



BMJ Open Vedolizumab treatment across antiretroviral treatment interruption in chronic HIV infection: the HAVARTI protocol for a pilot dose-ranging clinical trial to assess safety, tolerance, immunological and virological activity

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ABSTRACT

Introduction Continuous antiretroviral therapy (ART) suppresses HIV plasma viral load (pVL) to very low levels, which allows for some immune recovery. Discontinuation of ART leads to pVL rebound from reservoirs of persistence and latency, and progressive immunodeficiency. One promising but controversial strategy targeting CD4⁺ T lymphocytes with a monoclonal antibody (mAb) against α 4 β 7 integrin has shown promise through sustained virological remission of pVL (SVR) in SIV₂₃₉-infected rhesus macaques. We propose to assess the safety and tolerability of vedolizumab, a licensed humanised mAb against human α 4 β 7 integrin, in healthy HIV-infected adults on ART. This study will also assess, by analytical treatment interruption (ATI), whether vedolizumab treatment can induce SVR beyond ART and vedolizumab treatment.

Methods and analysis The HIV-ART-vedolizumab-ATI (HAVARTI) trial is a single-arm, dose-ranging pilot trial in healthy HIV-positive adult volunteers receiving ART. Twelve consenting persons will be enrolled in sequential groups of 4 to each serial dosing vedolizumab regimen (300 mg, 150 mg, 75 mg). The primary outcomes are: (1) to assess the safety and tolerability of seven serial infusions of vedolizumab at each of three doses; (2) to identify the immunovirological measures, including pVL and T-cell kinetics, that characterise HIV/ART cases before, during, after vedolizumab treatment and ATI; and (3) to seek SVR of pVL after ATI. Secondary outcomes will include immune reconstitution and pVL suppression as well as immune reconstitution and long-term safety following re-initiation of ART in the absence of SVR.

Ethics and dissemination The study protocol was approved by the Ottawa Health Science Network-REB and by the Health Canada Therapeutic Products Directorate. A Data Safety Monitor will review safety information at regular intervals. The final manuscript will be submitted to an open access journal within a year of study completion.

Strengths and limitations of this study

- Vedolizumab is a biologic already licensed to treat other conditions including inflammatory bowel disease.
- This is the first study to employ a range of vedolizumab doses to assess safety, tolerability and best anti-HIV activity effect in the context of chronic HIV infection.
- This study will assess the safety of vedolizumab using analytical treatment interruptions up to and beyond 12 weeks' duration, which may be essential to assessing the anti-HIV activity effects of this therapy.
- Non-human primate studies use significantly higher doses of anti- α 4 β 7 integrin mAb than the highest licensed human dose of 300 mg/infusion of vedolizumab (~4 mg/kg); however, safety outcomes at this maximum licensed dose in this population will be needed before higher-dose arms can be assessed.
- Larger-scale clinical trials will be needed to confirm any anti-HIV activity observed in this pilot trial.

Trial registration number ClinicalTrials.gov NCT03147859; <https://clinicaltrials.gov/ct2/show/NCT03147859>

BACKGROUND

HIV is a chronic active infection of leucocytes resulting in a progressive and profound depletion of lymphocytes, and ultimately in AIDS. Newly infected cells may undergo lytic productive infection on activation (lymphocytes) or undergo chronic productive infection (macrophages). In addition, an infected lymphocyte may remain dormant with latent, integrated HIV infection, which expands the

latent reservoir of infected cells. Continuous antiretroviral therapy (ART) suppresses HIV viraemia and allows some degree of immune healing, so as to permit near-normal health and life expectancy. However, ART is not a cure for HIV infection. ART interruption is nearly always followed by rebound of plasma viral load (pVL) to the pre-treatment viraemia levels, referred to as the viral set point, followed by resumption of progressive immunodeficiency.^{1 2}

Induction of post-treatment control in rhesus macaques with SIV treated by a monoclonal antibody against $\alpha 4\beta 7$ integrin

