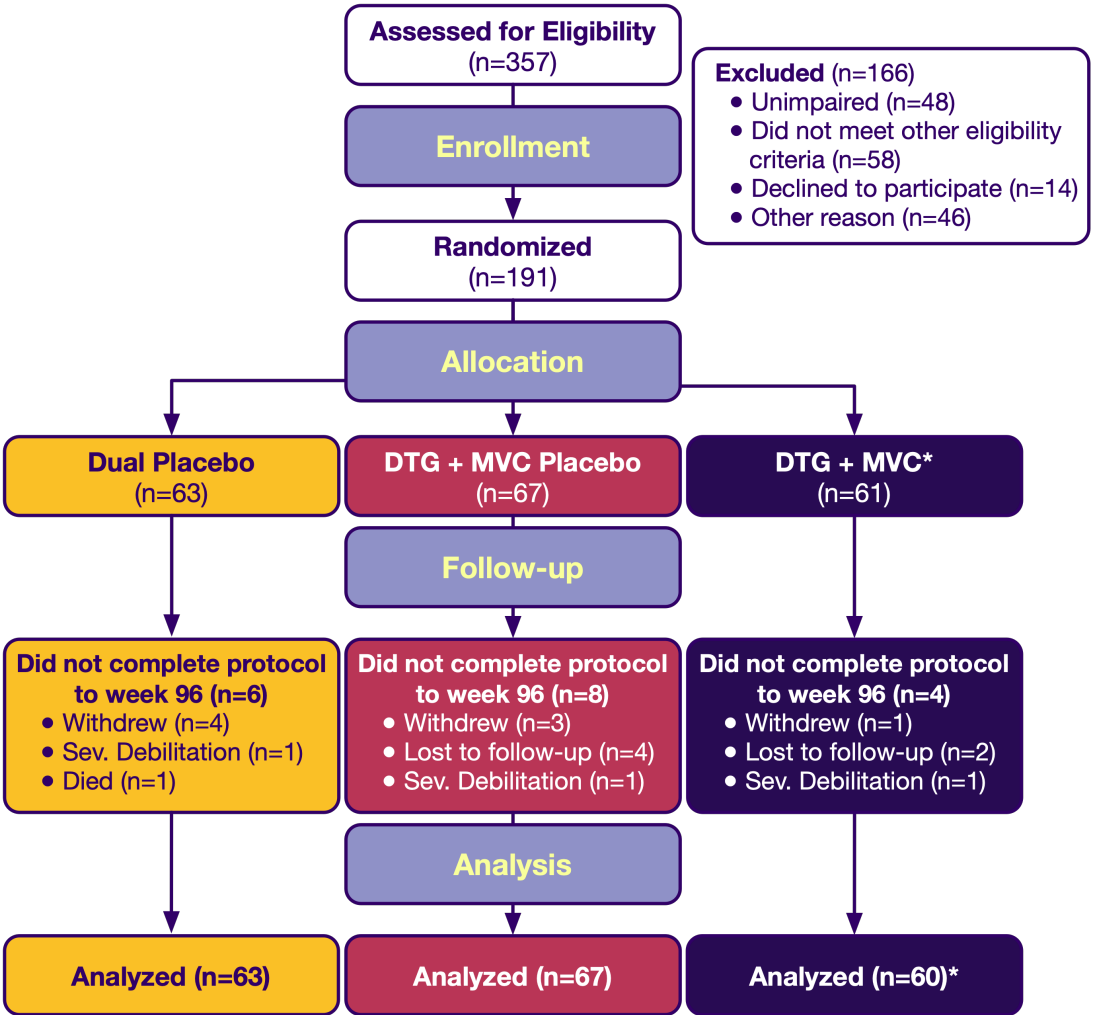
Supplemental Material

Supplemental Figure 1. CONSORT Diagram. Participants who did not complete the protocol were included in modified intent-to-treat analyses but not per-protocol analyses. *One participant was randomized to Arm C did not receive the randomized intervention and was excluded from analyses.



Supplemental Table 1. Exclusion Criteria.

