Appendix Material

Allogeneic Bone Marrow Transplant for HIV Patients with Hematologic Malignancies with Post-transplant Cyclophosphamide: a Feasibility Study

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PROTOCOL SYNOPSIS

Optimized antiretroviral therapy during allogeneic hematopoietic stem cell transplantation in HIV-1-infected individuals

Principal Investigators: Richard Ambinder, M.D., Ph.D., and Christine Durand, M.D.

Primary Outcomes: The primary outcome is the fraction of patients who maintain antiretroviral therapy (ART), through day 60 of allogeneic hematopoietic stem cell transplant (alloHSCT).

Secondary Outcomes:

1. Frequency of resting $CD4_+$ T cells harboring infectious HIV-1 at baseline, then every 12 weeks through study end
2. Copies of HIV-1 DNA per million peripheral blood mononuclear cells at baseline, weeks 4, 8, and 12, then every 12 weeks through study end
3. Plasma HIV-1 RNA at baseline, weeks 4, 8, and 12, then every 12 weeks through study end and weekly during any periods of enfuvirtide monotherapy
4. Donor chimerism at weeks 4, 8, and 12, then every 12 weeks through study end
5. Describe the incidence and severity of graft-versus-host disease
6. Describe the incidence and severity of reactions to enfuvirtide

Accrual Objective: The trial will accrue 20 patients.

Eligibility Criteria: Patients ≥ 18 years old, HIV-infected who plan to undergo alloHSCT, for a standard clinical indication, including:

a) Myeloablative, HLA matched or partially HLA-mismatched (haploidentical), alloHSCT
b) Nonmyeloablative, HLA matched or partially HLA-mismatched, alloHSCT

Treatment Description: A multi-faceted approach to maintain ART through alloHSCT will be implemented, wherein:

a) An optimized oral ART regimen will be determined by a multidisciplinary team prior to transplant and all attempts will be made to maintain this regimen through transplant.
b) The subcutaneous antiretroviral enfuvirtide will be added during any periods when oral ART cannot be tolerated.
c) If patients are on enfuvirtide alone, this will be considered maintenance of ART.
d) Failure to maintain ART is defined as ≥ 24 hours without any antiretroviral agents.

Study Duration: Patients will be followed for 2 years following alloHSCT.

Stopping Rule: Safety: More than one Grade 3 adverse event related to enfuvirtide.

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CHAPTER 1

1.0 BACKGROUND AND RATIONALE

1.1 Background

Individuals with HIV-1 infection are now living longer due to effective antiretroviral therapy (ART). Consequently, cancer diagnoses are increasing in this population, and in the post-ART era, more than 25% of deaths are related to cancer.[1] Hematologic malignancies such as non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and acute myelogenous leukemia (AML) account for more than one third of cancers in this population.[2] HIV-1-infected patients treated with standard chemotherapy now achieve long-term lymphoma-free survival comparable to that in individuals without HIV-1 infection.[3] However standard guidelines developed in an earlier era for lymphoma salvage therapy and leukemia therapy with hematopoietic stem cell transplantation (HSCT) excluded HIV-1-infected patients. The improvements afforded by ART on functional and immunologic parameters in HIV-1-infected patients, have provided an opportunity to extend therapeutic options for hematologic malignancies and myelodysplastic syndromes to HIV-1-infected individuals.

1.2 Autologous Stem Cell Transplantation in HIV-1-infected individuals

Several trials have demonstrated that autologous HSCT (autoHSCT) is safe and effective therapy in HIV-1-infected patients with primary refractory or relapsed lymphoma. Treatment-related complications appear to be comparable to those seen in the non-HIV-infected patient population[4-9].

1.3 Allogeneic Stem Cell Transplantation in HIV-1-infected individuals

The experience with allogeneic HSCT (alloHSCT) is more limited. The largest retrospective study includes 23 patients from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry. Only 2 of 14 individuals who received alloHSCT prior to 1996 survived, whereas 4 of 9 patients transplanted after 1996 survived.[10] A recent literature review of all published reports of alloHSCT in HIV-1-infected patients includes 56 cases. The survival was less than 15% in the pre-ART era compared to a survival of greater than 50% in the post-ART era.[11] We reviewed the literature for reports of alloHSCT in HIV-1-infected patients on ART with HIV-1 RNA levels less than 200 copies/mL plasma, shown in Table 1. Seventeen cases were identified with 11/17 alive at six months. Three of the six deaths were due to tumor relapse.

Table 1 Cases of alloHSCT in HIV-1-infected patients on suppressive ART

Patient	Tumor[a]	Donor	Follow-up, months, cause of death	Ref
1	NHL	Related, matched	Died, 12 mos, relapse	12
2	NHL	Related, gene modified	Alive 39 mos	13
3	ALL	Unrelated, matched	Alive 15 mos	14
4	AA	Unrelated, matched	Alive 8 mos	15
5	AML	Unrelated, matched	Died, 6 mos, sepsis	16
6	PEL	Related, matched	Alive 31 mos	17
7	AML	Unrelated, matched	Died, 11 mos, relapse	18
8	AML	Unrelated, matched	Alive, 6 mos	18
9	NHL	Related, matched	Alive, > 12 mos	19
10	NHL	Unrelated, matched	Alive, > 12 mos	19
11	AML	Unrelated, CCR5Δ32	Alive, > 60 mos	20
12	MDS	Unrelated, matched	Died, renal failure	21

13	AML	Related, matched	Died, sepsis	21
14	T-ALL	Unrelated, matched	Died, relapse	21
15	AA	Unrelated, matched	Alive, > 12 mos	22
16	AML	Related, matched	Alive, 21 mos	23
17	AML	Not reported	Alive, 12 mos	24

[a]AML – acute myeloid leukemia, NHL – Non-Hodgkin's lymphoma, ALL – acute lymphoid leukemia, AA – aplastic anemia, PEL– primary effusion lymphoma, MDS- myelodysplastic syndrome, T-ALL – T cell acute lymphoblastic leukemia

In the CIBMTR series, primary engraftment and rates of acute and chronic graft versus host disease (GVHD) were comparable to that seen in HIV-1-negative patients.[10] In summary, these data suggest alloHSCT is feasible for HIV-1-infected patients and in patients on effective ART, outcomes are likely comparable to HIV-uninfected individuals.

1.4 Effect of Allogeneic Hematopoietic Stem Cell Transplantation on HIV-1 Reservoirs

HIV-1 persists in a latent form in memory CD4+ T cells despite ART,[25-28] and this hematopoietic reservoir is the best-described obstacle to cure.[29] Recently, there has been significant interest in the potential of alloHSCT to eradicate HIV-1 reservoirs. In 2009, the New England Journal of Medicine reported the case of an HIV-1-infected individual, now widely known as "the Berlin patient," who was treated for AML with myeloablative chemotherapy and alloHSCT from a donor with genetic resistance to HIV-1 infection.[20] It had long been known that about 1% of Caucasians are homozygous for the mutation known as CCR5Δ32.[30] This mutation results in lack of expression of the cell surface chemokine receptor CCR5, used by HIV-1 to infect cells, and consequently confers high-level resistance to HIV-1 acquisition.[31, 32] This knowledge was used to select a CCR5Δ32 homozygous donor among over 60 HLA-matched unrelated donors. In 2007, the Berlin patient received an alloHSCT from the rare donor; ART was stopped at the time of alloHSCT and there is no evidence of HIV-1 infection.[33, 34] This approach has not been duplicated in the context of alloHSCT due to difficulty in identifying CCR5Δ32 HLA-matched donors.

AlloHSCT may be capable of eradicating HIV-1 reservoirs without the use of HIV-1-resistant donors. In the process of alloHSCT, all host hematopoietic cells are killed and replaced. This is achieved in part by cytotoxic conditioning chemotherapy and in part, by the allogeneic effect of donor CD8+ lymphocytes that kill host hematopoietic cells. The importance of the allogeneic effect has been recognized as a critical component of alloHSCT over the past several decades and underlies GVHD and graft-versus-tumor effects. It is likely that elimination of HIV-1 reservoirs in the Berlin patient was due in part to a "graft-versus-reservoir" effect afforded by the allogeneic effect.

If HIV-1 reservoirs are eliminated due to the allogeneic effect, this should apply to all cases of alloHSCT in which full donor chimerism is achieved. Small amounts of residual HIV-1 are likely present during the engraftment process; thus, to achieve eradication, the donor cells need to be protected from acquiring HIV-1 during this critical period. In the Berlin patient, the donor cells were protected by the CCR5Δ32 mutation. In the context of alloHSCT without resistant donors, ART may provide the same protection, just as ART prevents HIV-1 acquisition *in utero*, or prior to a high-risk exposure. Support for the hypothesis that alloHSCT and ART might cure HIV-1 is provided by a recent report at International AIDS Society (IAS) conference that peripheral blood HIV-1 reservoirs became undetectable in two individuals who received non-myeloablative alloHSCT on effective ART.[35] ART has not been interrupted in these cases and further studies are needed to confirm whether lack of detection of HIV-1 in these individuals is due to a dilutional effect from the influx of donor cells or whether eradication is truly complete.

1.5 Antiretroviral therapy during allogeneic hematopoietic stem cell transplantation

If the allogeneic effect can eradicate HIV-1 reservoirs, maintaining ART throughout alloHSCT to protect the graft/donor cells will be critical. In clinical practice, the standard of care – that is maintenance of effective ART – is often not achieved in the setting of alloHSCT. ART interruptions are frequent due to serious drug-drug interactions and due to intolerance of oral medications in the setting of mucositis, nausea and vomiting related to chemotherapy.

Excluding the Berlin patient[20] there have been 16 cases of alloHSCT in patients on suppressive ART published in the literature (see Table 1). Of these patients, 7 stopped ART during the process of or shortly after alloHSCT; all of these patients had rebound of HIV-1 viremia. Two of these patients also developed a clinical syndrome identical to the acute retroviral syndrome of primary HIV-1 infection, indicating acute infection of donor cells.[12, 36] Of the 9 patients reported in the literature that remained on ART throughout alloHSCT, data on HIV-1 reservoirs/HIV-1 persistent is reported only in 2 patients.[18] One patient had undetectable HIV-1 in peripheral blood mononuclear cells (PBMCs) but died due to tumor relapse.[18] The other patient was found to have HIV-1 detected in PBMCs but this patient did not achieve full donor chimerism; presumably the HIV-1 detected was present in residual recipient cells though this was not specifically addressed in the study.[18] Interestingly, there has also been a report that HIV-1 reservoirs disappeared in two HIV-1-infected patients who received alloHSCT from standard donors, achieved full donor chimerism, and remained on ART.[35] These fascinating cases support the hypothesis that the allogeneic effect in conjunction with continued ART could lead to HIV-1 cure.