A promising finding of sustained virological remission of pVL (SVR) and stable CD4 cell count was reported in *Science* by Dr Byrareddy and colleagues in a rhesus macaque Simian Immunodeficiency Virus (SIV) infection model.³ SIV (and HIV) appears to preferentially infect CD4⁺ T lymphocytes expressing $\alpha 4\beta 7$ integrin, a lymphocyte homing receptor for trafficking to gut mucosal-associated lymphoid tissue (GALT) that was the target of mAb therapy in this study. This anti- $\alpha 4\beta 7$ mAb was administered serially every 3 weeks at 50 mg/kg for eight doses to acutely infected macaques on ART and was followed by ATI and subsequent discontinuation of mAb administration. SVR and low GALT-associated VLs for 24 months was observed in eight of eleven animals, after a low-level pVL rebound in five of the eight. In these animals, subsequent iatrogenic CD8 T-cell depletion resulted in viral rebound, indicating control but not eradication of virus (Byrareddy, unpublished). The mechanism of this post-treatment control is unknown, and later attempts to replicate this finding have been unsuccessful.⁴⁻⁶ One small human trial of vedolizumab in HIV infection did not observe SVR,⁷ but was limited in its ability to detect post-rebound suppression. In human HIV infection, SVR over time without evidence of progressive immunodeficiency in the absence of ART would meet definitional criteria of a 'functional cure', where pVL suppression is maintained without ART and without eradication of virus.

Human monoclonal antibodies against $\alpha 4\beta 7$ integrin

Humanised anti- $\alpha 4\beta 7$ integrin mAb (vedolizumab, Entyvio^{8 9}) is a licensed treatment for inflammatory bowel disease (IBD). Vedolizumab has a safety record of 4811 person-years observation, in which 2830 patients received vedolizumab from one to 1977 (median 328) days, during which there was no increased risk of any infections (<1% overall for tuberculosis (TB) or other serious infection), and no reported case of progressive multifocal leucoencephalopathy (PML), compared with placebo and standard non-biological therapy.¹⁰ Modelling shows that cumulative exposure to vedolizumab still has a very low risk of PML compared with other biologics such as natalizumab that non-selectively targets $\alpha 4$ integrin.¹¹

Study rationale

A human clinical trial of anti- $\alpha 4\beta 7$ integrin monoclonal antibody is feasible, given that a safe humanised product

is available. A pilot study to assess the translation of this intervention's anti-HIV effects from a non-human primate model to humans is needed to inform the design of larger trials. We describe a dose-finding and exposure-finding pilot trial in healthy adults with ART-treated chronic HIV infection to assess vedolizumab safety and anti-HIV activity or SVR after ATI. This trial proposal is of a short duration (~1 year) and simple design to assess short-term safety and tolerance of vedolizumab according to dose. It will also assess whether pVL rebound and/or SVR occurs after ATI, in relation to dose, duration and systemic exposure to vedolizumab.

In planning novel HIV treatment strategies, a combination of approaches will be necessary in order to address all aspects of HIV infection including the active, latent and concealed reservoirs of persistent infection. The anticipated mechanism of possible SVR with short-term vedolizumab intervention is not eradication or a virological cure, but a functional cure with immunological-maintained viral suppression in absence of ART and after withdrawal of the intervention. This trial design accommodates the collection and cryopreservation of biological specimens (sera, plasma, peripheral blood lymphocytes, rectal biopsy samples, cerebrospinal fluid (CSF) and stool) that will permit mechanistic immunological and virological studies in the event that treatment effects are seen.

