from previous intensive PK data [**73**, **74**], **participants**' limited drug concentrations will be used to estimate key PK parameters (exposure, as indicated by area under the concentration curve, AUC and clearance, Cl/F). The population PK analyses incorporating plasma and CSF data will be based on nonlinear mixed effects models. These **participant** level estimates will then be used for comparison of drug exposure between **participants** with and without neurocognitive changes (with non-parametric tests and with PK models). Pharmacodynamic analyses will evaluate the relationship between the model derived **participant-**specific estimates of PK parameters (AUC and Cl/F) and neurocognitive changes.

10.4 Anticipated Outcomes

We anticipate that **participants** in A5324 will enter the study on a variety of ART regimens. These **participants** will receive the recommended doses of DTG and MVC, as per tables A **and** B in section 5.1.1, but there will be a wide range of individual plasma and CSF exposures based on expected interpatient variability. The proposed clinical pharmacology objectives will provide PK data and strengthen the multivariate analysis that will help identify specific covariates that are associated with the primary outcomes as well as provide an additional adherence confirmation.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

CRF will be **made available to sites for data entry**. **Participants** must not be identified by name on any **data submitted to the DMC**. **Participants** will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization.

Participants' background ART will be recorded at randomization on randomization logs.

11.2 Role of Data Management

11.2.1 Instructions concerning **entering** study data on CRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

11.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

11.3 Clinical Site Monitoring and Record Availability

11.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual **participant** records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study **participants**, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

11.3.2 The site investigator will make study documents (eg, consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB/EC, the site monitors, **the FDA,** the NIAID, the OHRP, and the industry supporters or designee for confirmation of the study data.

11.4 Expedited Adverse Event Reporting to DAIDS

11.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at **http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual**.

The DAIDS Adverse Events Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES **(now part of the NIAID Clinical Research Management System)** at **CRMSsupport@niaid.nih.gov**. Site queries may also be sent from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website **at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual**. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

11.4.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

- The study agents for which expedited reporting are required are:
  - MVC and placebo for **MVC**
  - DTG and placebo for **DTG**
- **In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are:**
  - Symptomatic or asymptotic AST/ALT and bilirubin elevations that result in discontinuation of study medications
  - **Suicidal thoughts or attempts that meet the EAE reporting category**

11.4.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric AEs (DAIDS AE Grading Table), **Version 2.1, March 2017**, must be used and is available on the DAIDS RSC **website** at **http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables**.

11.4.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is per the EAE manual.
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

12.0 PARTICIPANTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the **participant** (or legally authorized representative, ie, a person with power of attorney to consent to participation in a clinical trial on behalf of a **participant** who cannot provide informed consent). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the **participant** or legally authorized representative, and this fact will be documented in the **participant's** record. The IRB and site must comply with state and local laws regarding legally authorized representatives.

12.2 **Participant** Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain **participant** confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the **participant**, except as necessary for monitoring by the ACTG, IRB/EC, **FDA,** NIAID, OHRP, other government agencies as part of their duties, or the industry supporter or designee.

12.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, **FDA,** NIAID, OHRP, industry supporter, or other government agencies as part of their duties to ensure that research **participants** are protected.

13.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

14.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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APPENDIX I

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT

For protocol A5324
A Randomized, Double-Blinded, Placebo-Controlled Trial Comparing Antiretroviral Intensification with Maraviroc and Dolutegravir with No Intensification or Intensification with Dolutegravir Alone for the Treatment of Cognitive Impairment in HIV
Final Version 2.0 dated 08/25/17

SHORT TITLE FOR THE STUDY: Integrase and Maraviroc Intensification in Neurocognitive Dysfunction (InMIND), **Final Version 2.0 dated 08/25/17**

INTRODUCTION

You are being asked to take part in this research study because you are infected with the human immunodeficiency virus (HIV), the virus that causes AIDS. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It tells you about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

There are now several HIV treatment options for a person with HIV infection who has not yet been treated. Most people who receive treatment and take their medications as directed have a good test result. This is usually determined by measuring the amount of HIV in the blood (viral load). The best response is when HIV cannot be found (undetectable) in the blood. However, it has recently become clear that some people with HIV who are receiving effective HIV drugs continue to have more health problems than people without HIV infection. Sometimes, there is damage to organs in the body, including bone, kidneys, and the brain.