The goal of this trial is to determine whether maintaining ART throughout alloHSCT is feasible using a combination of FDA approved antiretrovirals including the subcutaneous antiretroviral medication enfuvirtide. The optimal combination of antiretrovirals that will be used for each patient will be determined by a multidisciplinary team of HIV-1 and oncology experts based on the patient's specific treatment history. Criteria used in selecting the optimal ART regimen include (1) avoidance of serious drug-drug interactions, (2) achieving maximum potency, (3) achieving maximum tissue penetration, (4) inclusion of antiretroviral drugs with long half-lives to maximize antiviral activity in the event of a few missed doses due to mucositis, nausea or vomiting and (5) the use of a subcutaneous anti-HIV-1 medication, enfuvirtide, during any periods when oral medications cannot be tolerated (e.g. nausea and vomiting or mucositis) and also during any other periods of oral medication intolerance. More details regarding each of these selection criteria are provided below. The primary outcome will be the fraction of patients who are able to maintain ART through day 60 of alloHSCT. For the purposes of this study, continued administration of subcutaneous enfuvirtide alone even if oral ART is not tolerated is considered maintenance of ART. Failure to maintain ART is defined as a period of > 24 hours when a patient does not receive any antiretroviral medication, including enfuvirtide injections. Justification for the temporary use of enfuvirtide monotherapy is provided below (section: subcutaneous enfuvirtide).

Avoiding drug interactions. Approved antiretroviral drugs to treat HIV-1 infection fall into the following classes: nucleoside or nucleotide analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), fusion inhibitors, and entry inhibitors. Interactions between ART and drugs used in alloHSCT are primarily due to the PIs, as a result of potent inhibition of cytochrome P450 enzyme system, which also metabolize antineoplastic agents and immunosuppressants.[37] In clinical practice, PI-containing regimens are interrupted during myeloablative conditioning and during the use of high-dose cyclophosphamide. The optimal ART regimen will exclude PIs whenever possible as these agents cause definite interactions that are difficult to manage. Alternative agents such as raltegravir, maraviroc, tenofovir, or other medications as determined by the ART regimen team will be used in place of PIs.

Potency. Within the HIV-1 field, there has been considerable debate regarding whether or not ART can completely inhibit HIV-1 replication.[38] Standard ART includes three active antiretroviral agents. Several "intensification" trials of four and five active antiretroviral combinations have been tried. Generally,

these studies have not measure a significant impact of intensified ART using standard measure of plasma HIV-1 RNA or other markers of immunologic activation. However, two studies have shown that the addition of the integrase inhibitor, raltegravir, to standard ART regimens results in a reduction in the detection of cell-associated 2 LTR circles, a proposed marker of recent HIV-1 infection,[39, 40] suggesting that perhaps ART intensification may further reduce single-round infection events that may or may not be clinically relevant. In the context of alloHSCT, if HIV-1 eradication is a theoretical goal, inhibiting even single-round infection events is critical. Therefore, optimal ART in this setting will be intensified if possible with agents such as raltegravir and maraviroc which do not interact with antineoplastic or immunosuppressant drugs.

Penetration. Some data suggest that there is differential penetration of antiretroviral agents within anatomic sanctuary sites, including lymphoid and gastrointestinal tissues.[41] Again, in the context of alloHSCT, if HIV-1 eradication is a theoretical goal, obtaining maximal penetration of antiretrovirals at the tissue level will be critical. Two antiretroviral agents, the integrase inhibitor, raltegravir[42] and the CCR5 antagonist, maraviroc[43] have been shown to have excellent penetration into these sites and have not been observed to interact with antineoplastic and immunosuppressive agents.[37] These agents may constitute a component of optimal ART in this trial if possible.

Maximum half-lives. The optimal ART regimen will preferentially include antiretroviral medications with longer half-lives, specifically efavirenz and tenofovir, $t_{1/2}$ 36-100 hours and 12-50 hours respectively. This will maximize exposure to antiretroviral activity in the event of a few missed doses.

Subcutaneous enfuvirtide. The HIV-1 fusion inhibitor enfuvirtide (T20, Fuzeon), will be administered as needed during periods of nausea and vomiting, and during any other periods when oral medications cannot be tolerated, e.g. periods of severe mucositis. Enfuvirtide or T20, is the only available non-oral antiretroviral approved for treatment of HIV-1 infection, besides the intravenous form of zidovudine (AZT) which is contraindicated during alloHSCT due to bone marrow suppression.[37]

In most cases, enfuvirtide monotherapy is not sufficiently potent to suppress active viral replication in most patients; however we believe that the temporary use of enfuvirtide monotherapy in patients undergoing alloHSCT population is justified for several reasons. First, it has been demonstrated ART simplification to less potent regimens, such as protease inhibitor monotherapy, is effective; this suggests that less antiretroviral activity is required to maintain viral suppression compared to the amount of antiretroviral activity required to induce viral suppression. Second, patients undergoing alloHSCT are likely to be profoundly lymphopenic due to conditioning chemotherapy; viral dynamic theory states that the amount of viral replication is directly related to the number of lymphocytes. Therefore in cytopenic patients with already suppressed plasma HIV-1 RNA levels, there should be less viral replication to inhibit.

During any periods of enfuvirtide monotherapy, weekly viral loads will be measured using real-time PCR with a sensitivity of 20 copies HIV-1 RNA per milliliter of plasma. If there is virologic failure/breakthrough, defined as 2 consecutive measures of > 200 copies HIV-1 RNA/mL, enfuvirtide will be discontinued. The patient would then be off all antiretroviral medications and this would be considered a failure to maintain ART. Enfuvirtide monotherapy does present the risk of development of enfuvirtide resistance. In clinical trials of enfuvirtide monotherapy, it took 14 days for resistance to develop.[44] In this clinical trial, we anticipate the use of enfuvirtide monotherapy on the order of days. If virologic failure is observed with this strategy, resistance testing for enfuvirtide will be performed. If resistance does develop it is highly unlikely to compromise future management of the patient's HIV infection; enfuvirtide is rarely used in clinical practice due to the availability of many other oral antiretrovirals and there is no cross-resistance between enfuvirtide and other antiretroviral classes.

2. OBJECTIVES

2.1 Primary objective

Determine the feasibility of maintaining optimal ART in HIV-1 infected patients during alloHSCT, wherein:

a) The primary outcome is the fraction of patients who maintain any form of antiretroviral therapy through day 60 post-transplant.
b) If patients are unable to take oral antiretroviral medications, but are able to tolerate subcutaneous enfuvirtide monotherapy this will be considered maintenance of ART.
c) Failure to maintain ART will be defined as > 24 hours without any antiretroviral therapy.

2.2 Secondary objectives

1. Measure the frequency of resting $CD4_+$ T cells harboring infectious HIV-1 at baseline, then every 12 weeks through study end
2. Measure the copies of HIV-1 DNA per million peripheral blood mononuclear cells at baseline, weeks 4, 8, and 12, then every 12 weeks through study end
3. Measure plasma HIV-1 RNA level at baseline, weeks 4, 8, and 12, then every 12 weeks through study end and weekly during any periods of enfuvirtide monotherapy
4. Determine donor chimerism at weeks 4, 8, and 12, then every 12 weeks through study end
5. Describe the incidence and severity of acute and chronic graft-vs-host disease
6. Describe the incidence and severity of injection site reactions due to enfuvirtide.

3. SELECTION OF PATIENTS AND DONORS

1. HIV-1 infection, as documented by a rapid HIV-1 test or any FDA-approved HIV-1 enzyme or chemiluminescence immunoassay (E/CIA) test kit and confirmed by western blot at any time prior to study entry. Alternatively, two HIV-1 RNA values > 200 copies/mL at least 24 hours apart performed by any laboratory that has CLIA certification, or its equivalent may be used to document infection.

2. Patients must be ≥ 18 years of age.

3. Eligible participants will only be transplanted for standard clinical indications, which include hematologic malignancies such as acute leukemia, high risk lymphoma, and multiple myeloma. Much less commonly there are non-malignant indications for transplants; these include aplastic anemia and severe hemoglobinopathies. No patients will be transplanted for the primary purpose of HIV eradication. Patients will undergo one of the following types of transplant:
   a) Myeloablative, HLA matched or partially HLA-mismatched (haploidentical), alloHSCT that includes high-dose post-transplantation Cy.
   b) Nonmyeloablative, HLA matched or partially HLA-mismatched, alloHSCT that includes high-dose post-transplantation Cy.

4. Signed Informed Consent.

3.2 Patient Exclusion Criteria

1. Patients with a history of enfuvirtide resistance.

4.0 REGISTRATION PROCEUDRES

4.1 Registration requirements

Patients will be registered in the CRMS. The following are additionally required:

- Signed and dated informed consent
- Patient eligibility checklist

A registration may be cancelled, provided that protocol treatment has not begun.

4.2 Accrual goal

The goal is to enroll up to 20 patients to receive optimized ART during alloHSCT. Every effort will be made to recruit women and minorities to this study.

5.0 TREATMENT PLAN

5.1 Overview of study design

This is a one arm single institution study. HIV-1 infected patients undergoing alloHSCT are eligible. Dual enrollment in other study protocols is allowed. A multidisciplinary team will select an optimal ART regimen and every effort will be made to maintain this oral ART regimen through day 60 day post-alloHSCT. In addition, the subcutaneous antiretroviral, enfuvirtide, will be added during any periods when oral medications cannot be tolerated for any reason (e.g. nausea and vomiting or mucositis).

5.2 Optimal antiretroviral therapy for HIV-1 infection

5.21 Optimal ART regimen

A multidisciplinary team will review each patient and determine the optimal baseline ART regimen to institute. This regimen will generally include some or all of the following: raltegravir 400 mg po twice daily, maraviroc 600 mg twice daily, and atripla one tablet daily (co-formulated efavirenz 600 mg, tenofovir 300 mg and emtricitabine 200 mg) in order to minimize drug-drug interactions, maximize potency and penetration, and include components with long half-lives to maximize antiviral activity in the event of missed doses. Alternative antiretrovirals may need to be added or substituted as determined by the multidisciplinary team depending on patient specific factors.

