

PROTOCOL NAME:

Switch to Maraviroc and Integrase Strand Transfer Inhibitor Combination Therapy (a Triple Class-Sparing Regimen) for the Treatment of HIV-1-Infected Patients on Suppressive Antiretroviral Regimens

PROTOCOL STUDY NUMBER:

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SPONSOR:

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1. Protocol Summary

Full Title	Switch to Maraviroc and Integrase Strand Transfer Inhibitor Combination Therapy (a Triple Class-Sparing Regimen) for the Treatment of HIV-1-Infected Patients on Suppressive Antiretroviral Regimens
Short Title	SWIMII: Switch to Maraviroc and Integrase Inhibitor
Clinical Trial Phase	III
Conducted By	Institute of Human Virology
Principal Investigator	David Riedel, MD
Sample Size	N = 30
Study Population	HIV-infected adults on suppressive antiretroviral therapy for ≥ 1 year
Accrual Period	One year.
Study Design	Open label, single arm pilot study
Study Duration	Duration per participant is 96 weeks; total planned study duration is 3 years.
Study Agent/ Intervention Description	Maraviroc 300 mg PO BID + either Raltegravir 400 mg PO BID or Dolutegravir 50 mg QD
Primary Objective	Efficacy (virologic suppression proportion) of a regimen containing maraviroc and raltegravir/dolutegravir at 48 weeks.
Secondary Objectives	Evaluate safety, tolerability, and metabolic effects of the new regimen.
Exploratory Objectives	To determine the effects of the maraviroc + integrase inhibitor regimen on telomerase activity and telomere length.
Endpoints	HIV RNA at 48 weeks.

2. Background Information and Scientific Rationale

2.1 Background Information

Outcomes of antiretroviral therapy (ART) have improved over the past two decades, leading to substantial reductions in morbidity and mortality related to HIV and AIDS. HIV-infected patients now have significantly longer expected life spans than in the 1980s or 1990s. Studies have also demonstrated lower rates of toxicity and improved immune (CD4) reconstitution when ART is initiated at higher CD4 counts. This, in addition to the improved efficacy, tolerability, and simplicity of new agents, has led to revisions in treatment guidelines to begin ART earlier after HIV infection.

At the same time, many studies have demonstrated metabolic complications of antiretroviral agents that lead to mitochondrial dysfunction, hyperlipidemia,¹ cardiovascular events,²⁻⁵ insulin resistance, renal toxicity,⁶ and other morbidities. Many of these complications are secondary to side effects and toxicities from specific antiretroviral agents, especially those within the original

three ART classes: nucleoside/tide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). These toxicities are thought to play a role in the accelerated aging process that is seen in HIV-infected patients. Recent work has also shown an effect of NRTIs on telomerase activity which may link the long-term use of these drugs directly to the process of accelerated aging, providing a mechanism for some of the various co-morbidities associated with long-term HIV infection.⁷

As the average HIV-infected individual will now spend literally decades on ART, these metabolic complications have become important causes of morbidity and mortality in the treated patient. Nucleoside/tide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) have been linked with many of these metabolic complications, leading to expanded interest in combination regimens that minimize metabolic complications by avoiding use of these agents. Numerous studies have examined class-sparing regimens focusing on exclusion of NRTIs⁸⁻¹², but few studies have examined regimens excluding all 3 major classes of ART, i.e. NRTIs, NNRTIs, and PIs. Maraviroc (a CCR5 co-receptor antagonist) and raltegravir (an integrase strand transfer inhibitor) represent two new classes of antiretroviral agents with favorable toxicity profiles. Both were approved for the treatment of HIV infection by the FDA in 2007. Both agents have been documented to be extremely potent and well-tolerated in antiretroviral naïve and experienced patients, making them promising candidates for inclusion in regimens which minimize metabolic complications.^{13,14} A second integrase inhibitor, dolutegravir, was approved by the FDA in late 2013. It has a similarly favorable metabolic profile as raltegravir and has the dual advantages of increased potency and once-daily dosing. (A third integrase inhibitor, elvitegravir, has also recently been FDA approved; however, it requires pharmacokinetic boosting with a second drug (cobicistat) leading to potential hepatic/metabolic side effects. Additionally, elvitegravir is marketed as Stribild™ which is a 4-drug co-formulation with cobicistat, emtricitabine, and tenofovir, the latter two drugs (NRTIs) which are specifically excluded from this protocol.)

2.1.1 Description of the study agents

Maraviroc is a CCR5 co-receptor antagonist, while raltegravir is an integrase strand transfer inhibitor. Both were approved for the treatment of HIV infection by the FDA in 2007.

Dolutegravir, another integrase strand transfer inhibitor, was approved by the FDA in late 2013.

HIV gains entry to cells by first binding to the CD4 receptor, after which it requires a secondary binding to a co-receptor before attachment is complete. HIV uses one of two receptors, CCR5 (CC chemokine receptor 5) or CXCR4 (CXC chemokine receptor 4) to secure its attachment to cells.¹⁵ HIV that uses CCR5 is denoted as R5- or CCR5-tropic, and HIV that uses CXCR4 is called X4- or CXCR4-tropic. Occasionally, the virus is capable of using either co-receptor (dual tropism), and some patients harbor mixed populations of viruses (mixed tropism).

Transmission of HIV is nearly always via R5-tropic strains, and so patients with early HIV infection (i.e. high CD4 counts) nearly always have R5-tropism. Cross-sectional studies of HIV-infected patients have shown that patients who are treatment naïve or otherwise with early infection (CD4 count > 300) are much more likely to have R5-tropic virus.¹⁶⁻¹⁹ As HIV disease and duration progresses, a higher percentage of viruses will shift to X4- or dual tropism.¹⁶⁻¹⁹ Most reports on HIV tropism have been from cohorts of patients with subtype B virus (which predominates in the U.S. and Europe). Some studies have found higher proportions of X4- and

dual tropic virus in patients with subtype A and D HIV infections (which are found largely in East/central Africa).²⁰⁻²²

There are two laboratory tests currently used to determine viral tropism. The first is a Trofile. The Trofile requires a circulating viral load of > 1,000 copies/ml, and so it is generally performed before initiation of ART. The second is a genotypic assay of the HIV envelope V3 loop.²³ Its main advantage is that it can be performed when the viral load is < 1,000 copies/ml, even when the patient is receiving ART.²⁴

Maraviroc is the first drug of a class used to treat HIV that does not target the virus itself, but instead works by blocking access to the host's cellular receptors and thereby limiting the ability of the virus to infect new cells and propagate. The drug is only effective against virus that is R5-tropic and has no effect on HIV that is CXCR4 tropic, dual tropic, or mixed tropic. Advantages of maraviroc include its robust efficacy against R5 tropic strains, good tolerability with few adverse reactions, lack of cross-resistance with other ART drugs.^{14,15,25} Disadvantages include the requirement of twice-daily dosing and its limitation to R5 tropic strains.²⁵ Maraviroc is currently recommended by U.S. guidelines²⁶ as part of an acceptable regimen for ART naïve patients and experienced patients failing initial ART. Maraviroc is being investigated for use in HIV prevention, intensification, and immune modulation/reconstitution studies.^{27,28}

Raltegravir was the first drug in a class of antiretrovirals known as integrase strand transfer inhibitors. The HIV integrase enzyme transfers viral DNA into the host chromosome, an essential step in retrovirus replication.²⁹ Integration is also the mechanism by which HIV establishes itself for the life of the cell, contributing to life-long persistence of HIV infection. Raltegravir has been widely used for the treatment of HIV since its initial approval. Advantages of raltegravir include high potency, solid efficacy, low frequency of adverse reactions, and minimal drug-drug interactions.^{13,30,31} Disadvantages include the requirement of twice-daily dosing and a relatively low genetic barrier to resistance.^{30,31} Raltegravir is currently recommended by U.S. guidelines²⁶ as part of a preferred regimen for ART naïve and experienced patients and is often used in trials of class-sparing novel ART regimens.^{9-12,32-34}

Dolutegravir is also an integrase strand transfer inhibitor. It has a similar, favorable metabolic profile as raltegravir and shares the other advantages of high potency, solid efficacy, low frequency of adverse reactions, and minimal drug-drug interactions.³⁵ It also has the advantage of a higher barrier to resistance than raltegravir and once-daily dosing. Dolutegravir is also now recommended by the U.S. guidelines³⁶ as part of a preferred regimen for ART naïve patients.