Exclusion Criteria
Current or past medical conditions that, in the opinion of the investigator, prevents attribution of the cause of cognitive impairment to HIV, such as:
- Major depressive disorder with psychotic features
- Traumatic Brain Injury (TBI) with a clear impact on activities of daily living
- Developmental delay, intellectual deficit, and/or severe educational disability resulting in some dependence for activities of daily living
- Active substance use with significant impact on activities of daily living
- Evidence of intoxication or withdrawal during the screening evaluation
- CNS infections or opportunistic conditions, e.g., Brain abscess, meningitis with persistent neurologic impairment, primary CNS lymphoma, progressive multifocal leukoencephalopathy, or another structural brain lesion with neurological sequelae
- Other CNS conditions, e.g., 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 (e.g., Alzheimer's disease)
- Symptomatic medical illness (e.g., persistent unexplained fever, diarrhea, significant weight loss, disabling weakness) within 30 days of screening
- Known untreated vitamin B12 deficiency or malnutrition with body mass index <18 kg/m^2 at screening
Active hepatitis C virus infection
Unstable, advanced liver disease defined by the presence of at least one of the following: ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice
Presence of an AIDS-defining opportunistic infection within 180 days of entry
Prior or current use of a CCR5 antagonist or integrase inhibitor
Breastfeeding
Active syphilis or treatment for syphilis within 90 days of study entry
Known allergy/sensitivity or any hypersensitivity to components of study drugs or their formulation

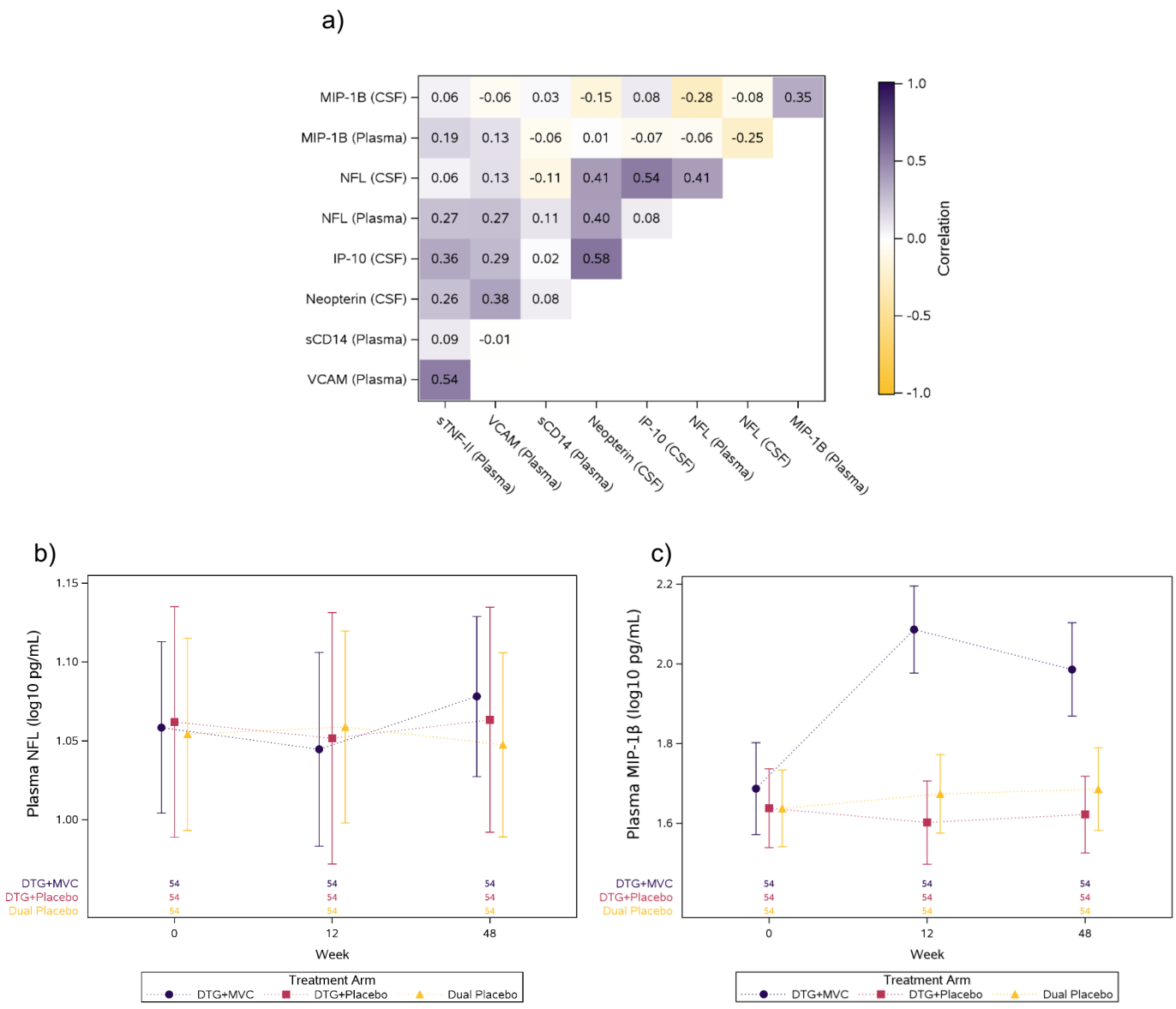
Supplemental Table 2. Assessments.