METHODS AND ANALYSIS

Rationale for dosing

In the macaque model, a mAb against $\alpha 4\beta 7$ integrin was used at a dose of 50 mg/kg per infusion, with infusions given every 3 weeks.³ In humans, 300 mg per infusion given every 4 to 8 weeks is the highest licensed dose of vedolizumab (equivalent to 4 mg/kg/infusion in a 70 kg adult) and therefore was the highest dose used in this study protocol. A dose reduction in sequential groups will be implemented to assess for a dose-related treatment effect on pVL rebound kinetics or SVR. As compared with the existing human study by Sneller *et al*,⁷ our protocol provides the majority of vedolizumab doses after ATI, with only initial loading occurring before ATI. Ongoing vedolizumab exposure after treatment interruption is hypothesised to be important for the development of remission and is more in keeping with the original animal model.

Primary outcomes

The primary outcomes will be (1) the safety and tolerability of vedolizumab treatment at different doses in seven infusions as defined by the incidence of adverse events (AEs) and pre-specified side effects, and (2) the incidence and (3) duration of pVL remission during and after vedolizumab treatment following ATI determined by serial measurement of pVL.

Secondary outcomes

The secondary outcomes will be (1) the incidence and (2) magnitude of pVL rebound after ATI during and after treatment with vedolizumab, (3) the success of re-suppression of pVL with ART in the event of recurrent sustained pVL, and (4) the kinetics of pVL and CD4 T lymphocyte count during the study period.

Study design, settings, sample size and recruitment strategy

HAVARTI is a single-arm, dose-ranging pilot trial of serial vedolizumab infusions for the induction of HIV SVR in adults with chronic HIV infection on ART. Twelve consenting volunteers respecting all inclusion and exclusion criteria will be enrolled sequentially in groups of four to receive vedolizumab by infusion in 2-week to 4-week intervals for a total of seven doses. After three doses of vedolizumab, the participants will initiate the ATI portion of the study. During the ATI, participants will discontinue ART but continue with the four remaining scheduled vedolizumab treatments and monitoring of pVL and immunological markers. They will also have regular clinical assessment at each infusion visit. Participants will restart ART according to CD4 T-cell count and pVL threshold levels and trajectory, personal choice, or consensus judgement of the volunteer patient, treating physician and/or study investigators. Decisions to continue ATI or restart ART in the presence of CD4, pVL and clinical indicators will be reviewed by an independent expert medical monitor and reported to the Data Safety Monitoring Board (DSMB) in a timely manner.

Study participants will be recruited from The Ottawa Hospital (TOH) HIV clinic and referring primary care facilities. Informed consent will be obtained from those patients who are documented to be eligible for the trial after pre-screening. [Table 1](#) shows the safety laboratory tests and concomitant medication surveys to be done during screening. Individuals who wish to discuss enrolment in the trial with family, partner, friends or their treating physician may take the time and choose to enrol at a subsequent clinic visit. Once enrolled, the participant will be followed concomitantly by the principal investigator and study staff at TOH for the duration of the trial.

Inclusion criteria

Participants will meet the following criteria to be eligible for entry into the study: (1) documented HIV infection by Western blot or confirmatory enzyme immunoassay with documented pre-ART pVL; (2) be aged 18–65 years; (3) have received ART for between 2 and 10 years; (4) have no other significant comorbidity; (5) are receiving no other immune-modulating treatments; (6) have well-controlled HIV infection as defined by stable pVL of <50 copies/mL and CD4 counts >500 cells/ μ L with nadir CD4 counts >200 cells/ μ L. Adults may be male, female or transgender.

Exclusion criteria

Patients who meet any of the following criteria will be ineligible to participate: (1) women who are pregnant or lactating; (2) those who are non-adherent with contraception and safer sex practices; (3) patients with a history of AIDS-defining illness, drug-resistant HIV or treatment-refractory pVL response; (4) those with a history of non-adherence to ART; (5) current co-infection with hepatitis B or C; (6) current untreated TB including latent TB; (7) past HIV or non-HIV related autoimmune disease requiring immunomodulatory or immunosuppressive therapy.