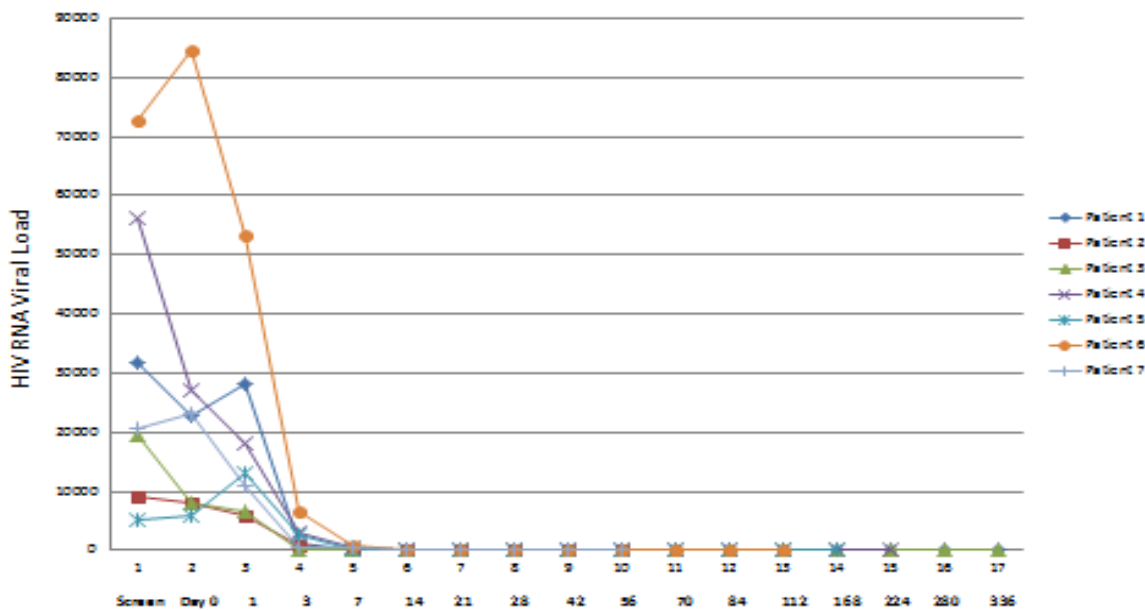
2.1.2 Summary of relevant clinical studies

Maraviroc and raltegravir have been used together as part of salvage combination therapy with etravirine in triple-class experienced patients.¹⁰ This study prospectively enrolled 28 triple-class experienced patients with R5 tropic virus who were virologically failing their previous regimen. At the end of 48 weeks, 26 of 28 (92%) achieved virologic suppression success with HIV RNA < 50 copies/ml. Continuation of this study to 96 weeks was subsequently published.³⁷ Twenty-five of the original 28 enrolled patients (89%) completed 96 weeks of treatment. By week 96, 24 of 25 patients (96%) attained HIV RNA <50 copies/ml. Safety and tolerability profiles of this 3-drug combination were excellent.

A pilot study conducted in France was recently published.³⁸ This study enrolled 44 patients on suppressive ART and switched to the maraviroc/raltegravir combination regimen. The inclusion/exclusion criteria for this study were problematic since the median duration of HIV infection was 20 years (IQR 14-24) and the median CD4 nadir was 210 (IQR 150-276), suggesting that not all patients were actually R5 tropic, despite DNA trofile assays showing R5. This may have led to limited activity of maraviroc in the setting of dual tropic virus. The study was stopped early due to five virologic failures, but the decision to stop the study was likely premature since a rate of 5/44 failures (11%) is similar to the expected rate of failure in most ART switch studies (~10%). Two of the virologic failures had drug levels below the threshold for efficacy, suggesting that medication adherence was the proximate cause of failure rather than the regimen itself. These significant flaws in the French study make conduct of an appropriately conducted clinical trial of this new regimen even more vital at this time.

A recent pilot study combining maraviroc with raltegravir in seven antiretroviral naïve patients conducted at the Institute of Human Virology demonstrated potency and efficacy of the combination (R. Redfield, unpublished data). In this study, all seven patients achieved rapid viral suppression by week 2 (Figure 1). Three patients who have completed the trial to week 48 remained suppressed throughout the trial. The safety profile to date has been excellent with no serious adverse events related to the study drugs.

Figure 1.



4/22/13

2.2 Rationale

This clinical study proposes to evaluate the combination of maraviroc with an integrase strand transfer inhibitor (either raltegravir or dolutegravir) in antiretroviral-experienced patients to document the efficacy, safety, and tolerability of this combination in order to provide clinicians with a treatment regimen that minimizes the risk of metabolic complications by avoidance of

NRTI/NNRTIs and PIs. The development of an alternative ART regimen which lessens the risk of metabolic complications could improve long-term adherence and reduce the risk of certain co-morbidities associated with long-term ART use. If this new combination is found to be as efficacious as the standard regimen with enhanced tolerability and improved metabolic effects, there is great potential for altering the current practice of HIV medicine.

2.3 Potential risk and benefits

The drugs used in this study are currently approved by the U.S. FDA for treatment of HIV infection.

2.3.1 Potential risks

Risks of drawing blood

Drawing blood may cause discomfort, bleeding, and bruising where the blood is drawn. Occasionally, there is swelling in the area where the needle enters the body, and there is a small risk of infection. There is also a risk of lightheadedness, fainting, and blood clots.

Risks with the new drugs

The drugs used in this study may have side effects, some of which are listed below.

*Risks with use of **Raltegravir** (RAL, Isentress™)*

The most common adverse events reported with raltegravir are headache, other nervous system effects and gastrointestinal events; the majority were mild and transient in nature.¹³ Nervous system events (mainly headache) were noted at a similar incidence to placebo in the phase III approval studies.

Skin rashes and hypersensitivity reactions were mild, uncommon and occurred at similar rates with raltegravir as with placebo (5.3 vs. 2.5%), and in most cases have been confounded by use of concomitant drugs.¹³

Rare cases of Stevens–Johnson syndrome possibly associated with raltegravir have been reported in post-marketing surveillance, although it has not been possible to establish a true causal relationship.

Also seen in post marketing reports have been thrombocytopenia and rhabdomyolysis.^{39,40} Additional serious reactions include allergic reactions.

Abnormal blood tests which have been seen in studies of raltegravir in combination with other HIV drugs include elevated liver function tests, increase in pancreatic amylase, and asymptomatic increase in creatinine phosphokinase.

Cancers have been seen in people who took raltegravir with other HIV drugs. However, the malignancies reported were diverse, with no pattern evident in the number or type, and no trend in the time of onset.¹³ It is unknown if the cancers were related to raltegravir use.

*Risks with use of **Dolutegravir** (DTG, Tivicay™)*

The most common adverse events reported with dolutegravir are mild to moderate diarrhea, fatigue, and headache. Other adverse reactions like insomnia, dizziness, and nausea occurred at similar rates (1-3%) as with comparator drugs in clinical trials. Other uncommon (<2%) adverse reactions included abdominal pain, abdominal discomfort, flatulence, vomiting, myositis, renal impairment, and pruritus (itching).