The reasons this study is being done are the following:

- To see how the study drug combinations affect your ability to use your fingers and hands, concentrate, learn and remember, speak and write, think, solve problems and make decisions.
- To see how well the study drug combinations lower your HIV viral load.
- To see how safe the study drug combinations are, how well people are able to take the study drug combinations, and how well their immune systems respond to the study drugs.

- To see how well the study drug combinations get into your blood.

The drugs we are testing in this study are maraviroc (MVC) and dolutegravir (DTG). Both of these drugs have been approved by the Food and Drug Administration (FDA) for treatment of HIV. **MVC** and DTG will be added to your current drug regimen.

Some participants in the study will not be given the drugs that we are testing. Instead, they will be given a placebo. Placebo pills are just pills with no active ingredient in them.

You will be given one of the following three drug combinations:
- Placebo for MVC and placebo for DTG
  OR
- DTG active drug and placebo for MVC
  OR
- MVC and DTG active drugs

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you would like to be in this study, after you have read and signed this informed consent form, you will come to the clinic for a screening exam to make sure you meet the requirements for joining the study.

<u>At Screening</u>
This visit will take about 1 to 2 hours. The tests for this visit may be done in more than one day if that will be easier for you. At the screening visit:

- Your HIV infection status will be confirmed. If there is no record available, another HIV test will be done. You may have to sign a separate consent form before this is done.
- We will ask you questions about your medical history, any medications you are taking or have taken within the last 30 days, and about the anti-HIV drugs you are taking (such as how long you have been taking the anti-HIV drugs you are currently taking, if you stopped taking them for any reason for more than 7 days, etc.).
- You will have a physical exam and will be asked questions about your health.
- You will have about 1-2 tablespoons (25mL) of blood drawn to measure your viral load (the amount of HIV in your blood), to see if you are infected with the hepatitis C virus (an infection of the liver) if there is no record available, to see if you have syphilis (a type of sexually transmitted disease), and to have some other routine tests for safety. You will be told the results of these tests when they become available. If the syphilis test shows that you have syphilis, your result, by state law, will be forwarded to the _____ Board of Health *(sites please modify as appropriate per your state/local law)*.
- We will ask you to give a urine sample for safety testing. We will give you the results of this test as soon as it becomes available.
- You will be given a liver enzyme test, formerly called liver function test (LFT) to see if you have damage to your liver and if your liver is working well.

- You will be asked some questions about yourself, such age, educational level and primary language.
- You will take neuropsychological tests, which will take about 1 hour. During the neuropsychological tests you will answer questions, list items (such as naming foods, or animals, or some other groups you know), **and** do simple tasks. You will be asked questions to see if you forget things, have difficulty understanding facts, or difficulty with your behavior and interacting with others.
  - Problems with thinking and decision making are an important effect of HIV-1 infection on the brain. These problems are known as neurocognitive impairment, and impact specific areas of brain functioning such as your ability to use your fingers and hands, concentrate, learn and remember, speak and write, think, solve problems and make decisions. **Neurocognitive impairment has** been classified into diagnoses, HIV Associated Neurocognitive Disorders, which is abbreviated as HAND. The diagnosis of HAND can go from least to most severe.
  - **The study team will determine if you have HAND and are eligible for the study based on** combining the results of **the** neuropsychological testing, gathering data on other conditions that can impact brain functioning and therefore your thinking, and also seeing how these changes in thinking ability have affected your home, social and work life.
- If you are a woman able to become pregnant, we will ask you to give a urine sample or have an additional 1 teaspoon (5mL) of blood drawn to see if you are pregnant. You will not be able to enroll in this study if you are pregnant. You will be told the result of the test when it becomes available.
- You will be asked to complete some questionnaires that ask about how you are feeling**,** how well you are able to perform your daily activities**, and about your alcohol and drug use**.

<u>At Pre-Entry</u>
If you are eligible for the study, you will come in for a pre-entry visit. This visit will last about 30 minutes. At this visit you will have about 5 tablespoons (75 mL) of blood drawn, which will be stored for future testing.