All attempts will be made to avoid the use of ritonavir-boosted protease inhibitors due to serious drug-drug interactions. If the patient has history of treatment failure and/or genotypes that suggest inclusion of the protease inhibitor is absolutely necessary to maintain control of HIV-1 replication, the use of protease inhibitors will be allowed. ART regimens that include ritonavir-boosted PIs are discontinued 96 hours prior to conditioning and resumed after conditioning for the following regimens: all myeloablative conditioning regimens and reduced-intensity conditioning regimens that contain busulfan and fludarabine. ART regimens that include ritonavir-boosted PIs must also be held during the use of high dose cyclophosphamide (Cy) and for 24 hours following Cy. Subcutaneous enfuvirtide can be administered during this time. Additional dosing considerations related to the use of tacrolimus and PIs is outlined in Appendix B.

5.22 Addition of Enfuvirtide

The plan is to maintain oral ART at all times if possible. Enfuvirtide 90 mg subcutaneously twice daily will be administered to patients during any periods when oral medications are not tolerated due to mucositis or nausea and vomiting. In these cases, enfuvirtide will be discontinued based on improved clinical status, i.e. when the patient has not had vomiting

for > 24 hours, and has successfully resumed oral antiretrovirals for >24 hours. Enfuvirtide can also be used during periods when oral ART or components of ART are held due to drug-drug interactions or organ toxicities.

6.0 MEASUREMENT OF EFFECT AND ENDPOINTS

6.1 Definition of maintenance of ART:

The primary outcome will be maintenance of ART, wherein:

a) A multidisciplinary team will select an optimized baseline oral ART regimen
b) All attempts will be made to maintain this oral ART regimen through day 60 of transplant
c) Subcutaneous enfuvirtide will be added during any periods of nausea and vomiting and when oral ART is not tolerated (e.g. mucositis).
d) If participants are unable to take oral ART but are maintained on subcutaneous enfuvirtide alone, this will be considered maintenance of ART.
e) Failure to maintain ART will be defined as ≥24 hours without any antiretroviral therapy

6.11 Inpatient Adherence Monitoring: During any periods that patients are admitted to the hospital, ART doses will be directly observed and documented**.**

6.12 Outpatient Adherence Monitoring: During any periods that patients are in IPOP or are outpatients, adherence will be assessed by questioning regarding missed doses and adherence to ART. A member of the study team will speak to the patient in-person or by phone at least monthly from baseline screening through Week 52 to assess adherence to ART. Documentation of ART adherence will be made in the medical record.

Virologic parameters

An overview of planned analyses and general laboratory methodologies are provided below. Modification of the planned methodologies described here may be made as appropriate.

6.21 Frequency of resting CD4+ T cells harboring infectious HIV-1: Resting $CD4^+$ T cells will be isolated from 120 mL blood using monoclonal antibodies conjugated to magnetic Beads. Cells will be plated in limiting dilution format and HIV-1 RNA production is stimulated using mitogen phytohemagglutin and irradiated allogeneic peripheral blood mononuclear cells from a healthy donor.[46] Cells from the MOLT 4/CCR5 T lymphoblastoid cell line will be added as target cells to allow growth of virus released from $CD4^+$ T cells.[47] Virus growth will be detected by enzyme-linked immunosorbent assay for p24 antigen in the supernatant. The frequency of cells harboring infectious virus will be determined by the maximum likelihood method and expressed as Infectious Units per Million cells (IUPM).[48]

6.22 Copies of HIV-1 DNA per million peripheral blood mononuclear cells: PBMC-associated HIV-1 DNA will be quantified using real-time PCR which can detect 2 copies of HIV-1 DNA/10^5 cells.[49]

6.23 Copies of HIV-1 RNA in plasma: Copies of HIV-1 RNA in plasma will be measure by two assays. The currently used clinical assay, COBAS AMPLICOR Monitor test version 2·0 (Roche Molecular Diagnostics) with a lower limit of detection of 20 copies of HIV-1 RNA/mL of plasma, will be used as a first screen. If <20 copies of HIV-1 RNA are detected by the COBAS assay, a more sensitive real-time reverse transcriptase PCR assay that detects residual plasma

HIV-1 RNA in patients on ART down to one copy per ml, known as the single copy assay (SCA) will be performed.[50, 51]

6.3 Donor chimerism

Prior to transplantation, a sample of peripheral blood from the patient, and either harvested bone marrow or blood from the donor, are collected for genetic studies to establish a baseline for subsequent chimerism assays. See section 7 for the schedule of planned collections.

Donor chimerism from T-cells (CD3+ sorted) and whole blood (total nucleated cells) from the peripheral blood will be determined. The method uses a highly informative set of microsatellites or short tandem repeats (ABI, AmpflSTR) to distinguish donor from recipient. The limit of detection is approximately 1% using an optimized computer interpretation algorithm. If appropriate, other cell compartments may be sorted and the degree of chimerism analyzed. Chimerism may also be determined from the bone marrow, but follow-up bone marrow biopsies are not required.

6.4 Graft-versus-host disease

Acute GVHD is graded by the Keystone criteria.[52] Chronic GVHD is graded by NIH consensus criteria[53] and Seattle criteria[54]

6.5 Injection site reactions to enfuvirtide

After enfuvirtide administration the injection site will be checked by the administering nurse for any reaction. If there is a reaction noted, a member of the study team will evaluate and document injection site reactions to enfuvirtide using a scale developed by the AIDS Clinical Trial Group). Specifically, the level of discomfort, area of erythema, induration, pruritis, nodule/cyst formation, and bruising will be recorded. See Appendix A for the report form with the parameters that will be measured to assess the injection site reactions. Photographs will be taken of the injection site. Permission for this is included in the study informed consent.

To document the injection site reaction, usually two photographs will be taken. One will typically be a close-up view of the injection site. The photograph should include a millimeter ruler to demonstrate the size of the reaction. A second photograph will typically be a medium view showing the injection site reaction with respect to location and will include a recognizable body landmark so that the location is obvious. For example, for reactions on the abdomen include the umbilicus in the medium distance shot). Photographs will be stored electronically under the participant ID number and back-up electronic storage will be kept.

Appropriate measures will be taken to protect participant confidentiality. No photographs of participants' faces will be taken. Only dedicated study staff and the sponsor will have access to the photographs. No identifying information will be included with the digital picture file. See Appendix C for detailed protocol.

7.0 STUDY PARAMETERS

7.1 Core evaluations

Table 2 summarizes minimum testing and clinical assessments required. This is in addition to other assessments regarded as standard of care, which may be collected for study purposes. Data collection will be performed +/- 5 days from the specified time-point to allow for flexibility in the event of weekends, holidays, or other events affecting study team and study patient availability.

Table 2 Core evaluation[g]

	Baseline[a]	Week 4	Week 8	Week 12	Week 24	Week 36	Week 52	Weeks 64, 76, 88, and 100	As indicated[h]
Directly observed therapy for ART	Continuous through day 60								
ART Adherence Monitoring	At least monthly when participant is in the Inpatient Outpatient Unit and outpatient setting								
Frequency of latently-infected resting CD4+ T cells[b]	X			X	X	X	X	X	
Copies of HIV-1 DNA per million PBMCs[c]	X	X	X	X	X	X	X	X	
HIV-1 plasma RNA	X	X	X	X	X	X	X	X	
Donor marrow or blood for STR analysis	X								
Patient blood for baseline STR analysis	X								
Peripheral blood chimerism	X	X	X	X	X	X	X	X	
HIV antibody test[d]	X			X	X	X	X	X	
GVHD[e]		X	X		X	X	X		
Photographs of ENF injection site[f]									X
Scale of ENF injection site[f]									X

[a]Baseline evaluations should occur ≤ 1 month before initiation of conditioning therapy. Standard of care assessments that were collected prior to registration may be used for study purposes.

[b]Collect (15) 8·5 mL yellow top tubes. This will not be collected if participant's hematocrit is less than 27%.

[c]Collect (3) 8·5 mL yellow top tubes. At week 4 and week 8, instead collect (6) 8·5 mL yellow top tubes.

[d]This does not require additional blood draws.

[e]GVHD and other morbidity assessments are also performed weekly until Day 100. Results of these and subsequent assessments may be collected for research purposes. Patients may be asked to complete GVHD questionnaires.

[f]If participants develop an injection site reaction during the administration of enfuvirtide, a member of the study team will complete an Injection Site Report Form (See Appendix A) to grade the reaction and a photograph of the reaction will be taken with informed consent by the participant. This assessment will be repeated as indicated if there is a change in the injection site reaction.

[g]If subject is enrolled in another study which requires the same evaluation performed by the same laboratory, the sample will not be drawn in duplicate for both studies. One sample will be run and the result can be used for both studies to avoid unnecessary blood draws.

8.0 RISKS AND REPORTING REQUIREMENTS

8.1 Enfuvirtide (Fuzeon for injection, ENF, T-20)

Enfuvirtide is a 36-amino acid synthetic HIV-1 fusion inhibitory peptide composed of naturally occurring L-amino acid residues. The primary sequence was derived from a naturally occurring motif within the gp41 transmembrane glycoprotein of HIV-1. ENF for injection in combination with other antiretrovirals is FDA-approved for the treatment of HIV-1 infection.

Injection site reactions (ISRs) are very common in patients who use ENF. In Phase 3 trials, 50% of patients developed mild skin reactions with erythema and mild tenderness and 42% developed moderate tenderness without any limitation of normal activities. Only 1.2% discontinued use because of ISRs through 24 weeks of treatment.[55]

ENF is largely catabolized and is not a known CYP450 inducer, inhibitor, or substrate. Dosing modifications are not required for renal or hepatic function impairment.

ENF will be administered via the usual needle and syringe method Subjects receiving anticoagulants or those with hemophilia, or other coagulation disorders, may have a higher risk of post-injection bleeding.

ENF is designated as FDA pregnancy Category B.