Abnormal blood tests which have been seen in studies of dolutegravir in combination with other HIV drugs include elevated liver function tests, increase in pancreatic lipase, and asymptomatic increase in creatinine phosphokinase.

Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 24 to 48 weeks. In treatment-naïve subjects, a mean change from baseline of 0.11 mg/dL (range: -0.60 mg/dL to 0.62 mg/dL) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in 1% or fewer subjects.

*Risks with Use of **Maraviroc** (MVC, Selzentry™)*

Common side effects reported with maraviroc that may or may not be causally related include: cough, fever, colds/upper respiratory tract infections, rash, muscle and joint aches, stomach pain, diarrhea, edema, sleeping problems, and dizziness.^{14,27}

Serious side effects may include serious skin rash and allergic reactions, and elevations in liver function tests. People who are co-infected with hepatitis B or C might be at higher risk of having liver problems, although data from trials showed similar rates of liver function test abnormalities in patients on maraviroc compared to placebo groups.¹⁴

Postural hypotension was reported in patients taking higher doses (than currently approved) of maraviroc in clinical studies.¹⁴

Post-marketing experience has reported skin and subcutaneous tissue disorders including Stevens-Johnson syndrome (a severe and sometimes fatal form of skin rash).

Maraviroc blocks the CCR5 receptor on T cells; this might interfere with some of the normal function of CCR5 in the body and may increase the risk of certain infections or cancer. There have been higher rates of herpes virus infections in people who took maraviroc compared with placebo in studies so far. Cancers have been reported with the use of another drug that works the same way as maraviroc. Cancers have occurred in people taking maraviroc, but so far, there has not been an increased risk of cancers or any types of cancers when comparing people taking maraviroc with either people taking other HIV drugs or placebo.

Maraviroc contains soya lecithin. Therefore if you have a medical history of allergy to soya or peanuts, you may develop an allergy reaction to maraviroc.

Risks with the novel combination of maraviroc and raltegravir/dolutegravir

There is a risk that the new regimen may not maintain viral suppression as well as the patient's prior regimen. However, viral load monitoring will be conducted frequently in order to detect failure at the earliest juncture and minimize the risk of resistance development (see below under 2.3.3). If virologic failure occurs, resistance may develop to one or both of these drugs, eliminating their possible use from future antiretroviral regimens for the individual patient. Resistance to maraviroc, however, is quite rare, and is therefore unlikely. There is no cross-resistance between maraviroc and other classes of antiretroviral drugs. Because the patient was on a previously successful regimen, it is likely that the patient will be able to resume his/her old regimen should virologic failure and resistance to the study drugs develop.

There may be risks due to the medications or their combination in this study which are not yet known.

2.3.2 Potential benefits

Subjects may not have personal benefit from this study. It is possible that this new regimen could improve certain metabolic parameters and maintain viral suppression to the same degree as their previous regimen. Additionally, participation in this study may benefit the community, scientists, and doctors who work with HIV by providing increased knowledge about treatment of this disease.

2.3.3 Risk to benefit ratio and minimization of risks

The potential risks versus the benefits are reasonable. These are FDA approved drugs for the treatment of HIV infection. The selection criteria and study design of this protocol have been carefully chosen to minimize the risks of the study to patients in the following ways: 1) the inclusion/exclusion criteria have been designed to minimize the risk that any patient with CXCR4-tropic virus (i.e. one who would not respond to maraviroc) will be excluded using a high CD4 nadir cut-off threshold; 2) patients to be included are already virologically suppressed, which means they have demonstrated the ability to adhere to antiretrovirals, which minimizes the risk of poor adherers that could lead to drug resistance; and 3) virologic monitoring will be done frequently to minimize the risk of undetected virologic failure and development of resistance. Overall, the study has been designed to minimize potential risks.

3. Study objectives

3.1 Primary objective

The primary objective of this study is to evaluate the efficacy of a regimen containing maraviroc and raltegravir/dolutegravir at 48 weeks.

3.2 Secondary objective

The secondary objectives of this study are to evaluate the safety, tolerability, and metabolic effects of the new regimen as well as the efficacy at 96 weeks.

3.3 Exploratory objectives

To determine the effects of the maraviroc + integrase inhibitor regimen on telomerase activity and telomere length.

4. Study design

This is a pilot, open-label study of maraviroc with either raltegravir or dolutegravir in combination for the treatment of ART-experienced adult patients who are currently virologically suppressed.

4.1 Description of the study design

The study will enroll 30 HIV-infected patients on a stable ART regimen with a suppressed HIV RNA < 50 copies/ml for at least one year. Patients will be switched to the experimental regimen (maraviroc plus either raltegravir or dolutegravir) and followed for 96 weeks. The decision to use raltegravir or dolutegravir will be left to investigator/subject preference, as the two integrase inhibitors are largely interchangeable aside from twice daily (raltegravir) vs. daily (dolutegravir) dosing.

4.2 Study endpoints

4.2.1 Primary endpoint

- The primary endpoint is the proportion of patients virologically suppressed (HIV RNA < 50 copies/ml) at 48 weeks.

Definitions:

- Virologic suppression is an HIV RNA < 50 copies/ml.
- Virologic failure is an HIV RNA \geq 50 copies/ml confirmed on 2 separate occasions, separated by > 1 week after viral suppression.

4.2.2 Secondary endpoints

The secondary endpoints are:

- The percent change in total cholesterol, LDL, and HDL at 48 and 96 weeks.
- The number of adverse events.
- The proportion of patients who are virologically suppressed (HIV RNA < 50 copies/ml) at 96 weeks.

4.2.3 Exploratory endpoints

- Telomerase activity and telomere length measured at baseline and 24, 48, and 96 weeks.

5. Study population

5.1 Description of the study population

This study will be conducted among adult patients infected with HIV-1 who are ART-experienced.

5.1.1 Participant inclusion criteria

- HIV-1 infection
- Age between 18 and 75 years
- CD4 count nadir ≥ 250 cells/mm³
- HIV RNA ≤ 50 copies/ml for ≥ 12 months while taking any ART regimen
 - One virologic blip ≤ 400 copies/ml permissible within the 12 months
- CCR5 tropic virus as defined by:
 - trofile/tropism testing if available, OR
 - DNA trofile if no trofile/tropism test available and CD4 nadir 250-499 cells/mm³, OR
 - CD4 nadir ≥ 500 cells/mm³

5.1.2 Participant exclusion criteria

- Age < 18 or > 75 years
- CD4 count nadir < 250 cells/mm³
- Dual/mixed or X4 tropic virus if tested prior to viral suppression or if performed by DNA trofile testing at any time
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times the upper limits of normal
- Women who:
 - are currently pregnant or breastfeeding
 - are of child-bearing age and do not agree to remain abstinent or use (or have their partner use) an acceptable method of birth control throughout the study. Acceptable method of birth control is defined as intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, condom, vasectomy.
- History of any malignancy except non-melanoma skin cancer
- Concomitant use of drugs known to impact or be impacted in terms of pharmacokinetics or drug-drug interactions with either raltegravir, dolutegravir, or maraviroc. This includes:
 - Inducers of UGT1A1 (such as rifampin, phenytoin, phenobarbital, rifabutin, St. John's wort)
 - CYP3A inhibitors (such as ketoconazole, itraconazole, clarithromycin, nefazodone, and telithromycin)
 - CYP3A inducers (such as rifampin, carbamazepine, phenobarbital and phenytoin)
 - Dofetilide
- Subject requires or is anticipated to require any of the prohibited medications noted in the protocol
- Enrollment in an experimental protocol having received investigational agents (antiretroviral or non-antiretroviral) within 30 days of study enrollment
- Chronic active hepatitis B infection as defined by presence of HBsAg
- Subject has a history or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might interfere with the patient's participation for the full duration of the study, such that it is not in the best interest of the patient to participate.
- Subject is unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study.