The screening and pre-entry visits may be on different days or on the same day.

<u>At Study Entry Visit</u>
If you are eligible for the study, you will come in for an entry visit. This visit will last about 1 hour. At this visit:

- You will have a physical exam and will be asked questions about your health and about any medicines you have taken or are taking.
- You will have about 1-2 tablespoons (25mL) of blood drawn to measure your viral load, to measure your CD4+ cell count (CD4+ cells are cells in your blood that fight infection), and to have some other routine safety tests including liver enzyme test. You will be told the results of these tests when they become available.
- If you are a woman able to become pregnant, you will have a pregnancy test within 2 days before entry into the study. Pregnant women cannot enter the study.

- You will have about 5-6 tablespoons (80 mL) of blood drawn, which will be stored for future testing.
- We will ask you to fill out a questionnaire to see how well you are taking your anti-HIV drugs.

We will randomize you to one of three groups:
- Group A: placebo for MVC and placebo for DTG
- Group B: DTG active drug and placebo for MVC
- Group C: MVC and DTG active drugs

Randomized means that we will assign you by chance to one of three groups. You have an equal chance of being assigned to any group, like flipping a coin. *[Sites please modify the randomization analogy as appropriate to your local culture].*

This study is a double-blind study. This means that you and your study staff will not know which group we assign you to. We are doing this research because we do not know which treatment group is best for you.

You will continue taking the anti-HIV drugs that you are currently taking. You will also be given a combination of MVC, DTG or placebo based on the group that you are randomly assigned to. You must start the new medications within three days after you are randomized.

<u>After Entry</u>
After your entry visit, you will come to the clinic at weeks 2, 4, 12, 24, 48, 72, and 96. These study visits will last about 1 to 2 hours, except week 12 which will last about 4 hours. During these visits:

- You will have a physical exam, and will be asked questions about your health and about any medicines you have taken or are taking, at every visit.
- You will take neuropsychological tests at weeks 24, 48, 72, and 96.
- We will draw about 2-7 tablespoons (30-105mL) of blood for routine safety tests, to measure your viral load, and to measure your CD4+ cell count. You will be told the results of these tests when they become available. You will have routine safety tests, including liver enzyme test, at weeks **4,** 12, 24, 48, 72, and 96; viral load measured at weeks 12, 24, 48, **72,** and 96; and CD4+ cell count measured at weeks 12, 24, 48, 72, and 96. We will also store some of your blood for future testing at every visit.
- We will draw an additional 1 teaspoon-1 tablespoon (5-15mL) of blood for pharmacokinetic studies **(PK)** to measure the amount of study drug in your blood at weeks 12, 24, and 48. At these visits we will draw blood before you take the study drugs. At week 12 we will also draw blood 2 and 4 hours after you take the study drugs. **If one of the study drugs you will be taking are taken in the evening, 3 days before the PK studies at weeks 12, 24, and 48, you will have to switch taking that study drug from the evening to the morning. The study staff will contact you before that time to remind you when to make the switch. You must also not take the study drugs in the morning on the day of the weeks 12, 24, and 48 visits, and instead bring the study drugs with you to the clinic. The study staff will give you the doses in the clinic.**
- **We will ask you to give a urine sample at week 96 for safety testing. You will be told the result when it is available.**

- We will ask you to fill out some questionnaires at weeks 24, 48, 72, and 96 **that ask about** how you are feeling, how well you are able to perform your daily activities, and **your alcohol and drug use**. We will also ask you to fill out a questionnaire about how well you are taking your current anti-HIV drugs at weeks **4,** 12, 24, 48, 72, and 96. If you are having problems taking your anti-HIV drugs correctly, a site staff member will try to help.
- If you are a woman and you think you might be pregnant, you will have a pregnancy test. You will be told the result of this test when it becomes available.
- **At weeks 12, 24, 48, and 72, your study drugs will be refilled.**

At weeks 36, 60, and 84, you will return for refill of your study drugs. These refills should take about 30 minutes or less. No other evaluations will be done.

You should inform the study doctor before changing the other anti-HIV drugs that you are taking.