8.2 Toxicity grading

Toxicities are graded using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. This is in addition to the planned assessment used to describe the secondary outcome of incidence and severity of injection site reactions to enfuvirtide (see section 6.5 and Appendix A).

8.3 Toxicity reporting

Patients undergoing alloHSCT will be expected to frequent adverse events (AEs) related to the antineoplastic agents and immunosuppressants which are not the subject of this protocol. This protocol focuses on the use of antiretroviral therapy, including enfuvirtide in patients undergoing alloHSCT. Adverse events directly related to enfuvirtide will be collected. Examples of adverse events directly related to enfuvirtide include hypersensitivity or allergic reactions that occur with administration of enfuvirtide, and enfuvirtide injection site reactions. One of the Principal investigators (Durand, Ambinder) will review all adverse reactions as they occur in a timely manner. A panel of three medical experts will review any grade 3 or higher AEs within three months of the AE submission in order to determine whether the AE was likely to be related to enfuvirtide. Members of the expert panel will include an HIV-1 expert, a bone marrow transplant expert, and a pharmacist who are not members of the study team.

8.4 Monitoring plan

This is a Level III study under the Sidney Kimmel Comprehensive Cancer Center (SKCCC) Data and Safety Monitoring Plan. The SKCCC Clinical Research Office Quality Assurance Group will perform periodic study audits. All trial monitoring and reporting will also be reviewed annually by the SKCCC Safety Monitoring Committee. The PI will review data to assure the validity of data, as well as the safety of the subjects. The PI will also monitor the progress of the trial. The PI will review safety reports and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study. In addition, a medical expert panel will review adverse events related to enfuvirtide. (See section 8.3)

8.5 Risks and benefits

Enfuvirtide carries the risk of painful injection site reactions, bleeding, bruising or skin infection which may be increased in the setting of thrombocytopenia. If enfuvirtide monotherapy is required due to intolerance of other oral antiretroviral medications, there is the risk of developing enfuvirtide resistance. Enfuvirtide resistance does not confer cross-resistance to other classes of antiretroviral medications and is unlikely to significantly compromise future treatment options for HIV-1 infection. Potential benefits of continuing antiretroviral therapy throughout alloHSCT including avoiding rebound viremia which can present with an acute retroviral syndrome including fevers, rash and myalgias. In addition, maintenance of antiretroviral therapy throughout alloHSCT my lead to eradication of HIV-1 infection.

9.0 STATISTICAL PLAN

9.1 Statistical Considerations:

The primary endpoint of this study is the maintenance of antiretroviral therapy through day 60 following alloHSCT. If ART can be continued through day 60, it is possible that donor cells would be prevented from becoming infected with HIV, and that HIV reservoirs in the patient would be eradicated. Given the potential to cure HIV, we would consider a probability of at least 20% of maintaining ART to be evidence of clinically meaningful activity warranting further investigation.

We will use a probability-based decision rule for the study to decide if ART is effective enough for further testing. The prior for this decision rule is Beta(1,1), based on the uniform distribution to reflect the lack of experience with this strategy. We will not recommend this treatment strategy if, given the data, there is at least 90% probability that fewer than 20% of patients can continue ART maintenance. Using this benchmark, if none of the first 10 patients are able to maintain at least one antiretroviral drug through day 60 from transplant, there would be less than 10% probability that the underlying proportion of patients who can continue antiretroviral therapy is 20% or higher and the strategy will be reassessed.

Operating characteristics:

The operating characteristics of this feasibility rule have been calculated based on 5000 simulations. If the posterior certainty that feasibility is 20% or less, based on Bayes rule and the assumption of a uniform prior, is 90% or higher ($\geq$ 9:1 odds against the treatment being able to be continued), further study would not be recommended. For data simulated with known probabilities of feasibility (θ), the table 3 shows the percent of the time that the feasibility rule will determine that the underlying proportion of patients who can continue antiretroviral therapy is below the benchmark of 20%.

Table 3 Probabilities of feasibility

True feasibility (θ)	0·05	0·10	0·15	0·20	0·25	0·30	0·35	0·40
% of times not recommended	60·9%	35·0%	20·6%	11·0%	5·6%	2·7%	1·3%	0·6%

9.2 Analysis of Primary Outcome:

The following table 4 shows the 90% credible intervals for the underlying probability of maintenance, based on different numbers of patients able to continue out of ten patients on the trial, using a Beta(1,1) prior. The analysis plan is two-sided (5% in each tail), allowing for the full range of possible outcomes, while sample size is based on a one-sided consideration (10% in the upper tail).

Table 4 Underlying probability of maintenance with 90% credible intervals

	90% Credible Interval
0 out of 10	(0·0, 18·9)
1 out of 10	(3·3, 36·4)
2 out of 10	(7·9, 47·0)
3 out of 10	(13·5, 56·4)
4 out of 10	(20·0, 65·0)
5 out of 10	(27·1, 72·9)
6 out of 10	(35·0, 80·0)
7 out of 10	(43·6, 86·5)
8 out of 10	(53·0, 92·1)
9 out of 10	(63·6, 96·7)
10 out of 10	(81·1, 100·0)

9.3 Analysis of Secondary Outcomes:

Secondary endpoints measured over time will include (1) frequency of resting $CD4_+$ T cells harboring infectious HIV-1 at 12, 24, 36, 52 weeks (2) copies of HIV-1 DNA per million peripheral blood mononuclear cells at 12, 24, 36, and 52 weeks (3) plasma HIV-1 RNA levels at 4, 8, 12, 24, 36 and 52 weeks (4) donor chimerism at weeks 4, 8, 12, 24, 36, and 52 weeks, (5) incidence and severity of graft versus host disease, and (6) incidence and severity of injection site reactions to enfuvirtide. While the analysis of each of these endpoints may be slightly different, we will summarize these data with appropriate transformations, boxplots and summary statistics. The incidence and severity of graft versus host disease will be reported and summarized with standard cumulative incidence curves.

10.0 RECORDS TO BE KEPT

Records to be filed include the following:

1. Patient consent form
2. Eligibility check-list
3. Case report forms
4. Adverse event report form(s)
5. Follow-up assessments
6. Photographs of enfuvirtide injection site reactions

The principal investigator will review case report forms on a regular basis. Case report forms will be supported by primary source documents.

11.0 PATIENT CONSENT AND PEER JUDGMENT

Current federal, NCI, state, and institutional regulations regarding informed consent will be followed.

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APPENDIX A
INJECTION SITE REACTION REPORT FORM

Protocol Number	Subject Initials	Subject Number	
			Date: ___/___/___

Record reactions at the enfuvirtide injection site according to the assessment scale (A-E) by circling the corresponding parameter.

Parameter	Level A	Level B	Level C	Level D	Level E
Pain/Discomfort	no pain or discomfort	mild tenderness at injection site	moderate pain without limitation of usual activities	severe pain limiting usual activities	N/A
Erythema - Ø (mm) of skin redness	no erythema	present but < 25mm	• 25 mm but < 50 mm	• 50 mm but < 85 mm	• 85 mm
Induration - Ø (mm) of palpable skin hardness	no induration	slight	present but < 25 mm	• 25 mm but <50 mm	• 50 mm
Pruritus- degree of itchiness	no pruritus	mild, not requiring any treatment	requiring topical treatment	refractory to topical treatment, OR requiring oral or parenteral treatment	N/A
Nodules (small mass of defined shape) or cysts (fluid-filled sac)	no nodules or cysts	• 20 mm	> 20 mm but • 30 mm	> 30 mm	if draining
Ecchymosis - degree of discoloration	no ecchymosis	• 20 mm	> 20 mm but • 30 mm	> 30 mm but • 50 mm	> 50 mm
Parameter w/ Biojector Use	Level A	Level B	Level C	Level D	Level E
Hematoma at injection site	no hematoma	• 20 mm	> 20 mm but • 30 mm	> 30 mm	requiring surgical evacuation
Nerve pain or paresthesias at injection site	no nerve pain or paresthesias			severe pain limiting usual activities	N/A
Pain/Discomfort at injection site	no pain or no discomfort	mild tenderness at injection site	moderate pain without limitation of usual activities	severe pain limiting usual activities	N/A

APPENDIX B
Dosing considerations for Tacrolimus and Antiretroviral Medications

Serious toxicity is possible for patients concurrently receiving ritonavir-based (boosted-PI) or cobicistat-based (boosted elvitegravir) therapy and the immunosuppressive agent tacrolimus. This is due to the potent inhibition of CYP3A4 and P-glycoprotein by ritonavir, resulting in the delayed metabolism and consequently higher serum levels of tacrolimus. When possible, patients will be changed from ritonavir-containing HAART regimens to regimens that do not contain ritonavir. If this is not possible due to a lack of other active antiretroviral agents to use as substitutes, dosing should be determined by a multidisciplinary team familiar with the use of tacrolimus and ritonavir. The following dosing considerations are suggested, but are not required.

1) Suggested starting dose (WITHOUT ritonavir or cobicistat)
    a. IV: 0·03 mg/kg every 24 hours based on Ideal body weight
    b. PO: 0·2 mg/kg/day divided into two doses
2) Suggested starting dose (WITH ritonavir or cobicistat)
    a. PO: Consult with a pharmacist. Generally in the range of 1 mg weekly.
3) Target Trough Level: 5 – 15 ng/mL
    a. Serum trough levels should be obtained on day 5 of tacrolimus therapy
    b. If signs or symptoms of toxicity are present OR if serum trough levels of tacrolimus exceed 25 ng/mL, then BOTH ritonavir and tacrolimus should be held, a level repeated in 24 hours and therapy resumed once the level is within the target range.

With etravirine, nevirapine, or efavirenz co-administration, tacrolimus dose may need to be increased at steady-state (7-10 days).

Concomitant Medications	**Effect on Tacrolimus**	**Recommendation**
Protease Inhibitors (boosted) • Atazanavir/ritonavir (ATZ/r) • Fosamprenavir/ritonavir (fAPV/r) • Indinavir/ritonavir (IND/r) • Lopinavir/ritonavir (LPV/r) • Saquinavir/ritonavir (SQV/r) • Tipranavir/ritonavir (TPV/r) **Cobicistat-containing regimens**	↑↑↑ Tacrolimus Levels May result in severe and prolonged tacrolimus toxicity.	Monitor trough levels daily Consult with experienced pharmacist regarding dosing adjustments Once dosing is stable, tacrolimus levels may be monitored according to standard clinical practice Most patients on ritonavir are maintained on 0·5 – 1 mg/week

APPENDIX C
Procedure for taking photographs of enfuvirtide injection site reactions

Photographs will be taken to document any injection site reactions to enfuvirtide that occur.
Efforts will be made to standardize these photographs using the suggested guidelines below.