6. Study interventions

6.1 Study agent acquisition

Both Maraviroc and Raltegravir/Dolutegravir will be obtained by writing a prescription for the subject and obtaining through their insurance.

Note that in Maryland, every subject who does not have insurance can apply for the AIDS Drug Assistance Program (ADAP) so that potential study subjects will be able to access this medication even if they do not have insurance.

6.1.1 Study agent #1: Maraviroc (Selzentry™)

Maraviroc tablets are blue, oval, film-coated tablets debossed with "MVC 300" on one side and plain on the other and contain 300 mg of maraviroc. The tablet also contains the following inactive ingredients: dibasic calcium phosphate (anhydrous), magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The film coat (Opadry® II Blue [85G20583]) contains FD&C blue #2 aluminum lake, soya lecithin, polyethylene glycol (macrogol 3350), polyvinyl alcohol, talc, and titanium dioxide. Maraviroc is chemically described as 4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl] -cyclohexanecarboxamide.

6.1.2 Study agent #2: Raltegravir (Isentress™)

Raltegravir tablets are film-coated, pink, oval-shaped, film-coated tablets with "227" on one side and contain 400 mg of raltegravir. Each 400 mg film-coated tablet of ISENTRESS for oral administration contains 434.4 mg of raltegravir (as potassium salt), equivalent to 400 mg of raltegravir free phenol and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, calcium phosphate dibasic anhydrous, hypromellose 2208, poloxamer 407 (contains 0.01% butylated hydroxytoluene as antioxidant), sodium stearyl fumarate, magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, red iron oxide and black iron oxide. The chemical name for raltegravir potassium is N-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt.

6.1.3 Study agent #3: Dolutegravir (Tivicay™)

TIVICAY Tablets, 50 mg, are yellow, round, film-coated, biconvex tablets debossed with SV 572 on one side and 50 on the other side. Each film-coated tablet of TIVICAY for oral administration contains 52.6 mg of dolutegravir sodium, which is equivalent to 50 mg dolutegravir free acid, and the following inactive ingredients: D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, and sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients iron oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide. The chemical name of dolutegravir sodium is sodium (4R,12aS)-9-[[(2,4-difluorophenyl) methyl]carbamoyl]-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido [1',2':4,5] pyrazino[2,1-b][1,3]oxazin-7-olate.

6.2 Assessment of participant compliance with the study agent/intervention

The investigator/study coordinator will review the subject's estimated adherence to study drugs at each visit.

6.3 Concomitant medications and procedures

No drugs are to be taken within 14 days of the start of the study without the knowledge of the investigator.

Non-ART investigational agents must be discontinued for 30 days prior to treatment in this study.

Permitted Concomitant Therapy

The concomitant use of other medications/therapies is allowed unless specifically prohibited in the Prohibited Concomitant Medications/Therapies section below. It is the responsibility of the investigator to check on potential drug-drug interactions of the study antiretroviral agents with other concomitant medications, before placing a subject on a specific medication/therapy.

6.4 Precautionary and prohibited medications and procedures

Raltegravir and dolutegravir are eliminated mainly via a UDP-glucuronosyltransferase (UGT) 1A1-mediated glucuronidation pathway and, therefore, the compound may be subject to drug-drug interactions when co-administered with drugs that are known to be UGT1A1 inducers or inhibitors. However, raltegravir/dolutegravir is not anticipated to affect the metabolic clearance of drugs metabolized by UGT1A1 given its low UGT1A1 inhibitory (IC₅₀ for the inhibition of UGT1A1 >50 uM) and induction potential. Since raltegravir is neither a substrate nor an inhibitor of cytochrome P-450 enzymes, raltegravir is not expected to exhibit metabolic drug interactions with substrates of cytochromes P-450. Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. Darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, tenofovir, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole had no clinically significant effect on the pharmacokinetics of dolutegravir.

Maraviroc is a CYP3A4 and Pgp substrate and therefore is expected to be modulated by inducers and inhibitors of these enzymes and transporters. Maraviroc is unlikely to inhibit co-administered drugs metabolized by the following cytochrome enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A) as it did not inhibit these enzymes in vitro.

Prohibited Medications

- The medications/therapies below are contraindicated in this study because they are potent broad inducers of drug metabolism, inducers of CYP3A (thus potential inducers of glucuronidation), and/or inhibitors of glucuronidation and their co-administration with raltegravir/dolutegravir and maraviroc will likely result in altered drug levels of raltegravir/dolutegravir and/or maraviroc.
 - Rifampin
 - St. John's Wort
 - Dofetilide
- Any other medications/therapies that may adversely affect the drug levels of the antiretroviral agents in the treatment regimen should be avoided to ensure adequate

therapeutic levels of the study medications. Medications specifically contraindicated to the study antiretroviral agents selected are prohibited.

- Non-ART investigational agents.
- Immunosuppressive therapy other than intra-lesional or localized electron beam therapy for cutaneous Kaposi's sarcoma. If a patient develops a malignancy (for example lymphoma) after allocation, the patient may receive chemotherapy and remain in the study if, in the opinion of the investigator, the benefits outweigh the risks. Depending on the type of chemotherapy, study medication may need to be interrupted until completion of chemotherapy.

6.5 Diet

Doses of raltegravir/dolutegravir and maraviroc will be consumed without regard to food.

7. Study procedures/evaluations

Study procedures should be performed as close to the scheduled time as possible. See the study flow chart in Section 8 for a complete listing of study procedures required at each visit.

7.1 Informed consent

The investigator will obtain documented consent from each potential subject. Prior to signing the document, all potential subjects will be evaluated with a standardized "Evaluation to sign consent" form (appendix). Consent must be documented by the subject's dated signature on an official University of Maryland Baltimore Consent Form along with the dated signature of the person conducting the consent discussion.

If the subject is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterwards, the subject should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e., study staff personnel).

A copy of the signed and dated consent form will be given to the subject before participation in the trial. The initial informed consent form and any subsequent revised written informed consent form, and any written information provided to the subject must receive the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative must be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form and in the research chart.

7.2 Assignment of research study number

For identification purposes during the screening period, each subject will be assigned a unique study number. Subjects who are screened multiple times retain the original study number assigned at the initial screening visit for any subsequent screening.

7.3 Clinical and Laboratory evaluations

7.3.1 Procedures to be performed at screening visit (Day -56 to Day -14)

- Complete Medical History - A complete medical history is required.
- Complete Physical Examination - A complete physical examination (including body weight, height, and vital signs [temperature, pulse, respiratory rate, and blood pressure]) must be obtained.
- Complete Medication History – A complete review of all medications and supplements the patient is currently taking.
- Urinalysis
- Serum Pregnancy test for women of child bearing potential
 - Female subjects of childbearing potential will have a serum pregnancy test (HCG) performed prior to the study start date. Women who are found to be pregnant will be excluded from the study.
- Blood for Screening Labs obtained within 56 days of study entry) –
 - CBC with differential
 - Serum Chemistry
 - LFT's (including AST, ALT, Total bilirubin)CK
 - Hepatitis B
 - Hepatitis B serologies will only be done if documentation of previous tests cannot be obtained.
 - Hepatitis B surface Antigen must have been done within the past 12 months unless evidence of immunity to hepatitis B (i.e. hepatitis B surface antibody positive).
 - Hepatitis C
 - Hepatitis C serology will only be done if documentation of previous test cannot be obtained
 - HIV-1 Elisa/Western Blot
 - HIV-1 Elisa/Western Blot will only be done if documentation of either a) previously positive Elisa/Western Blot test or b) 2 separate HIV-1 RNA viral loads ≥ 500 copies/ml cannot be obtained.
 - HIV-1 RNA PCR
 - CD4 Cell Count
 - DNA Trofile test
 - DNA Trofile test will only be done if none available and:
 - nadir CD4 250 – 499, or
 - patient originates from a region where HIV subtypes A or D are prevalent (includes West and East/central Africa)
 - Blood for Serologic/PBMC assays/storage