Optional Lumbar Puncture

In this study, there is an optional lumbar puncture. A lumbar puncture (also called a "spinal tap") removes fluid that surrounds the brain and spinal cord. This is done by numbing a small patch of skin on your back and inserting a needle in between the bones in your lower back. You will be asked to lie in a flat position (with one or no pillows) at the clinic for up to 30 minutes after the test. You should also drink plenty of liquids and not do too much activity for up to 24 hours after the test. Your clinic may ask that you sign a separate consent form before you have this procedure.

The lumbar puncture will be performed to measure inflammatory markers (a measure of the body's response to infection or damage) to see if your brain is affected by HIV.

- If you agree to participate in the optional lumbar puncture study, you will have a neurological exam at study entry and week 48. The neurological exam will see if you have any nerve damage or nervous system problems and will take about 30 to 45 minutes.
- If you had abnormal bleeding or bruising in the past or the study doctor feels you may be at risk of having abnormal bleeding, you will also have about 1 teaspoon (6mL) of blood drawn to check the number of platelets (the cells in the blood that stop bleeding) in your blood and to see how long it takes your blood to clot at **study entry** and week 48. You will be told the results of the tests when they become available.
- If you are eligible for the lumbar puncture, you will have a lumbar puncture at study entry and week 48. About 2 to 3 teaspoons of spinal fluid will be collected for routine and study-specific tests and HIV viral load.

Please indicate and initial below whether you agree to participate in the optional lumbar puncture.

_____ YES, I agree _____ NO, I disagree

Virologic Failure

You will be tested for virologic failure at weeks 12, 24, 48, **72,** and 96. Virologic failure is when your anti-HIV drugs are not fully suppressing HIV in the blood. If the study staff sees that your

viral load has gone up, you will be asked to have another viral load test done within 30 days. About 2 teaspoons (10mL) of blood will be drawn for the viral load test. We will also draw an additional 1-2 teaspoons (6mL) of blood that will be used for tests that check which anti-HIV drugs have stopped working on the HIV in your blood (resistance test) and if a specific type of anti-HIV drug will be able to control your HIV (tropism test) if the repeat viral load test shows that your viral load is still up. **We will also ask you to fill out a questionnaire about how well you are taking your current anti-HIV drugs.**

If your viral load is still up and you are still taking study drug, you will be asked to stop the study drug, and come to the clinic within 2 weeks. You will be followed on study and off study treatment until the final study visit, week 96. If you have virologic failure at week 96, you will have a confirmation of virologic failure within 30 days, and you will be off study.

After you start your study drugs, you should not stop taking any of them unless you have discussed it with the study doctor. If you do not take your study drugs or other HIV medications consistently, this may result in viral rebound, a condition in which HIV levels in your blood become detectable. This could lead to drug resistance and a chance that the study drugs, or your other HIV medications, will no longer be effective. Discontinuing HIV medications can also result in immune system decline. If your blood test shows evidence of drug resistance, you will be taken off the study drugs but will be asked to continue follow-up in the study until you complete all visits and procedures.

Although very unlikely, you could develop viral rebound or drug resistance during this study. If drug resistance develops, your choices of HIV medications in the future could be limited.

<u>If You Have to Stop Taking the Study Drugs Early or You Have to Stop the Study Early</u>
If you have to stop taking the study drugs early or you have to stop the study early, you will come to the clinic for an additional visit. At this visit:

- You will have a physical exam and will be asked questions about your health and about any medicines you have taken or are taking.
- You will take neuropsychological tests.
- We will draw about 1 tablespoon (15mL) of blood to measure your viral load and CD4+ cell count. We will tell you the test results of when they become available.
- We will draw about 2 tablespoons (30mL) of blood and store the blood for future study-related virologic testing.
- If you are a woman and you think you might be pregnant, you will have a pregnancy test. We will tell you the test result when it becomes available.
- We will ask you to fill out some questionnaires to see how you are feeling, how well you are able to perform your daily activities, if you have been hospitalized recently, and how well you are taking your current anti-HIV drugs
- We will ask you to give a urine sample for safety testing. We will give you the results of this test as soon as it becomes available.

If you do not enroll into the study
If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, some demographic (age, gender, race), clinical (disease condition, diagnosis), and laboratory (CD4 cell count, viral load) information is being collected from you so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study.