In most cases, two photos will be taken. The first photo will be a close-up of the reaction. A millimeter ruler should be included in the photograph to demonstrate the size of the reaction. The second photo will be a medium view showing the reaction with respect to location and should include a recognizable body landmark so that the location is obvious. For example, for reactions on the abdomen include the umbilicus in the medium distance shot).

Photographs will be stored electronically under the participant ID number and back-up electronic storage will be kept. Appropriate measures must be taken to protect participant confidentiality. Photographs of participants' faces will not be taken. No identifying information should be included with the digital picture file.

Photography Guidelines

1. A 5 megapixel camera minimum is suggested.
2. Include the participants PID in all of the photos.
3. Always try to take the photos in the same setting with respect to participant positioning, lighting, background, and camera setting.
4. Use auto-focus.
5. Use the "macro" mode for close-ups. The universal symbol for "macro" mode is a flower.
6. Use the flash mode as often as possible when the lighting is poor, but avoid getting too close to the lesions as overexposure may wipe out the details.
7. For very close shots, oblique views may be preferred
8. Eliminate all distractions from the background. Try to take all photographs with a plain blue or green background.

Saving, Storing, and Uploading Files

1. SAVE as a JPG file.

The major advantage of the JPG format is that the image size can be compressed considerably without significant visible loss of resolution. The back-up copies can also be saved in the compressed JPG format so that the space taken up can be minimized. It always makes sense to delete images that are blurred as they are unlikely to be used by you and will unnecessarily clutter up the hard disk space.

2. Make it a point to catalog all saved images (or containing folders) tagging them with the participant's name, and date.

Statistical Considerations for HIV Latent Reservoir Changes

Changes in the HIV LR size were estimated using a mixed-effects Bayesian model.[56] For participant i and sample j from that participant, the frequency V_{ij} is the infection frequency; i.e., the probability that a single cell in the sample is able to cause outgrowth. The number of cells causing outgrowth in each well was assumed to follow a Poisson distribution with rate equal to $\left(V_{ij} \times \text{Number of input cells in the well}\right)$. An observation of outgrowth in a well indicates that at least one outgrowth-causing cell was plated in that well.

Frequency parameter V_{ij} is determined by adding four effects on log scale:

$$V_{ij} = exp\left(v_i + a_i T_{ij} + b_i S_{ij} + c_{ij}\right)$$

In this expression, v_i is the (log) baseline infected cell frequency for each study participant. The variable a_i is the complete donor replacement treatment effect, modeled as a random effect, $a_i \sim \mathcal{N}(\mu_a, \sigma_a)$, with T_{ij} an indicator variable set to 1 if the sample occurs after complete replacement, and 0 otherwise. The variable b_i is a more general bone marrow transplant treatment effect, modeled as a random effect, $b_i \sim \mathcal{N}(\mu_b, \sigma_b)$, with S_{ij} an indicator variable set to 1 if the sample occurs after bone marrow transplant, and 0 otherwise. The variable c_{ij} is a random effect representing sample-to-sample variation beyond the Poisson noise inherent in the assay; it may be treated as residual error, $c_{ij} \sim \mathcal{N}(0, \sigma_c)$. It was assumed that the amount of time post-alloBMT that a sample was taken had no effect on the measurement (all samples were taken between 12 and 100 weeks post-alloBMT). No trend in residuals c_{ij} over time was observed, supporting this assumption (Figure 1).

A normal prior was used for v_i (mean –14, standard deviation 2·5; i.e., 95% of baseline infection frequencies falling within 100-fold of 1 IUPM). A zero-centered normal prior was used for typical treatment effects μ_a, μ_b (standard deviation 2·5; i.e., 95% probability that alloBMT causes less than a ~100-fold shift in IUPM, up or down). A half-Cauchy prior was used for standard deviations σ_a, σ_b, and σ_c (scale parameter 1). In qVOA datasets of comparable size, similarly weak priors were found to assist model convergence without biasing results.[56]

Simpler versions of the above model were also tested, leaving out one or both treatment effects. All models performed similarly based on Watanabe-Akaike Information Criterion (WAIC), with the full model only 4·4 points better than the null model without treatment effects. The null model, however, had far larger residual error (posterior median estimate of σ_c 6·42, (95% credible interval CI 3·46 - 15·85)) than the full model did (1·69, (95% CI 1·12 - 4·68)), and so was deemed an inferior fit. A previous estimate of sample-to-sample variation in qVOA (σ = 2·0 (95% CI 1·6 - 2·7)), "aliquot & batch" variation in Table 1 of Rosenbloom et al. (2019)[56] is consistent with σ_c in the full model here.

Each parameter was estimated using PyStan 2·7 (Tables 5 and Supplemental Mixed-effects Bayesian Model Output). The Markov chain Monte Carlo was run with four parallel chains of 10,000 iterations each. All trace plots of chains were inspected for mixing. Diagnostics N_{eff} (effective sample size) >200 (values as low as 100 in some cases considered acceptable) and $\widehat{R}$ (scale reduction factor) <1·01 (values as high as 1·04 in some cases considered acceptable) were also observed, indicating convergence to a valid fit (Table 6).

Source File Data for Mixed-effects Bayesian Model

Table 5 Raw data used to generate the source file for the Mixed-effects Bayesian Model.

CELLS	WELLS	POS	SourceID	Time point
1000000	5	0	Pt1	Pt1_Baseline
200000	2	0	Pt1	Pt1_Baseline
40000	2	0	Pt1	Pt1_Baseline
8000	2	0	Pt1	Pt1_Baseline
1600	2	0	Pt1	Pt1_Baseline
320	2	0	Pt1	Pt1_Baseline
300000	1	0	Pt1	Pt1_Baseline
1000000	10	0	Pt1	Pt1_Week 12
200000	2	0	Pt1	Pt1_Week 12
40000	2	0	Pt1	Pt1_Week 12
8000	2	0	Pt1	Pt1_Week 12
1600	2	0	Pt1	Pt1_Week 12
320	2	0	Pt1	Pt1_Week 12
1000000	7	0	Pt1	Pt1_Week 24
200000	2	0	Pt1	Pt1_Week 24
40000	2	0	Pt1	Pt1_Week 24
8000	2	0	Pt1	Pt1_Week 24
1600	2	0	Pt1	Pt1_Week 24
320	2	0	Pt1	Pt1_Week 24
400000	1	0	Pt1	Pt1_Week 24
1000000	20	5	Pt2	Pt2_Baseline
200000	2	0	Pt2	Pt2_Baseline
40000	2	0	Pt2	Pt2_Baseline
8000	2	0	Pt2	Pt2_Baseline
1600	2	0	Pt2	Pt2_Baseline
320	2	0	Pt2	Pt2_Baseline
1000000	5	1	Pt2	Pt2_Week 12
200000	2	0	Pt2	Pt2_Week 12
40000	2	0	Pt2	Pt2_Week 12
8000	2	0	Pt2	Pt2_Week 12
1600	2	0	Pt2	Pt2_Week 12
320	2	0	Pt2	Pt2_Week 12
1000000	5	2	Pt2	Pt2_Week 24
200000	2	0	Pt2	Pt2_Week 24

40000	2	0	Pt2	Pt2_Week 24
8000	2	0	Pt2	Pt2_Week 24
1600	2	0	Pt2	Pt2_Week 24
320	2	0	Pt2	Pt2_Week 24
1000000	12	1	Pt2	Pt2_Week 36
200000	2	0	Pt2	Pt2_Week 36
40000	2	0	Pt2	Pt2_Week 36
8000	2	0	Pt2	Pt2_Week 36
1600	2	0	Pt2	Pt2_Week 36
320	2	0	Pt2	Pt2_Week 36
1000000	8	0	Pt2	Pt2_Week 52
200000	2	0	Pt2	Pt2_Week 52
40000	2	0	Pt2	Pt2_Week 52
8000	2	0	Pt2	Pt2_Week 52
1600	2	0	Pt2	Pt2_Week 52
320	2	0	Pt2	Pt2_Week 52
700000	1	0	Pt2	Pt2_Week 52
1000000	15	0	Pt2	Pt2_Week 64
200000	2	0	Pt2	Pt2_Week 64
40000	2	0	Pt2	Pt2_Week 64
8000	2	0	Pt2	Pt2_Week 64
1600	2	0	Pt2	Pt2_Week 64
320	2	0	Pt2	Pt2_Week 64
500000	1	0	Pt2	Pt2_Week 64
1000000	19	2	Pt2	Pt2_Week 76
200000	2	1	Pt2	Pt2_Week 76
40000	2	0	Pt2	Pt2_Week 76
8000	2	0	Pt2	Pt2_Week 76
1600	2	0	Pt2	Pt2_Week 76
320	2	0	Pt2	Pt2_Week 76
400000	1	0	Pt2	Pt2_Week 76
1000000	3	0	Pt2	Pt2_Week 90
200000	3	0	Pt2	Pt2_Week 90
40000	2	0	Pt2	Pt2_Week 90
8000	2	0	Pt2	Pt2_Week 90
1600	2	0	Pt2	Pt2_Week 90
320	2	0	Pt2	Pt2_Week 90
1000000	23	3	Pt2	Pt2_Week103