7.3.2 Procedures to be performed at Entry visit, Day 0

Initiation of study treatment will be performed on Day 0 once all inclusion criteria, and no exclusion criteria, are met. For subjects who meet the eligibility criteria, the following will be performed:

- Directed Medical History
- Directed Physical Examination (including body weight and vital signs [temperature, pulse, respiratory rate and blood pressure]). Vital signs and body weight must be measured prior to allocating the patient and initiating therapy.
- Complete Medication History – A complete review of all medications and supplements the patient is currently taking.
- Review of Adverse Events
- Blood will be collected for safety assessments
 - CBC with differential
 - Serum Chemistry
 - LFT's (including AST, ALT, Total bilirubin)
 - Lipid Panel (including total cholesterol, LDL, HDL, triglycerides)
 - CK
 - HIV RNA PCR
 - CD4 cell count
 - Tropism
 - Blood for Serologic/PBMC Assays/Storage.
- Urine Pregnancy Test - For female subjects of childbearing potential, a urine pregnancy test will be performed at the site. If the urine pregnancy test result is negative, the subject will be eligible for enrollment and the remainder of the Day 0 testing/procedures will be performed. If the urine pregnancy test result is positive, the patient will be excluded from participation.

Patients must be in a fasted state (for at least 8 hours) for collection of the blood samples for safety assessment at the Day 0 visit.

Plasma/PBMCs for archiving will be collected for potential future use regarding virologic suppression/resistance, ultra-low copy assays, and/or immunological markers associated with the HIV virus.

It is recommended that the subjects take their initial dose of open-label therapy in the clinic.

Subjects will be instructed to take the study medications as follows:

Take 1 tablet from bottle labeled Raltegravir (Isentress™) 400 mg twice a day, ~12 hours (10 to 14 hours) apart. The tablets can be consumed without regard to food.

Or

Take 1 tablet from bottle labeled Dolutegravir (Tivicay™) 50 mg once a day, ~24 hours (22 to 26 hours) apart. The tablets can be consumed without regard to food.

And

Take 1 tablet from bottle labeled Maraviroc (Selzentry™) 300 mg twice a day, ~12 hours (10 to 14 hours) apart. The tablets can be consumed without regard to food.

All containers of study drug will be returned to the study coordinator at each visit, at which time the drug supplies for the following time period will be dispensed. The number of tablets remaining in the bottle will be counted and recorded in the source documentation. Note that neither Maraviroc nor Raltegravir/Dolutegravir is provided through the study.

At the Day 0 visit, each patient will be given a diary card to record study drug administration.

7.3.3 Procedures to be performed during study treatment (Visit 1 to Visit 15 and unscheduled visits)

All subjects must return to the clinic at Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, and early discontinuation (if applicable) as noted in the study flow sheet.

During the study visits, the following will be performed:

- Directed Medical History
- Directed Physical Examination (including body weight and vital signs [temperature, pulse, respiratory rate and blood pressure])
- Review of Adverse Events
- Complete Medication History – A complete review of all medications and supplements the patient is currently taking.
- Blood will be collected as noted in the study flow sheet, including for:
 - HIV RNA at Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96 and early discontinuation (if applicable).
 - Safety measurements will be assessed at weeks 2, 6, 12, 24, 36, 48, 60, 72, 84, 96 and early discontinuation (if applicable), including:
 - CBC with differential
 - Serum Chemistry
 - LFT's (including AST, ALT, Total bilirubin)
 - CK
 - CD4 will be measured at Weeks 12, 24, 48, 72, 96 and early discontinuation (if applicable).
 - Lipid parameters will be measured at week 24, week 48, week 96, and early discontinuation (if applicable).

Subjects must be in a fasted state (for at least 8 hours) for collection of the blood samples for safety assessment at Weeks 12, 24, 48, 96 and early discontinuation (if applicable).

Women of childbearing potential will have a urine pregnancy test performed if clinically indicated (i.e. if menses are missed or a clinical suspicion of pregnancy) at Weeks 12, 24, 36, 48, 60, 72, 84, and 96.

Tropism assay will be done at the next visit when the preceding viral load is > 1,000 copies/ml.

Blood samples will be collected (Plasma and PBMCs) for archiving at Weeks 12, 24, 48, 96 and early discontinuation (ED) or virologic failure (VF) (if applicable) for potential future use

regarding virologic suppression/resistance, tropism assay, ultra-low copy assays, CCR5 density, lipid subfraction analyses and/or immunological markers associated with the HIV virus.

Blood samples will be collected at early discontinuation (if applicable) for possible resistance testing/tropism assay.

7.3.4 Virologic failure confirmation visit

This visit will occur at least 1 week following suspected virologic failure. Virologic failure is defined as:

- HIV RNA > 50 copies/ml confirmed on two separate occasions after viral suppression <50 copies/ml

Blood will be collected for the following:

- HIV RNA
- CD4 cell count
- Possible HIV resistance testing
- Possible HIV tropism testing
- Plasma/PBMC storage from subjects who are suspected of having virologic failure

7.3.5 Discontinuation/Withdrawal from the study

Subjects may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator if he/she violates the study plan or for administrative and/or other safety reasons. When a subject/patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 9 Safety. The subject will then be referred back to their primary care physician for determination of appropriate management of the patient's HIV infection.

Because there have been no adequate and well controlled studies of raltegravir/dolutegravir and maraviroc in pregnant women, if a patient becomes pregnant during the course of the study, the investigator, in consultation with the patient, should consider whether the potential benefit justifies the potential risk to the fetus of continuing the study therapy. If it is determined that the potential benefit does not outweigh the potential risk to the fetus, the patient should be discontinued from the study.

All pregnancies must be reported immediately. The outcome of all pregnancies must be reported. Subjects who become pregnant will be asked to join a pregnancy registry which collects information about the outcome of the pregnancy.

Should a subject develop evidence of dual or X4 tropism during the study, the patient will be removed from the study and placed on an appropriate antiretroviral regimen optimized using the

genotype obtained at study discontinuation. This could include use a combination of NRTIs, NNRTIs, and PIs as determined by the patient's primary HIV physician.

7.4 Clinical and research laboratory evaluations and specimen collection

The primary measurement for efficacy in the overall study is HIV RNA. Additional measurements for efficacy include CD4 counts and viral resistance testing. The key timepoint for evaluation of efficacy is Week 48.

Subjects will have ~560 mL (38 tablespoons) of blood drawn during the study. See study flow sheet for more detailed information.

Plasma HIV RNA determination will be performed by the same laboratory during the study unless that laboratory is no longer able to perform the needed assays.

To evaluate possible development of resistance to raltegravir/dolutegravir and maraviroc, blood samples will be collected/archived at Weeks 24, 48, at virologic failure confirmation visit, and at early discontinuation visit (if not already obtained at virologic failure confirmation visit) to assess resistance to raltegravir/dolutegravir and maraviroc.