Other
Some of your blood or spinal fluid (if you have a lumbar puncture) that is left over after all required study testing is done may be stored (with usual protectors of identity) and used for ACTG-approved HIV-related research. Storage of leftover blood or spinal fluid is not a requirement to participate in the study and you may withdraw your approval for the storage of your leftover blood or spinal fluid at any time, and your samples will be destroyed. These samples may be held for an indefinite length of time. We cannot ensure that you will be told of the results of the research done on these samples. Please indicate and initial below whether you approve the use of your leftover blood or spinal fluid.

_____ YES _____ NO

At sites outside the US, biological specimens may be shipped and stored outside the country from which they were collected (e.g., sites that do not have a central testing laboratory in-country and storage of left-over specimens).

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 186 people will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 24 months (2 years).

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- your primary care physician no longer thinks that participating in the study is in your best interest
- the study is stopped or cancelled
- you are not able to attend the study visits or perform the assessments as required by the study

The study doctor may need to take you off the study drugs without your permission if:
- you become pregnant **or start breastfeeding**
- continuing the study drug(s) may be harmful to you
- you need a treatment that you may not take while on the study

- you are not able to take the study drug(s) as required by the study

If you must stop taking the study drug(s) before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

<u>If I have to permanently stop taking study-provided drugs, or once I leave the study, how would they be provided?</u>

During the study:
If you must permanently stop taking study-provided drugs before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:
After you have completed your study participation, the study will not be able to continue to provide you with the drugs you received on the study. If continuing to take these or similar drugs would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects. If you have questions concerning the additional study drug side effects please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study drugs are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all drugs you are taking (including non-prescription drugs, vitamins and herbal supplements) before you start the study and also before starting any new drugs while on the study. You must also tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

<u>Use of Combination Antiretroviral Drugs</u>
Immune Reconstitution Syndrome:
In some people with advanced HIV infection, symptoms from other infections or certain diseases may occur soon after starting combination anti-HIV treatment but can also occur later. Some of these symptoms may be life-threatening. If you start having new symptoms, or notice that existing symptoms are getting worse after starting your antiretroviral therapy, tell your healthcare provider right away.

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:
- **Increase in fat around the waist and stomach area**
- **Increase in fat on the back of the neck**
- **Thinning of the face, legs, and arms**
- **Breast enlargement**

Risks of Social Harm
Although the study site will make every effort to protect your privacy and confidentiality, it is possible that other people could find out that you are in a study and this could cause problems for you. For example, other people might figure out that you are infected with HIV. If this happens, people could treat you unfairly or family members, friends, and/or the community might not accept you.

Risks of Drawing Blood
Taking blood may cause some discomfort, lightheadedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases, fainting, or infection.

Risk of Spinal Tap
- **Leakage of cerebrospinal fluid (CSF) into the tissues in your back, which can cause headache**
- Back pain or pain where the needle is inserted in the back
- Decreased blood pressure
- **CSF leak**
- Infection
- Fever
- Nerve injury (very rare)
- Bleeding
- Allergic reaction to medication used to numb the area where the spinal tap will be done.
- Allergic reaction to the substance (such as iodine) that is used to clean the area of the spinal tap to prevent infection could include itching, hives, swelling, shortness of breath, difficulty breathing, changes in blood pressure and heart rhythm, loss of consciousness, or in a rare case, death.

Headaches can be helped by lying down face up and by taking over-the-counter headache medicine. Severe headaches should be reported to the study staff or study doctor.

It may be uncomfortable for you to lie on your side while the lumbar puncture is being done and to lie flat on your back for the required time afterwards.

Risks of MVC (Selzentry)
The following serious side effects have been associated with the use of MVC:

Liver problems (liver toxicity) have occurred in people who took MVC. An allergic reaction may happen before liver problems occur. Stop taking MVC and call the study doctor **or your healthcare provider** right away if you get any of the following signs or symptoms:
- Rash on your body (allergic reaction)
- Yellowing of the skin or whites of your eyes **(jaundice)**
- Dark urine
- Vomiting
- Stomach pain
- **Elevated** liver-related function test – People who are co-infected with hepatitis B might be at higher risk of having liver problems.