Study schedule

The study schedule is represented in [table 1](#) and [figure 1](#). At the screening visit, participants will be assessed for study inclusion with respect to inclusion and exclusion criteria. A physical examination will be performed, a medical history will be taken and any laboratory testing not available from the patient record will be collected. Screening laboratory tests include haematology values (complete blood cell counts (CBCs), differential white blood cell counts, erythrocyte sedimentation rate), serum chemistry, markers of HIV (pVL, CD4 lymphocyte count and percentage, CD4:CD8 ratio) and a urine dipstick pregnancy test where indicated. Those meeting eligibility criteria after screening will be consented by the investigators and will return for a baseline visit (within 1–12 weeks of screening).

Regular study visits, as per [table 1](#), will entail a history, physical examination, safety assessment and laboratory studies. In addition to the regular study visits, blood draws and AE assessments will be performed between weeks 6 and 7, at the time of ATI. Optional specimen collection to be performed in willing participants includes (1) stool samples prior to treatment initiation (baseline or week 0), 24 and 52 weeks after initiation for microbiome assessment; (2) rectal mucosal biopsies prior to treatment initiation and at 24 weeks and 52 weeks after initiation for assessment of HIV pro-viral DNA by PCR in GALT; and (3) CSF samples at 24 and 52 weeks after treatment initiation for characterisation of the lymphocyte populations and VL in the event of pVL remission after ATI. Unscheduled visits will be performed in the event of new neurological symptoms suspicious for PML or treatment side effects.

Study timeline and dates

As seen in [table 1](#), each participant is studied for 52 weeks. Study recruitment for the highest dose began late 2017 and follow-up continued to March 2019, when the study was interrupted for an amendment. The trial then resumed recruitment late 2019 with active treatment and follow-up continuing at this time. New recruitment has been postponed due to COVID-19 restrictions and therefore will likely resume in 2021.

Table 1 Study visit schedule

Study activity/visit*	Weeks										Weeks 28, 32, 36, 40, 44, 48						
	Screening	Baseline	Week 0	Week 2	Week 5	6 to 7†	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48
Informed consent	X	X	X	X													
Eligibility confirmation	X	X															
Concomitant medicines	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test if applicable‡	X																
Safety laboratories (CBC, WBC, serum chemistry§, ESR)	X¶	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum (10 mL)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma (10 mL)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PBMCs from whole blood**	X			X													
Plasma viral load	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4	X	X															
Vedolizumab intravenous infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
History and physical	X††	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Optional CSF specimen													X				
Optional rectal mucosal biopsy		X											X				X
Optional stool sample		X											X				X
AE assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*Study visits may occur \pm 1 week from the time points outlined in the table.

†ATI (analytical treatment interruption) will occur at weeks 6–7.

‡Pregnancy testing with urine dip for β -human chorionic gonadotropin may be repeated at any study visit where it is felt to be indicated by the patient or the study investigator.

§Serum chemistry includes albumin (total), alanine transaminase, alkaline phosphatase, amylase, aspartate transaminase, bilirubin (total), blood glucose (random), blood urea nitrogen, calcium, chloride, C reactive protein, creatinine, gamma-glutamyl transferase, potassium, protein (total) and sodium.

¶Safety laboratory items have been measured within 1 year of the screening visit; these results may be used for screening purposes.

**50–100 mL whole blood for separation and cryopreservation of PBMCs.

††The history taken at screening will be more thorough than subsequent visits (ie, height only taken once). Confirmation of HIV+ by western blot or other standard test required only at screening visit.

AE, adverse event; CBC, complete blood cell count; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; PBMC, peripheral blood mononuclear cell; WBC, white blood cell count.