8. Study schedule

Study procedures should be performed as close to the scheduled time as possible. See the study flow chart below for details:

STUDY VISIT	SCREEN	ENTRY	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	ED	VF
STUDY WEEK	-8 TO -2	0	2	4	6	8	10	12	16	20	24	36	48	60	72	84	96		
Obtain Informed Consent	X																		
Review Inclusion/ Exclusion Criteria	X		X			X			X		X		X				X		
Complete Medical History and Physical Examination	X												X				X	X	X
Directed Medical History and Physical Examination		X	X	X	X	X	X	X	X	X	X	X		X	X	X			
Complete Medication History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (serum)	X																		
Pregnancy test (urine)		X						⊗ ¹			⊗ ¹	⊗ ¹	⊗ ¹	⊗ ¹	⊗ ¹	⊗ ¹	⊗ ¹	⊗ ¹	⊗ ¹
Blood for Screening Labs: CBC with diff, Serum chemistry, LFT's, CK, Hep B ² , Hep C ² , HIV-1 ELISA/Western blot ²	⊗																		
Urinalysis	X																X	X	
HIV-1 RNA PCR	X	⊗	⊗	X	⊗	X	X	⊗	X	X	⊗	⊗	⊗	⊗	⊗	⊗	⊗	X	
CD4 Cell Count		⊗						⊗			⊗		⊗		⊗		⊗	X	
Blood for Safety Labs: CBC with diff, Serum chemistry, LFT's, CK		X	⊗		⊗			⊗			⊗	⊗	⊗	⊗	⊗	⊗	⊗	X	
Lipid Panel		⊗									⊗		⊗				⊗	X	
Tropism ³	X ³																	X ³	X ³
Genotype ⁴																		X ⁴	X ⁴
Blood for Serologic/PBMC Assays/Storage	X	X						X			X		X				X	X	X
Total blood volume (ml)	74-84 ml	69 ml	5 ml	5 ml	5 ml	16ml	5 ml	33ml	5 ml	13ml	61ml	13ml	69ml	13ml	16ml	13ml	69ml	79-84 ml	53-68 ml
Approximate Visit Duration (minutes)	60	60	20	20	20	20	20	30	20	20	30	20	60	20	20	20	60	60	60

Abbreviations: ED = Early Discontinuation; VF = Virologic Failure

Footnotes: ⊗ represent HIV standard of care blood draws; X represents research related tests/blood draws.

1. Pregnancy tests will be ordered if menses are missed or a clinical suspicion of pregnancy.
 2. HIV-1 ELISA/Western blot (HIV-1 antibody test) will only be done if documentation of either a) previously positive Elisa/Western blot test or b) 2 separate HIV-1 RNA viral loads ≥ 500 copies/ml cannot be obtained. Hepatitis B and C serologies will only be done if no prior documentation of results exists. Hepatitis B surface Antigen must have been done within the past 12 months unless there is evidence of immunity to hepatitis B (i.e. hepatitis B surface antibody positive).
 3. A trofile DNA test will be done during screening for patients with nadir CD4 250 – 499 if there is no trofile testing on record. Blood for tropism testing will be drawn at the follow-up visit after a first HIV VL is > 50 copies/ml (i.e. virologic failure confirmation visit) or at the early discontinuation visit if the prior VL is > 50 copies/ml. However, since assay sensitivity is poor if the viral load is $< 1,000$ copies/ml, the blood will be stored and only sent for testing if the VL returns $> 1,000$ copies/ml. Tropism will only be ordered at early discontinuation if the viral load is $> 1,000$ copies/ml.
 4. HIV resistance genotype (including genotype for integrase activity) will be done at early discontinuation or virologic failure confirmation if the prior VL is > 50 copies/ml.
- The virologic failure confirmation visit will occur if the viral load meets virologic failure criteria in the protocol. At that visit blood will be drawn for viral load, CD4 cell count, genotype, tropism, and pK trough for raltegravir/dolutegravir and maraviroc.

STUDY VISIT	SCREEN	ENTRY	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	ED	VF
STUDY WEEK	-8 TO -2	0	2	4	6	8	10	12	16	20	24	36	48	60	72	84	96		
Screening Labs: CBC with diff, Serum Chemistry, LFT's, CK Tropism, Hep B, Hep C ¹ HIV-1 ELISA/Western blot ¹	⊗																		
Blood for Safety Labs: CBC with diff, Serum Chemistry, LFT's, CK		X	⊗		⊗			⊗			⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗
Pregnancy Test (serum)	3 ml																		
HIV ELISA/Western Blot*	5 ml*																		
Hepatitis B/C Serologies*	5 ml*																		
HIV-1 RNA PCR	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml
CD4 Cell Count		3 ml						3 ml			3 ml		3 ml		3 ml		3 ml	3 ml	
CBC with diff	3 ml	3 ml	3 ml		3 ml			3 ml			3 ml	3 ml	3 ml	3 ml	3 ml	3 ml	3 ml	3 ml	3 ml
Serum Chemistry, LFT's, CK	5 ml	5ml	5 ml		5 ml			5 ml			5 ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml
Tropism ²	5 ml ²																	5 ml ²	5 ml ²
Genotype ²																		10 ml ³	10 ml ³
Lipid panel		3 ml									3 ml		3 ml				3 ml	3 ml	3 ml
Blood for Serologic /PBMC Assays/Storage	50 ml	50 ml						20 ml			50 ml		50 ml				50 ml	50 ml	50 ml
Total blood volume (ml)	66-81 ml	69 ml	13 ml	5 ml	13 ml	5 ml	5 ml	36 ml	5 ml	5 ml	69 ml	13 ml	69 ml	13 ml	16 ml	13 ml	69 ml	79-84 ml	53-68 ml

Abbreviations: ED = Early Discontinuation; VF = Virologic Failure

Footnotes: ⊗ represent HIV standard of care blood draws; X represents research related tests/blood draws.

* HIV ELISA/Western Blot and Hepatitis B and C serologies will only be done if the patient does not have documentation of previous studies. Hepatitis B serologies must have been done within the past 12 months.

1. HIV-1 ELISA/Western blot (HIV-1 antibody test) will only be done if documentation of either a) previously positive Elisa/Western blot test or b) 2 separate HIV-1 RNA viral loads ≥ 500 copies/ml cannot be obtained. Hepatitis B and C serologies will only be done if no prior documentation of results exists. Hepatitis B surface Antigen must have been done within the past 12 months unless there is evidence of immunity to hepatitis B (i.e. hepatitis B surface antibody positive).

2. A trofile DNA test will be done during screening for patients with nadir CD4 250 – 499 if there is no trofile testing on record. Blood for tropism testing will be drawn at the follow-up visit after a first HIV VL is > 50 copies/ml (i.e. virologic failure confirmation visit) or at the early discontinuation visit if the prior VL is > 50 copies/ml. However, since assay sensitivity is poor if the viral load is $< 1,000$ copies/ml, the blood will be stored and only sent for testing if the VL returns $> 1,000$ copies/ml. Tropism will only be ordered at early discontinuation if the viral load is $> 1,000$ copies/ml.

3. HIV resistance genotype (including genotype for integrase activity) will be done at early discontinuation or virologic failure confirmation if the prior VL is > 50 copies/ml.

The virologic failure confirmation visit will occur if the viral load meets virologic failure criteria in the protocol. It will occur at least 1 week following suspicion of virologic failure (viral load > 50). At that visit blood will be drawn for viral load, CD4 cell count, genotype, phenotype for integrase activity, tropism, and pK trough for raltegravir/dolutegravir and maraviroc

Total Blood Volume over whole study duration (96 weeks) for typical completion of study: 484-494 ml

9. Assessment of safety

9.1 Specification of safety parameters

Subjects will be asked about any adverse experiences/events during their clinic visits and the information will be recorded on the case report forms. Guidelines for grading the severity of adverse experiences are based on Division of Acquired Immunodeficiency Syndrome (DAIDS) criteria for grading severity of adverse events.