Heart problems, including heart attack.

Low blood pressure when standing up, which can cause dizziness or fainting. People who have serious kidney problems may be at increased risk for dizziness and fainting.

In addition to the serious side effects listed above, additional side effects include:
- Colds
- Cough
- Fever
- Rash
- **Dizziness**
- Diarrhea
- Swelling of parts of the body
- Flu and flu-like symptoms
- Muscle aches, spasms and pain
- Stomach pain and bloating
- Sleeping problems
- Runny, congested nose
- Problems with urination
- Low **amounts of** white blood cell counts (neutropenia)

NOTE: Because of how the drug works in your body, there is a possible increased risk for getting other infections or cancer, although there is no evidence from the clinical trials of an increase in serious infections or cancer.

MVC contains soy lecithin. If you have a medical history of allergy to soy (soya or soybeans) or peanuts, you may develop an allergic reaction to MVC. Before starting MVC, you should inform the study staff or study doctor if you are allergic to soy or peanuts.

Risks of DTG (Tivicay)
The following serious side effects have been associated with the use of DTG**. These include allergic reactions and liver problems, which may be life-threatening.**

Contact the study doctor **or your healthcare provider** right away if you develop a rash **while taking** DTG**, especially if it is associated with any of the symptoms listed below**. Stop taking DTG and get medical help right away if you **develop a rash with any of the following signs or symptoms**:
- Fever
- Generally ill feeling
- Extreme tiredness
- Muscle or joint aches
- Blisters or sores in mouth
- Blisters or peeling of the skin
- Redness or swelling of the eyes
- Swelling of the mouth, face, lips, or tongue

- Problems breathing

Contact the study doctor or your healthcare provider if you have any of the following symptoms **that could be signs** of liver problems:
- Yellowing of the skin or whites of the eyes
- Dark or tea-colored urine
- Pale-colored stools **or** bowel movements
- Nausea or vomiting
- Loss of appetite
- Pain, aching, or tenderness on the right side below the ribs

People with a pre-existing history of depression or other mental health illness may be at greater risk for suicidal thoughts, or attempts, which may lead to death. If your mental health illness worsens, or if you develop suicidal thoughts, call the study doctor or your healthcare provider right away.

Other side effects of DTG include:
- **Changes in liver test results, more common in people with hepatitis B or C**
- Trouble sleeping
- **Tiredness**
- Headache

Tell **the** study doctor **or your healthcare provider** about any side effect that bothers you or that does not go away.

ARE THERE RISKS RELATED TO PREGNANCY?

The drugs used in this study may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant. Because of the risk involved, you must use at least one method of birth control. You must continue to use birth control for 6 weeks after stopping your medicines. You must choose one of the birth control methods listed below:
- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormone-based contraceptive

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. If you think you may be pregnant at any time during the study, tell your study staff right away. If you are pregnant you will be taken off the study treatment, but asked to continue the study evaluations. The study staff will talk to you about your choices.

If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to

an international database that collects information about pregnancies in women taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

NOTE: It is not known whether the study drug passes through breast-milk and may cause harm to your baby. If you are breastfeeding, you cannot take part in this study.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:
- treatment with prescription drugs available to you
- treatment with experimental drugs, if you qualify
- no treatment

Please talk to your health care provider about these and other choices available to you. Your health care provider will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

For Sites in the US
We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have applied for/obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

People who may review your records include the ACTG, Office for Human Research Protections or other government agencies as part of their duties, **Food and Drug Administration (FDA),** (insert name of site) Institutional Review Board (a group that protects the rights and well-being of people in research), National Institutes of Health (NIH), study staff, study monitors, the drug company supporting this study, and its designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on 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 any time.

For Sites outside the US
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the ACTG, OHRP, FDA, (insert name of site) IRB, National Institutes of Health (NIH), study staff, study monitors, and drug company supporting this study.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

[Sites please indicate whether you will provide payment to participants]

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH **PARTICIPANT**?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research **participant**, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)	Participant's Signature and Date
Participant's Legally Authorized Representative (print) (As appropriate)	Legally Authorized Representative's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date