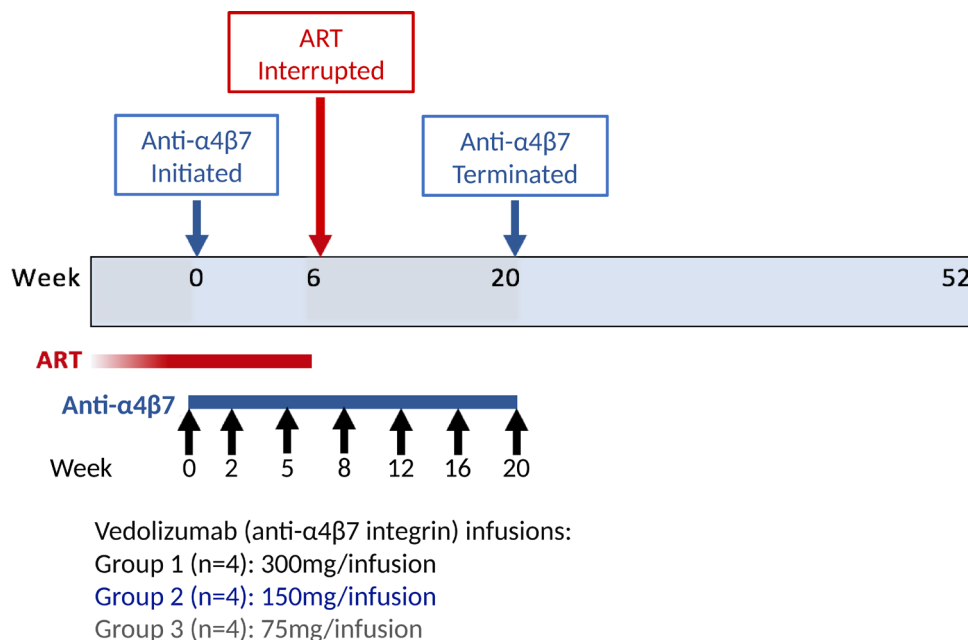


Figure 1 Overview of vedolizumab treatment intervention and analytical treatment interruption of antiretroviral therapy (ART). There are three groups of 4 participants each that will be sequentially recruited. Each group will receive 7 infusions of vedolizumab, at weeks 0, 2, 5, 8, 12, 26 and 20. Group 1 will be recruited first and receive 300mg of vedolizumab per infusion, the highest licensed dose. Group 2 and group 3 will receive 150 mg and 75 mg per infusion, respectively. Screening and baseline will take place approximately 3–6 months apart. Baseline and week 0 assessments can take place at one visit or be split into two visits (ie, the baseline rectal biopsy can take place up to 4 weeks prior to the week 0 visit (or at the same time) when the vedolizumab intervention is started. Participants will start vedolizumab at the week 0 visit, but continue on their pre-study ART regimen until week 6/7 (analytical treatment interruption, ATI). There will be four doses of vedolizumab after ATI at weeks 8, 12, 16 and 20 (each 4 weeks apart from each other). The participant will subsequently visit every 4 weeks until week 52 as per study visit schedule (table 1). ART will be re-initiated prior to week 52 if there is a sustained rebound of plasma viral load as detailed in Methods section.

Study intervention

Figure 1 shows the study schedule and table 1 shows the study visit schedule. Twelve HIV-infected adults on suppressive ART meeting all inclusion and exclusion criteria will be enrolled sequentially in groups of four to receive three different doses of vedolizumab (300 mg, 150 mg, 75 mg) by infusion for a total of seven doses at intervals as recommended for ulcerative colitis¹² (weeks 0, 2, 5, 8, 12, 16 and 20). Participants will undergo an ATI of their regular ART at weeks 6–7 (figure 1), with the duration of ATI being up to 48 weeks, or until sustained viraemia or immune dysfunction is documented (see re-treatment parameters below). After completion of the study protocol, patients will be seen quarterly or as needed according to pVL response and/or ART re-treatment status and response according to standard clinical practice.