Decisions to temporarily withhold therapy because of an adverse experience will be reviewed on a case-by-case basis by the investigator.

The investigator should consider temporarily withholding therapy if the severity of the adverse experience is Grade 3 or above and/or if clinically indicated. The decision to interrupt therapy should take into account the subject's baseline laboratory values and any concomitant medication that could be contributory. At the discretion of the investigator, therapy may generally be reinitiated when laboratory abnormalities or clinical adverse events return to near normal or baseline values.

If after the re-initiation of study therapy, there is a recurrence of the laboratory abnormality or clinical adverse event, consideration should be given to permanently discontinuing all study therapy. In general, when a clinical or laboratory adverse event occurs which requires interruption of study therapy, all study drugs should be interrupted to avoid having a subject receive suboptimal therapy which may predispose them to the development of resistance. In general, all study medications should be restarted at full dose concomitantly.

9.2 Definition of an adverse event (AE)

An adverse event is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study drugs, whether or not considered related to the use of the drugs. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of study drugs, is also an adverse event.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to onset of menses or menopause occurring at a physiologically appropriate time in a woman.

Adverse events may occur in the course of the use of the study drugs in clinical studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse, and from withdrawal.

Adverse experiences may also occur in screened subjects during the baseline period as a result of a protocol-specified intervention including washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure. Such events will be recorded at each examination on the Adverse Event Case Report Forms/Worksheets.

9.3 Unexpected Adverse Event

An unexpected adverse event is defined as an adverse event that is not listed in the current investigator's brochure and includes an event that may be symptomatically and pathophysiologically related to a listed event, but differs in having greater severity or specificity.

9.4 Grading of Adverse Events

The severity of adverse events will be graded according to the Division of Acquired Immunodeficiency Syndrome (DAIDS) scale. Events or laboratory abnormalities not listed will be graded as follows:

- Grade 1/Mild: Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required.
- Grade 2/Moderate: Mild to moderate limitation in activity. Some assistance may be needed; minimal or no medical intervention and/or therapy required.
- Grade 3/Severe: Marked limitation in activity, some assistance usually required; medical intervention and/or therapy required, hospitalization possible.
- Grade 4/Life-Threatening: Extreme limitation in activity, significant assistance required; significant medical intervention and/or therapy required hospitalization or hospice care probable.

9.4.1 Relationship to Study Drug

The investigator will make a determination as to whether the adverse event is related to study drug or not. Relationship to the study drug will be categorized as "Definite," "Probable," "Possible," or "Definitely Not".

- DEFINITE – There is a strong relationship to the study drug. The adverse event:
 - Follows a reasonable temporal sequence to the study drug's administration.
 - The adverse event resolved once the study drug was discontinued (de-challenge).
 - The adverse event reappeared upon re-exposure to the study drug (re-challenge).
- PROBABLE – There may be a relationship to the investigational product. The adverse event:
 - Follows a reasonable temporal sequence from drug administration.
 - Demonstrates a clinically reasonable response pattern to discontinuation of the study drug.
 - Is unlikely to be attributed to concurrent disease, drugs or procedures.
 - Could not be reasonably explained by the known characteristics of the patient's clinical state.
- POSSIBLE – The relationship may or can exist, but other factors may also be implicated; if the relationship cannot be ruled out, it must be considered possible. The adverse event:
 - Follows a reasonable temporal sequence from study drug administration.
 - Could have been produced by the patient's clinical state, environmental and toxic factors, or by other modes of therapy administered to the patient.
 - Follows a known pattern of response to the suspected drug.

- **DEFINITELY NOT** – The adverse event is definitely produced by the patient’s clinical state or by other modes of therapy administered to the patient and is therefore unrelated to administration of the study drug.

9.5 Methods and timing for assessing, recording, analyzing, and managing safety parameters

Adverse events will be evaluated at each study visit, any unscheduled visits, virologic failure confirmation visit, and discontinuation/withdrawal from the study visits.

9.6 Stopping rules for the protocol

Four confirmed virologic failures (13%) will be considered grounds for stopping the study.

10. Clinical monitoring structure

10.1 Safety monitoring plan

The study will have regularly scheduled monitoring by the IHV Data and Safety Monitoring Board (DSMB) and follow its standard protocol. The first DSMB review will occur 6 months after the first subject is enrolled and then every 6 months after that. It will meet earlier if any concerns are raised by the Medical Monitor as to virologic failure, toxicity, or serious adverse experiences related to the study medication.

11. Data analysis and statistical considerations

11.1 Description of the analyses

The primary objective of this open-label single arm study is to describe the efficacy and safety of raltegravir/dolutegravir in combination with maraviroc in antiretroviral treatment experienced patients.

The statistical analyses will therefore be primarily descriptive. The primary endpoint is the proportion of patients virologically suppressed (< 50 copies/ml) at 48 weeks. All efficacy and safety analyses will provide estimates only; no formal comparisons will be made. All efficacy and safety endpoints will be summarized for the whole population.

11.2 Sample Size and Power Calculations

This is a pilot study in 30 patients to evaluate the novel combination of an integrase inhibitor (raltegravir/dolutegravir) and maraviroc. As it is a small pilot study, power calculations are not appropriate.

12. Ethics/protection of human subjects

12.1 Institutional review board (IRB)

The investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonization Good Clinical Practice (ICH-GCP) regulations and guidelines, whichever affords the greater protection to the subject.

IRB approval from the University of Maryland Baltimore will be obtained prior to initiation of this trial.

12.2 Informed consent process

Before screening the patients, all candidates will be informed in detail about the study drug to be administered, and the nature of the clinical investigation, with its risks and benefits. The elements of the Informed Consent will be followed. Written consent will be obtained from each patient to be involved in the clinical trial by using a modified version the University of Maryland's IRB-approved Informed Consent Form. Consent will be verified by the investigator, or a member of the trial staff. The investigator will provide each patient with a signed copy of the informed consent, and a signed copy of the original will be placed in the study file. The patient will also be informed that they are free to withdraw their consent and discontinue their participation in the study at any time without penalty. Premature withdrawal from the study will not alter the patient's entitlement to care at any hospital/clinic supported by the Institute of Human Virology/University of Maryland.

12.3 Participant privacy and confidentiality

Confidentiality will be protected in the following ways: Limited use of identifiers beyond that needed for the study. Data abstraction sheets will be kept in a locked cabinet in a locked office at the clinical trials unit of the IHV. Data will be entered into a password protected file on a password protected computer.

Privacy will be protected by limiting any discussions with subjects to private or semi-private rooms. Stored blood for future research will only use the study identification number with no personal health information. Through each phase of the study, privacy protections will be maintained. Only the PI and study staff will have access to identifying data. Stored blood for future research will only use the study identification number with no personal health information.

13. Publication plan

It is expected that the results of the study would be presented at an infectious disease/HIV conference (e.g. CROI, IDSA/ICAAC, or IAS/IAC). It is anticipated that the study will generate 1-3 abstracts. We anticipate that the study will generate 1-2 manuscripts which will be submitted to a journal such as *AIDS*, *Clinical Infectious Diseases*, or other journals of a similar caliber. It is anticipated that a manuscript would be submitted within 6 months of completion of the final analysis of the study data.