200000	3	0	Pt2	Pt2_Week103
40000	2	0	Pt2	Pt2_Week103
8000	2	0	Pt2	Pt2_Week103
1600	2	0	Pt2	Pt2_Week103
320	2	0	Pt2	Pt2_Week103
1000000	7	0	Pt4	Pt4_Baseline
200000	2	0	Pt4	Pt4_Baseline
40000	2	0	Pt4	Pt4_Baseline
8000	2	0	Pt4	Pt4_Baseline
1600	2	0	Pt4	Pt4_Baseline
320	2	0	Pt4	Pt4_Baseline
1000000	3	0	Pt4	Pt4_Week 24
200000	2	1	Pt4	Pt4_Week 24
40000	2	1	Pt4	Pt4_Week 24
8000	2	0	Pt4	Pt4_Week 24
1600	2	0	Pt4	Pt4_Week 24
320	2	0	Pt4	Pt4_Week 24
370000	1	0	Pt4	Pt4_Week 24
1000000	2	0	Pt4	Pt4_Week 36
200000	2	0	Pt4	Pt4_Week 36
40000	2	0	Pt4	Pt4_Week 36
8000	2	0	Pt4	Pt4_Week 36
1600	2	0	Pt4	Pt4_Week 36
320	2	0	Pt4	Pt4_Week 36
1000000	5	2	Pt4	Pt4_Week 48
200000	2	0	Pt4	Pt4_Week 48
40000	2	0	Pt4	Pt4_Week 48
8000	2	0	Pt4	Pt4_Week 48
1600	2	0	Pt4	Pt4_Week 48
320	2	0	Pt4	Pt4_Week 48
1000000	7	0	Pt4	Pt4_Week 98
200000	2	0	Pt4	Pt4_Week 98
40000	2	0	Pt4	Pt4_Week 98
8000	2	0	Pt4	Pt4_Week 98
1600	2	0	Pt4	Pt4_Week 98
320	2	0	Pt4	Pt4_Week 98
1000000	11	2	Pt6	Pt6_Baseline
200000	2	0	Pt6	Pt6_Baseline

40000	2	0	Pt6	Pt6_Baseline
8000	2	0	Pt6	Pt6_Baseline
1600	2	0	Pt6	Pt6_Baseline
320	2	0	Pt6	Pt6_Baseline
700000	1	0	Pt6	Pt6_Baseline
1000000	9	0	Pt6	Pt6_Week 12
200000	2	0	Pt6	Pt6_Week 12
40000	2	0	Pt6	Pt6_Week 12
8000	2	0	Pt6	Pt6_Week 12
1600	2	0	Pt6	Pt6_Week 12
320	2	0	Pt6	Pt6_Week 12
1000000	16	0	Pt6	Pt6_Week 24
200000	2	0	Pt6	Pt6_Week 24
40000	2	0	Pt6	Pt6_Week 24
8000	2	0	Pt6	Pt6_Week 24
1600	2	0	Pt6	Pt6_Week 24
320	2	0	Pt6	Pt6_Week 24
1000000	7	0	Pt6	Pt6_Week 36
200000	2	0	Pt6	Pt6_Week 36
40000	2	0	Pt6	Pt6_Week 36
8000	2	0	Pt6	Pt6_Week 36
1600	2	0	Pt6	Pt6_Week 36
320	2	0	Pt6	Pt6_Week 36
1000000	7	0	Pt6	Pt6_Week 52
200000	2	0	Pt6	Pt6_Week 52
40000	2	0	Pt6	Pt6_Week 52
8000	2	0	Pt6	Pt6_Week 52
1600	2	0	Pt6	Pt6_Week 52
320	2	0	Pt6	Pt6_Week 52
500000	1	0	Pt6	Pt6_Week 52
1000000	22	19	Pt7	Pt7_Baseline
200000	2	1	Pt7	Pt7_Baseline
40000	2	1	Pt7	Pt7_Baseline
8000	2	1	Pt7	Pt7_Baseline
1600	2	0	Pt7	Pt7_Baseline
320	2	0	Pt7	Pt7_Baseline
1000000	11	0	Pt7	Pt7_Week 12
200000	2	0	Pt7	Pt7_Week 12

40000	2	0	Pt7	Pt7_Week 12
8000	2	0	Pt7	Pt7_Week 12
1600	2	0	Pt7	Pt7_Week 12
320	2	0	Pt7	Pt7_Week 12
1000000	6	0	Pt7	Pt7_Week 24
200000	2	0	Pt7	Pt7_Week 24
40000	2	0	Pt7	Pt7_Week 24
8000	2	0	Pt7	Pt7_Week 24
1600	2	0	Pt7	Pt7_Week 24
320	2	0	Pt7	Pt7_Week 24
170000	1	0	Pt7	Pt7_Week 24
1000000	40	0	Pt7	Pt7_Week 36
200000	2	0	Pt7	Pt7_Week 36
40000	2	0	Pt7	Pt7_Week 36
8000	2	0	Pt7	Pt7_Week 36
1600	2	0	Pt7	Pt7_Week 36
320	2	0	Pt7	Pt7_Week 36
1000000	28	0	Pt7	Pt7_Week 52
200000	2	0	Pt7	Pt7_Week 52
40000	2	0	Pt7	Pt7_Week 52
8000	2	0	Pt7	Pt7_Week 52
1600	2	0	Pt7	Pt7_Week 52
320	2	0	Pt7	Pt7_Week 52
1450000	1	0	Pt7	Pt7_Week 52
1000000	30	1	Pt7	Pt7_Week 64
200000	2	0	Pt7	Pt7_Week 64
40000	2	0	Pt7	Pt7_Week 64
8000	2	0	Pt7	Pt7_Week 64
1600	2	0	Pt7	Pt7_Week 64
320	2	0	Pt7	Pt7_Week 64
1000000	6	0	Pt7	Pt7_Week 88
200000	2	0	Pt7	Pt7_Week 88
40000	2	0	Pt7	Pt7_Week 88
8000	2	0	Pt7	Pt7_Week 88
1600	2	0	Pt7	Pt7_Week 88
320	2	0	Pt7	Pt7_Week 88
1000000	14	0	Pt7	Pt7_Week 100
200000	2	0	Pt7	Pt7_Week 100

40000	2	0	Pt7	Pt7_Week 100
8000	2	0	Pt7	Pt7_Week 100
1600	2	0	Pt7	Pt7_Week 100
320	2	0	Pt7	Pt7_Week 100
1000000	14	3	Pt9	Pt9_Baseline
200000	2	0	Pt9	Pt9_Baseline
40000	2	0	Pt9	Pt9_Baseline
8000	2	0	Pt9	Pt9_Baseline
1600	2	0	Pt9	Pt9_Baseline
320	2	0	Pt9	Pt9_Baseline
1000000	4	0	Pt9	Pt9_Week 36
200000	2	0	Pt9	Pt9_Week 36
40000	2	0	Pt9	Pt9_Week 36
8000	2	0	Pt9	Pt9_Week 36
1600	2	0	Pt9	Pt9_Week 36
320	2	0	Pt9	Pt9_Week 36
1000000	10	0	Pt9	Pt9_Week 52
200000	2	0	Pt9	Pt9_Week 52
40000	2	0	Pt9	Pt9_Week 52
8000	2	0	Pt9	Pt9_Week 52
1600	2	0	Pt9	Pt9_Week 52
320	2	0	Pt9	Pt9_Week 52
1000000	9	0	Pt9	Pt9_Week 100
200000	2	0	Pt9	Pt9_Week 100
40000	2	0	Pt9	Pt9_Week 100
8000	2	0	Pt9	Pt9_Week 100
1600	2	0	Pt9	Pt9_Week 100
320	2	0	Pt9	Pt9_Week 100
450000	1	0	Pt9	Pt9_Week 100

Mixed-effects Bayesian Model Stan Code

```
//Predictors: SourceID/CompleteEffect/TreatmentEffect/ReplicateEffect
functions {
    real logprob_neg_well(real logitLR, real numcells) {
        return -numcells * inv_logit(logitLR);
    }
    real logprob_pos_well(real logitLR, real numcells) {
        return log1m_exp(logprob_neg_well(logitLR,numcells)); // log1m_exp(x) = log(1-
exp(x)), prevents underflow
    }
}
data {
       int<lower=1> NUMWELLS;
       int<lower=1> NumSourceID;
       int<lower=1> NumCompleteEffect;
       int<lower=1> NumTreatmentEffect;
       int<lower=1> NumReplicateEffect;

       int<lower=1> SourceIDIndex[NUMWELLS];
       int<lower=1> CompleteEffectIndex[NUMWELLS];
       int<lower=1> TreatmentEffectIndex[NUMWELLS];
       int<lower=1> ReplicateEffectIndex[NUMWELLS];
       real<lower=1> CELLCOUNT[NUMWELLS];
       int<lower=0,upper=1> RESPONSE[NUMWELLS];
}
parameters {
       real fixedeffect_SourceID[NumSourceID];
       real<lower=0.> btwn_CompleteEffect_var;
       real randeffect_CompleteEffect[NumCompleteEffect];
       real btwn_CompleteEffect_avg;
       real<lower=0.> btwn_TreatmentEffect_var;
       real randeffect_TreatmentEffect[NumTreatmentEffect];
       real btwn_TreatmentEffect_avg;
       real<lower=0.> btwn_ReplicateEffect_var;
       real randeffect_ReplicateEffect[NumReplicateEffect];
}
transformed parameters {
       real LOGIT_LR_THISWELL[NUMWELLS];
       vector[NUMWELLS] LOGLIKS;
       real LOGLIK;
       real transformedeffect_SourceID[NumSourceID+1];
       real transformedeffect_CompleteEffect[NumCompleteEffect+1];
       real<lower=0.> btwn_CompleteEffect_sigma;
       real transformedeffect_TreatmentEffect[NumTreatmentEffect+1];
       real<lower=0.> btwn_TreatmentEffect_sigma;
       real transformedeffect_ReplicateEffect[NumReplicateEffect+1];
       real<lower=0.> btwn_ReplicateEffect_sigma;
       transformedeffect_SourceID[1] <- 0.;
       for (j in 2:NumSourceID+1) {
              transformedeffect_SourceID[j] <- fixedeffect_SourceID[j-1];
       }
       transformedeffect_CompleteEffect[1] <- 0.;
       for (j in 2:NumCompleteEffect+1) {
              transformedeffect_CompleteEffect[j] <- randeffect_CompleteEffect[j-1];
       }
       btwn_CompleteEffect_sigma <- sqrt(btwn_CompleteEffect_var);
       transformedeffect_TreatmentEffect[1] <- 0.;
       for (j in 2:NumTreatmentEffect+1) {
              transformedeffect_TreatmentEffect[j] <- randeffect_TreatmentEffect[j-1];
       }
```

```
	btwn_TreatmentEffect_sigma <- sqrt(btwn_TreatmentEffect_var);
	transformedeffect_ReplicateEffect[1] <- 0.;
	for (j in 2:NumReplicateEffect+1) {
		transformedeffect_ReplicateEffect[j] <- randeffect_ReplicateEffect[j-1];
	}
	btwn_ReplicateEffect_sigma <- sqrt(btwn_ReplicateEffect_var);
	for (j in 1:NUMWELLS) {
		LOGIT_LR_THISWELL[j] <- transformedeffect_SourceID[SourceIDIndex[j]] +
transformedeffect_CompleteEffect[CompleteEffectIndex[j]] +
transformedeffect_TreatmentEffect[TreatmentEffectIndex[j]] +
transformedeffect_ReplicateEffect[ReplicateEffectIndex[j]];
		if (RESPONSE[j] == 0)
			LOGLIKS[j] <- logprob_neg_well(LOGIT_LR_THISWELL[j],
CELLCOUNT[j]);
		else
			LOGLIKS[j] <- logprob_pos_well(LOGIT_LR_THISWELL[j],
CELLCOUNT[j]);
	}
	LOGLIK <- sum(LOGLIKS);
}
model {
	for (j in 1:NumSourceID) {
		fixedeffect_SourceID[j] ~ normal(-14.0,2.5);
	}
	btwn_CompleteEffect_sigma ~ cauchy(0.,1.0);
	increment_log_prob( log(0.5) - 0.5*log(btwn_CompleteEffect_var) );
	btwn_CompleteEffect_avg ~ normal(0.0, 2.5);
	for (j in 1:NumCompleteEffect) {
		randeffect_CompleteEffect[j] ~ normal(btwn_CompleteEffect_avg,
btwn_CompleteEffect_sigma);
	}
	btwn_TreatmentEffect_sigma ~ cauchy(0.,1.0);
	increment_log_prob( log(0.5) - 0.5*log(btwn_TreatmentEffect_var) );
	btwn_TreatmentEffect_avg ~ normal(0.0, 2.5);
	for (j in 1:NumTreatmentEffect) {
		randeffect_TreatmentEffect[j] ~ normal(btwn_TreatmentEffect_avg,
btwn_TreatmentEffect_sigma);
	}
	btwn_ReplicateEffect_sigma ~ cauchy(0.,1.0);
	increment_log_prob( log(0.5) - 0.5*log(btwn_ReplicateEffect_var) );
	for (j in 1:NumReplicateEffect) {
		randeffect_ReplicateEffect[j] ~ normal(0, btwn_ReplicateEffect_sigma);
	}
	for (j in 1:NUMWELLS) {
	}
	increment_log_prob(LOGLIK);
}
generated quantities {
	real IUPM[NumSourceID];
	for (j in 1:NumSourceID) {
		IUPM[j] <- inv_logit(fixedeffect_SourceID[j]) * 1000000.;
```