Re-treatment parameters

Threshold criteria for clinical consideration of ART re-initiation will include (1) sustained recurrence of HIV viraemia, (2) confirmed absolute CD4 count below 350 cells/ μ L or by more than 10% from pre-ART baseline CD4 value, or (3) development of an AIDS-defining or related illness. Following ATI, sustained recurrence of HIV viraemia will be defined by confirmation by repeat testing of (1) pVL reaching ≥ 0.5 log of the patient's viraemia

peak prior to ART and (2) pVL rebound extending beyond a period of 12 weeks from initial detection after ATI. If sustained viraemia is observed after ATI, ART may be re-initiated and participants monitored until pVL suppression is re-established. Study visits as per the study schedule will continue in these patients. The decision to re-initiate ART is a personal choice of the participant and non-study advisors, the trial investigators and staff, or an experienced and independent medical judgement on the aggregate of timely clinical and laboratory information at hand, with the interests of the patient primarily in mind.

Withdrawal

Participants may withdraw from the study for any reason at any time. Participants may also be withdrawn by the investigator due to an AE which would in the judgement of the investigator require discontinuation of study product or re-initiation of ART, or for non-compliance with the study protocol. Participants who withdraw from the study will be asked to follow up either with the study physician or their regular HIV physician.

Sample size justification and analytical plan

This is an exploratory pilot study of 12 HIV-infected adult volunteers, which will permit observation of the incidence, degree and duration of virological rebound and remission following vedolizumab treatment across ATI.

SVR in the absence of ART is rarely observed. If this effect can be repeatedly demonstrated in response to the intervention, the outcome would be remarkable and clinically meaningful. For this study, a small sample size is sufficient to observe such a categorical effect on virological rebound and SVR following vedolizumab treatment.

Virological rebound will be compared with individual patients' pre-ART pVL measures and with historical controls consisting of participants having undergone ATI in other reported trials. Mean and median levels of pVL rebound will be compared with steady-state pre-treatment levels using standard statistical tests, analogous to pharmacokinetic parameters.

Clinical and laboratory assessments

Screening and safety laboratory tests

Safety laboratory measures will include a CBC, white blood cell differential, electrolytes, erythrocyte sedimentation rate and serum chemistry (albumin, alanine transaminase, alkaline phosphatase, amylase, aspartate transaminase, bilirubin (total), blood glucose (random), blood urea nitrogen, calcium, chloride, C reactive protein, creatinine, gamma-glutamyl transferase, potassium, protein (total), and sodium).

HIV and HIV reservoir assessments

A pre-ART pVL will need to be obtained from the patient chart as part of study inclusion. HIV pVL will be assayed using the Abbott HIV 1 Viral Load Assay at indicated study visits. CSF may be collected from consenting participants at week 24 (end of vedolizumab treatment, during ATI) and week 52 for viral load assay in the event of pVL suppression, or if lumbar puncture for CSF is otherwise clinically indicated according to an AE.

HIV reservoirs will be measured in peripheral blood mononuclear cells (PBMCs) by viral outgrowth assay and HIV DNA by PCR.

Mononuclear cells will be isolated from rectal mucosal biopsy samples scheduled to be taken before vedolizumab treatment, and after ATI in cases with post-ATI suppression of pVL. DNA will be isolated from a fixed number of cells and subjected to PCR analysis and expressed as the number of copies per nanogram of host DNA.^{3 13}

CD4/CD8 T-cell counts and immunophenotyping

Routine CD4 and CD8 T-cell counts will be performed on whole blood using standard flow cytometric analysis. Flow cytometry will be performed on freshly isolated PBMCs and mononuclear cells isolated from peripheral blood, and the rectal mucosal biopsy samples to evaluate relative expression of levels of CD45A, CCR7 and CD27 to determine percentages of naïve, central memory, preterminal effector memory, transitional memory and terminally differentiated CD4⁺ and CD8⁺ T-lymphocyte subsets as previously described.¹⁴ The expression of activation markers such as HLA-DR and CD38 will also be assessed by flow cytometry.

Vedolizumab measurements

Serum samples taken over the course of the trial (each study visit starting at week 0) will be taken and cryopreserved for future measurement of vedolizumab levels, for anti-drug antibodies (ADA) and for neutralising ADA.