Assessment	In the U.S.	Outside the U.S.	Assessed Domain
Neuropsychological Test Battery			
Symbol Search	X		Attention/Working Memory
Trail Making A	X		Attention/Working Memory
Trail Making B	X		
Color Trails 1		X	Attention/Working Memory
Stroop Word	X		Speed of Information Processing
Stroop Color	X		Speed of Information Processing
Digit Symbol	X	X	Speed of Information Processing
Hopkins Verbal Learning Test – Revised (HVLT-R)	X	X	Verbal Learning
Delayed Recall – HVLT-R	X	X	Verbal Memory
Grooved Pegboard (Bilateral)	X	X	Fine Motor Skills/Complex Perceptual
Fingertapping (Bilateral)		X	Fine Motor Skills/Complex Perceptual
Wide Range Achievement Test 4 (WRAT-4)	X		Language/Premorbid Skills (English)
Word Accentuation test (WAT)	X		Language/Premorbid Skills (Spanish)
Color Trails 2		X	Executive Function
Category Fluency	X	X	Executive Function
Timed Gait		X	Gross Motor
Questionnaires and Adherence Assessment			
Revised Lawton & Brody Activities of Daily Living	X	X	
Beck Depression Inventory-II	X		
Patient Health Questionnaire-9		X	
ACTG Substance Abuse Questionnaire	X	X	
ACTG Adherence Questionnaire	X	X	
Study Drug Dispensing Records	X	X	
International HIV Dementia Scale		X	

Supplemental Table 3. Adverse Events Related to Study Drug. The cardiac disorder was hypertensive heart disease. Gastrointestinal disorders included abdominal pain, nausea, and diarrhea with grades that were either 2 (n=3) or 3 (n=2). The nervous system disorder was a grade 1 headache. The psychiatric disorder was grade 3 depressive symptoms. All creatinine clearance declines were grade 3 events. The serum bilirubin increase was also grade 3. Values indicate the number of adverse events, except the overall value, which indicates the total number of participants. The number of adverse events is not equivalent to the number of participants since some participants had more than one adverse event.

	Dual Placebo (n=63)	DTG+ Placebo (n=67)	DTG+ MVC (n=61)
Participants who had at least one adverse event	3 (4.8%)	5 (7.5%)	7 (11.5%)
Cardiac disorders	1 (1.6%)	0 (0%)	0 (0%)
Gastrointestinal disorders	2 (3.2%)	2 (3.0%)	1 (1.6%)
Nervous system disorders	0 (0%)	1 (1.5%)	0 (0%)
Psychiatric disorders	0 (0%)	0 (0%)	1 (1.6%)
Respiratory disorders	1 (1.6%)	0 (0%)	0 (0%)
Urinary tract infection	0 (0%)	0 (0%)	1 (1.6%)
Drug eruption	0 (0%)	0 (0%)	1 (1.6%)
Laboratory Investigations			
Creatinine clearance decreased	0 (0%)	2 (3.0%)	4 (6.6%)
Serum bilirubin increased	1 (1.6%)	0 (0%)	0 (0%)

Supplemental Figure 2. Soluble Biomarkers in Blood and CSF. a) Correlation matrix heatmap of soluble biomarkers in blood and CSF. b) Plasma Neurofilament-light chain (NfL) over time by treatment arm. c) Plasma macrophage inflammatory protein (MIP)-1β over time by treatment arm. IP-10=Interferon-inducible Protein-10, sCD14=Soluble Cluster of Differentiation 14, VCAM=soluble Vascular Cell Adhesion Molecule-1, sTNFR-II=Soluble Tumor Necrosis Factor Receptor-II



Supplemental Figure 3. and b) Body Mass Index (BMI) over time stratified by treatment arm.

DTG=Dolutegravir, MVC=Maraviroc