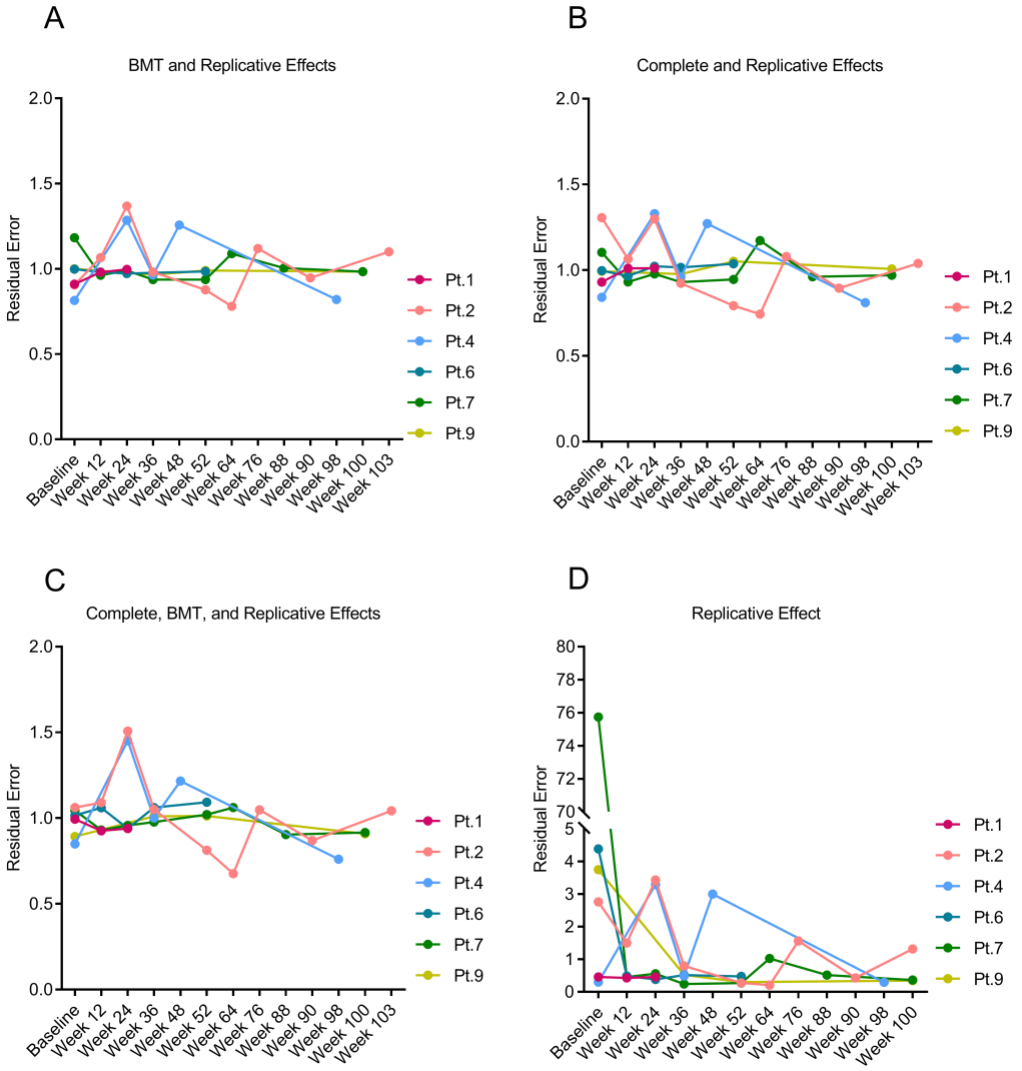
Summary of Mixed-effects Bayesian Model

Table 6 Data summary from the Source File used in the Mixed-effects Bayesian Model as described in the Supplemental methods for the Statistical Considerations for HIV Latent Reservoir Changes.