References

1. Moyle G. Metabolic issues associated with protease inhibitors. *J Acquir Immune Defic Syndr*. 2007;45 Suppl 1:S19-26.
2. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356(17):1723-1735.
3. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. 2008;371(9622):1417-1426.
4. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS*. 2008;22(14):F17-24.
5. Lang S, Mary-Krause M, Cotte L, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med*. 2010;170(14):1228-1238.
6. Young J, Schafer J, Fux CA, et al. Renal function in patients with HIV starting therapy with tenofovir and either efavirenz, lopinavir or atazanavir. *AIDS*. 2012;26(5):567-575.
7. Leeansyah E, Cameron PU, Solomon A, et al. Inhibition of telomerase activity by human immunodeficiency virus (HIV) nucleos(t)ide reverse transcriptase inhibitors: a potential factor contributing to HIV-associated accelerated aging. *J Infect Dis*. 2013;207(7):1157-1165.
8. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. 2008;358(20):2095-2106.
9. Allavena C, Mounoury O, Rodallec A, Reliquet V, Billaud E, Raffi F. Efficacy and safety of an NRTI-sparing dual regimen of raltegravir and ritonavir-boosted protease inhibitor in a triple antiretroviral class-experienced population. *HIV Clin Trials*. 2009;10(5):337-340.
10. Nozza S, Galli L, Visco F, et al. Raltegravir, maraviroc, etravirine: an effective protease inhibitor and nucleoside reverse transcriptase inhibitor-sparing regimen for salvage therapy in HIV-infected patients with triple-class experience. *AIDS*. 2010;24(6):924-928.
11. Kozal MJ, Lupo S, DeJesus E, et al. A nucleoside- and ritonavir-sparing regimen containing atazanavir plus raltegravir in antiretroviral treatment-naïve HIV-infected patients: SPARTAN study results. *HIV Clin Trials*. 2012;13(3):119-130.
12. Ofotokun I, Sheth AN, Sanford SE, et al. A switch in therapy to a reverse transcriptase inhibitor sparing combination of lopinavir/ritonavir and raltegravir in virologically suppressed HIV-infected patients: a pilot randomized trial to assess efficacy and safety profile: the KITE study. *AIDS Res Hum Retroviruses*. 2012;28(10):1196-1206.
13. Lee FJ, Carr A. Tolerability of HIV integrase inhibitors. *Curr Opin HIV AIDS*. 2012;7(5):422-428.
14. Wasmuth JC, Rockstroh JK, Hardy WD. Drug safety evaluation of maraviroc for the treatment of HIV infection. *Expert Opin Drug Saf*. 2012;11(1):161-174.
15. Gilliam BL, Riedel DJ, Redfield RR. Clinical use of CCR5 inhibitors in HIV and beyond. *J Transl Med*. 2011;9 Suppl 1:S9.
16. Moyle GJ, Wildfire A, Mandalia S, et al. Epidemiology and predictive factors for chemokine receptor use in HIV-1 infection. *J Infect Dis*. 2005;191(6):866-872.

17. Hunt PW, Harrigan PR, Huang W, et al. Prevalence of CXCR4 tropism among antiretroviral-treated HIV-1-infected patients with detectable viremia. *J Infect Dis.* 2006;194(7):926-930.
18. Wilkin TJ, Su Z, Kuritzkes DR, et al. HIV type 1 chemokine coreceptor use among antiretroviral-experienced patients screened for a clinical trial of a CCR5 inhibitor: AIDS Clinical Trial Group A5211. *Clin Infect Dis.* 2007;44(4):591-595.
19. Hoffmann C. The epidemiology of HIV coreceptor tropism. *Eur J Med Res.* 2007;12(9):385-390.
20. Huang W, Eshleman SH, Toma J, et al. Coreceptor tropism in human immunodeficiency virus type 1 subtype D: high prevalence of CXCR4 tropism and heterogeneous composition of viral populations. *J Virol.* 2007;81(15):7885-7893.
21. Kaleebu P, Nankya IL, Yirrell DL, et al. Relation between chemokine receptor use, disease stage, and HIV-1 subtypes A and D: results from a rural Ugandan cohort. *J Acquir Immune Defic Syndr.* 2007;45(1):28-33.
22. Church JD, Huang W, Mwatha A, et al. HIV-1 tropism and survival in vertically infected Ugandan infants. *J Infect Dis.* 2008;197(10):1382-1388.
23. McGovern RA, Thielen A, Mo T, et al. Population-based V3 genotypic tropism assay: a retrospective analysis using screening samples from the A4001029 and MOTIVATE studies. *AIDS.* 2010;24(16):2517-2525.
24. Poveda E, Paredes R, Moreno S, et al. Update on clinical and methodological recommendations for genotypic determination of HIV tropism to guide the usage of CCR5 antagonists. *AIDS Rev.* 2012;14(3):208-217.
25. MacArthur RD, Novak RM. Reviews of anti-infective agents: maraviroc: the first of a new class of antiretroviral agents. *Clin Infect Dis.* 2008;47(2):236-241.
26. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. February 12, 2013. Available at <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed May 2, 2013.
27. Boesecke C, Pett SL. Clinical studies with chemokine receptor-5 (CCR5)-inhibitors. *Curr Opin HIV AIDS.* 2012;7(5):456-462.
28. Maeda K, Das D, Nakata H, Mitsuya H. CCR5 inhibitors: emergence, success, and challenges. *Expert Opin Emerg Drugs.* 2012;17(2):135-145.
29. Hicks C, Gulick RM. Raltegravir: the first HIV type 1 integrase inhibitor. *Clin Infect Dis.* 2009;48(7):931-939.
30. Shamroe CL, Bookstaver PB, Rokas KE, Weissman SB. Update on raltegravir and the development of new integrase strand transfer inhibitors. *South Med J.* 2012;105(7):370-378.
31. Rokas KE, Bookstaver PB, Shamroe CL, et al. Role of raltegravir in HIV-1 management. *Ann Pharmacother.* 2012;46(4):578-589.
32. Cordery DV, Hesse K, Amin J, Cooper DA. Raltegravir and unboosted atazanavir dual therapy in virologically suppressed antiretroviral treatment-experienced HIV patients. *Antivir Ther.* 2010;15(7):1035-1038.
33. Taiwo B, Zheng L, Gallien S, et al. Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naive HIV-1-infected patients (ACTG A5262). *AIDS.* 2011;25(17):2113-2122.

34. Reynes J, Lawal A, Pulido F, et al. Examination of noninferiority, safety, and tolerability of lopinavir/ritonavir and raltegravir compared with lopinavir/ritonavir and tenofovir/emtricitabine in antiretroviral-naive subjects: the progress study, 48-week results. *HIV Clin Trials*. 2011;12(5):255-267.
35. Karmon SL, Markowitz M. Next-generation integrase inhibitors : where to after raltegravir? *Drugs*. 2013;73(3):213-228.
36. HHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Recommendation on integrase inhibitor use in antiretroviral treatment-naive HIV-infected individuals. October 30, 2013; http://aidsinfo.nih.gov/contentfiles/AdultARV_INSTIREcommendations.pdf. Accessed February 10, 2014.
37. Nozza S, Galli L, Bigoloni A, et al. Durability and safety of a novel salvage therapy in R5-tropic HIV-infected patients: maraviroc, raltegravir, etravirine. *J Acquir Immune Defic Syndr*. 2011;56(4):e113-115.
38. Katlama C, Assoumou L, Valantin MA, et al. Maraviroc plus raltegravir failed to maintain virological suppression in HIV-infected patients with lipohypertrophy: results from the ROCnRAL ANRS 157 study. *J Antimicrob Chemother*. 2014;69(6):1648-1652.
39. Croce F, Vitello P, Dalla Pria A, Riva A, Galli M, Antinori S. Severe raltegravir-associated rhabdomyolysis: a case report and review of the literature. *Int J STD AIDS*. 2010;21(11):783-785.
40. Lee FJ, Amin J, Bloch M, Pett SL, Marriott D, Carr A. Skeletal muscle toxicity associated with raltegravir-based combination anti-retroviral therapy in HIV-infected adults. *J Acquir Immune Defic Syndr*. 2012.