param	param_STANname	mean	se_mean	sd	0.025	0.05	0.25	0.5	0.75	0.95	0.975	n_eff	Rhat
WAIC	...	210.463											
LPD	...	-94.220											
p_WAIC	...	11.011											
LOGLIK	LOGLIK	-99.242	0.149	2.918	-105.141	-104.047	-101.039	-99.296	-97.373	-94.116	-93.491	383	1.012
IUPM[YS001]	IUPM[0]	0.112	0.005	0.253	0.002	0.003	0.017	0.047	0.128	0.403	0.578	2289	1.001
IUPM[DH002]	IUPM[1]	0.339	0.009	0.462	0.062	0.082	0.172	0.247	0.374	0.798	1.168	2854	1.001
IUPM[KW004]	IUPM[2]	0.297	0.051	0.498	0.015	0.025	0.076	0.157	0.301	1.212	1.832	94	1.042
IUPM[MS006]	IUPM[3]	0.242	0.007	0.418	0.024	0.033	0.087	0.156	0.277	0.678	0.962	3744	1.001
IUPM[JQ007]	IUPM[4]	2.370	0.094	2.077	0.343	0.482	1.310	2.018	2.835	5.372	6.360	487	1.009
IUPM[MB009]	IUPM[5]	0.355	0.023	0.621	0.040	0.058	0.127	0.227	0.385	0.904	1.544	723	1.007
fixedeffect_SourceID[YS001]	fixedeffect_SourceID[0]	-16.996	0.034	1.529	-20.311	-19.693	-17.909	-16.877	-15.875	-14.724	-14.364	1977	1.003
fixedeffect_SourceID[DH002]	fixedeffect_SourceID[1]	-15.183	0.013	0.700	-16.598	-16.319	-15.573	-15.215	-14.798	-14.042	-13.660	2961	1.002
fixedeffect_SourceID[KW004]	fixedeffect_SourceID[2]	-15.682	0.082	1.125	-17.990	-17.508	-16.390	-15.664	-15.015	-13.623	-13.210	187	1.020
fixedeffect_SourceID[MS006]	fixedeffect_SourceID[3]	-15.687	0.032	0.932	-17.540	-17.234	-16.253	-15.673	-15.101	-14.203	-13.854	849	1.003
fixedeffect_SourceID[JQ007]	fixedeffect_SourceID[4]	-13.192	0.037	0.719	-14.885	-14.546	-13.546	-13.113	-12.774	-12.134	-11.966	372	1.014
fixedeffect_SourceID[MB009]	fixedeffect_SourceID[5]	-15.304	0.049	0.886	-17.047	-16.666	-15.877	-15.299	-14.769	-13.916	-13.381	332	1.011
btwn_CompleteEffect_avg	btwn_CompleteEffect_avg	-3.955	0.036	1.660	-7.060	-6.517	-4.988	-4.097	-2.991	-1.073	-0.291	2096	1.003
btwn_CompleteEffect_sigma	btwn_CompleteEffect_sigma	1.504	0.092	2.355	0.151	0.173	0.417	0.850	1.735	4.462	6.468	651	1.006
randeffect_CompleteEffect[YS001_Complete]	randeffect_CompleteEffect[0]	-4.320	0.061	2.726	-9.346	-7.754	-5.302	-4.163	-3.025	-0.884	-0.094	1976	1.002
randeffect_CompleteEffect[MS006_Complete]	randeffect_CompleteEffect[1]	-4.689	0.156	2.692	-9.601	-9.312	-5.669	-4.446	-3.252	-1.324	-0.593	298	1.014
randeffect_CompleteEffect[JQ007_Complete]	randeffect_CompleteEffect[2]	-4.603	0.108	1.733	-7.834	-7.679	-5.619	-4.624	-3.584	-1.751	-1.039	257	1.019
randeffect_CompleteEffect[MB009_Complete]	randeffect_CompleteEffect[3]	-4.474	0.059	2.792	-9.547	-7.946	-5.398	-4.261	-3.035	-1.309	-0.586	2202	1.003
btwn_TreatmentEffect_avg	btwn_TreatmentEffect_avg	-0.953	0.050	1.043	-3.127	-2.641	-1.539	-0.873	-0.315	0.604	0.956	435	1.009
btwn_TreatmentEffect_sigma	btwn_TreatmentEffect_sigma	1.004	0.040	1.030	0.074	0.101	0.335	0.718	1.336	2.856	3.650	668	1.009
randeffect_TreatmentEffect[YS001_Treatment]	randeffect_TreatmentEffect[0]	-1.105	0.041	1.701	-5.081	-3.847	-1.800	-0.915	-0.220	1.179	1.805	1725	1.005
randeffect_TreatmentEffect[DH002_Treatment]	randeffect_TreatmentEffect[1]	-1.009	0.045	0.822	-2.707	-2.456	-1.463	-0.955	-0.445	0.236	0.495	329	1.014
randeffect_TreatmentEffect[KW004_Treatment]	randeffect_TreatmentEffect[2]	-0.271	0.069	1.209	-2.563	-2.381	-1.016	-0.330	0.432	1.812	2.350	304	1.013
randeffect_TreatmentEffect[MS006_Treatment]	randeffect_TreatmentEffect[3]	-1.245	0.048	1.852	-5.305	-4.071	-1.922	-1.003	-0.297	0.941	1.483	1496	1.004
randeffect_TreatmentEffect[JQ007_Treatment]	randeffect_TreatmentEffect[4]	-1.307	0.040	1.502	-4.914	-4.022	-2.079	-1.132	-0.345	0.714	1.181	1440	1.005
randeffect_TreatmentEffect[MB009_Treatment]	randeffect_TreatmentEffect[5]	-1.220	0.046	1.782	-5.363	-4.069	-1.938	-0.996	-0.275	1.003	1.573	1513	1.005
btwn_ReplicateEffect_sigma	btwn_ReplicateEffect_sigma	0.645	0.034	0.456	0.055	0.087	0.301	0.541	0.874	1.540	1.698	176	1.026
randeffect_ReplicateEffect[YS001_Baseline]	randeffect_ReplicateEffect[0]	-0.248	0.047	0.780	-2.059	-1.723	-0.543	-0.085	0.180	0.747	1.028	270	1.019
randeffect_ReplicateEffect[YS001_Week 12]	randeffect_ReplicateEffect[1]	-0.056	0.040	0.767	-1.593	-1.332	-0.415	-0.022	0.280	1.201	1.587	366	1.012
randeffect_ReplicateEffect[YS001_Week 24]	randeffect_ReplicateEffect[2]	-0.029	0.022	0.756	-1.615	-1.177	-0.379	-0.022	0.264	1.210	1.815	1143	1.002
randeffect_ReplicateEffect[DH002_Baseline]	randeffect_ReplicateEffect[3]	-0.020	0.013	0.615	-1.458	-1.068	-0.258	0.017	0.245	0.931	1.212	2196	1.001
randeffect_ReplicateEffect[DH002_Week 12]	randeffect_ReplicateEffect[4]	0.185	0.056	0.665	-0.986	-0.772	-0.141	0.087	0.429	1.454	2.128	140	1.030
randeffect_ReplicateEffect[DH002_Week 24]	randeffect_ReplicateEffect[5]	0.525	0.068	0.765	-0.517	-0.346	0.011	0.314	0.882	2.139	2.703	128	1.032
randeffect_ReplicateEffect[DH002_Week 36]	randeffect_ReplicateEffect[6]	-0.012	0.045	0.604	-1.273	-0.995	-0.299	-0.005	0.276	1.035	1.543	184	1.021
randeffect_ReplicateEffect[DH002_Week 52]	randeffect_ReplicateEffect[7]	-0.364	0.038	0.700	-2.095	-1.676	-0.651	-0.196	0.043	0.478	0.665	347	1.015
randeffect_ReplicateEffect[DH002_Week 64]	randeffect_ReplicateEffect[8]	-0.468	0.043	0.735	-2.354	-1.820	-0.804	-0.265	0.009	0.324	0.494	299	1.010
randeffect_ReplicateEffect[DH002_Week 76]	randeffect_ReplicateEffect[9]	0.200	0.053	0.587	-0.869	-0.781	-0.108	0.104	0.460	1.438	1.642	124	1.040
randeffect_ReplicateEffect[DH002_Week 90]	randeffect_ReplicateEffect[10]	-0.169	0.063	0.766	-2.055	-1.491	-0.473	-0.082	0.169	0.939	1.573	146	1.021
randeffect_ReplicateEffect[DH002_Week103]	randeffect_ReplicateEffect[11]	0.121	0.026	0.509	-0.836	-0.618	-0.154	0.066	0.382	0.994	1.250	397	1.012
randeffect_ReplicateEffect[KW004_Baseline]	randeffect_ReplicateEffect[12]	-0.510	0.074	0.886	-2.960	-2.534	-0.814	-0.244	0.030	0.437	0.631	143	1.034
randeffect_ReplicateEffect[KW004_Week 24]	randeffect_ReplicateEffect[13]	0.489	0.041	0.736	-0.543	-0.369	0.008	0.309	0.815	1.801	2.278	324	1.007
randeffect_ReplicateEffect[KW004_Week 36]	randeffect_ReplicateEffect[14]	-0.162	0.019	0.686	-1.830	-1.384	-0.446	-0.055	0.163	0.813	1.156	1247	1.003
randeffect_ReplicateEffect[KW004_Week 48]	randeffect_ReplicateEffect[15]	0.402	0.025	0.685	-0.606	-0.411	-0.011	0.238	0.705	1.708	2.132	754	1.006
randeffect_ReplicateEffect[KW004_Week 98]	randeffect_ReplicateEffect[16]	-0.347	0.032	0.728	-2.239	-1.705	-0.593	-0.186	0.053	0.519	0.722	528	1.009
randeffect_ReplicateEffect[MS006_Baseline]	randeffect_ReplicateEffect[17]	-0.045	0.014	0.664	-1.537	-1.198	-0.322	-0.016	0.280	0.954	1.311	2411	1.003
randeffect_ReplicateEffect[MS006_Week 12]	randeffect_ReplicateEffect[18]	0.076	0.093	0.911	-1.633	-1.227	-0.306	0.008	0.371	1.506	3.191	95	1.039
randeffect_ReplicateEffect[MS006_Week 24]	randeffect_ReplicateEffect[19]	0.004	0.045	0.784	-1.714	-1.183	-0.362	-0.010	0.313	1.454	1.598	299	1.016
randeffect_ReplicateEffect[MS006_Week 36]	randeffect_ReplicateEffect[20]	-0.033	0.042	0.760	-1.690	-1.279	-0.334	-0.004	0.308	1.096	1.484	324	1.014
randeffect_ReplicateEffect[MS006_Week 52]	randeffect_ReplicateEffect[21]	0.048	0.040	0.759	-1.542	-1.165	-0.280	0.014	0.389	1.191	1.587	362	1.008
randeffect_ReplicateEffect[JQ007_Baseline]	randeffect_ReplicateEffect[22]	0.181	0.030	0.677	-0.973	-0.688	-0.180	0.065	0.449	1.491	1.911	520	1.011
randeffect_ReplicateEffect[JQ007_Week 12]	randeffect_ReplicateEffect[23]	-0.116	0.065	0.809	-2.234	-1.634	-0.426	-0.041	0.243	1.115	1.588	154	1.023
randeffect_ReplicateEffect[JQ007_Week 24]	randeffect_ReplicateEffect[24]	-0.077	0.056	0.791	-1.777	-1.629	-0.394	-0.017	0.275	1.163	1.443	200	1.018
randeffect_ReplicateEffect[JQ007_Week 36]	randeffect_ReplicateEffect[25]	-0.153	0.017	0.694	-1.797	-1.349	-0.452	-0.063	0.165	0.827	1.110	1658	1.004
randeffect_ReplicateEffect[JQ007_Week 52]	randeffect_ReplicateEffect[26]	-0.176	0.080	0.846	-2.799	-1.831	-0.419	-0.038	0.240	0.912	1.262	113	1.036
randeffect_ReplicateEffect[JQ007_Week 64]	randeffect_ReplicateEffect[27]	0.340	0.048	0.782	-0.843	-0.580	-0.078	0.134	0.623	1.980	2.232	264	1.019
randeffect_ReplicateEffect[JQ007_Week 88]	randeffect_ReplicateEffect[28]	-0.047	0.021	0.727	-1.642	-1.198	-0.372	-0.018	0.277	1.106	1.430	1243	1.004
randeffect_ReplicateEffect[JQ007_Week 100]	randeffect_ReplicateEffect[29]	-0.064	0.026	0.715	-1.615	-1.182	-0.356	-0.034	0.241	1.062	1.552	761	1.008
randeffect_ReplicateEffect[MB009_Baseline]	randeffect_ReplicateEffect[30]	-0.075	0.054	0.746	-1.856	-1.281	-0.393	-0.031	0.248	1.212	1.383	192	1.019
randeffect_ReplicateEffect[MB009_Week 36]	randeffect_ReplicateEffect[31]	0.045	0.053	0.783	-1.622	-1.167	-0.282	0.009	0.373	1.498	1.863	216	1.017
randeffect_ReplicateEffect[MB009_Week 52]	randeffect_ReplicateEffect[32]	-0.059	0.018	0.734	-1.632	-1.264	-0.359	-0.014	0.248	1.017	1.416	1601	1.004
randeffect_ReplicateEffect[MB009_Week 100]	randeffect_ReplicateEffect[33]	-0.051	0.028	0.758	-1.850	-1.309	-0.371	-0.013	0.316	1.111	1.464	710	1.005

Residual Error of Mixed-effects Bayesian Models

Figure 1 Trends in residuals error over time. (A) Residuals for the model for a more general bone marrow transplant treatment effect (b_i) and sample-to-sample variation (c_{ij}). (B) Residuals for the model where there was a complete donor replacement treatment effect (a_i) and sample-to-sample variation. (C) Residuals for the 'Complete' model where there was a complete donor replacement treatment effect, a more general bone marrow transplant treatment effect and sample-to-sample variation. (D) Residuals for the model that only considered sample-to-sample variation.



Reference

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