Immunohistochemical staining

In addition to HIV reservoir quantification, immunohistochemical staining and standard histopathological microscopic examination will be performed on biopsy specimens.

Faecal microbiome assessment

Nucleic acid probe testing will be performed on frozen stool samples collected at three intervals (week 0, week 24 and week 52) for characterisation of the human faecal microbiome.³

Assessment of inflammatory cytokines in plasma

Frozen plasma samples collected at each study visit and stored at -80°C may be assayed for changes in specific inflammatory cytokines (eg, IFN- α , IL-1, IL-6, IP-10, TNF- α and LPS) pre-study and post-study intervention by ELISA.

Safety reporting and quality assurance

AEs are defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered to be related to the medicinal product; and/or pre-existing symptoms or conditions which worsen during a study.

Information about all AEs and severe AEs will be recorded and followed for resolution. In this trial, there will be vigilance for infusion-related AEs.

To enhance patient safety, and to comply with the Health Canada Food and Drug regulations programme and Good Clinical Practice, an independent DSMB has been established for this trial. The DSMB will be informed and review safety and activity data, and will raise questions or instruct on protocol performance and outcomes.

An Ottawa Hospital Research Institute (OHRI) Internal Monitor will conduct a monitoring visit shortly after enrolment commences. This monitoring by OHRI does not replace the routine quality control to be performed by the investigator or designee. Routine quality assurance will be completed by an assigned monitor to ensure that the study is being conducted according to the protocol and the monitoring plan.

Patient and public involvement

Cancure community advisory members were consulted during the design process and the Canadian Institutes of Health Research Canadian HIV Trials Network (CTN) Community Advisory Committee was involved in reviewing the study prior to a funding decision. We planned and did engage our study volunteers in the communication of interim and preliminary study results, and the planning of any needed protocol amendments during the trial.

Ethics and dissemination

The study protocol and informed consent documents have been approved by the Ottawa Health Science Network-REB (#20160928) and by the Health Canada Therapeutic Products Directorate (#HC6-024-c206120). Written informed consent will be obtained from all participants. The study will be conducted in accordance with Health Canada regulations, the International Conference on Harmonisation guidelines on current Good Clinical Practice and the Declaration of Helsinki. Patient recruitment has begun and continues.

Results will be disseminated through scientific peer-reviewed publications, national and international conferences, and the CTN according to CONSORT (Consolidated Standards on Reporting Trials)¹⁵ and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)¹⁶ guidelines.

DISCUSSION

The report of sustained SIV remission in rhesus macaques treated with an anti- $\alpha 4\beta 7$ mAb³ is the foundation on which the HAVARTI trial was developed. The present study will aim to determine if vedolizumab, the humanised anti- $\alpha 4\beta 7$ mAb available on the Canadian market, is safe for healthy HIV-infected adults at a licensed or permitted dosage. In addition, the goal is to assess vedolizumab for SVR after ATI. Towards these goals, several design elements were taken into special consideration during the development of the HAVARTI trial, with an effort to closely follow the macaque study while keeping the safety of the participants primarily in mind.

The HAVARTI trial is designed as a single-arm, dose-ranging pilot trial. No placebo control arm will be used because (1) this is an exploratory pilot study of a novel investigational agent; (2) pVL rebound occurs reliably after analytical or other ART interruption, and the SVR outcome of interest is not a small effect; and (3) in small trials, neither randomisation nor controls may protect from large expected biases related to biological variation. Placebo controls from an Ottawa/Montreal randomised controlled trial of therapeutic HIV vaccination using ALVAC with or without Remune experienced a median time to viral rebound of ~2 weeks¹⁷ after ATI and will be used as a historical control for comparison, among other more recent reports and studies.

ATI, the intentional interruption of suppressive ART to assess an investigational product's ability to induce virological control, remains the gold standard for investigation of novel therapies for HIV cure research.¹⁸ Although the SMART study conducted in the context of clinical management research showed that participants who interrupted ART were at higher risk of developing AIDS and non-AIDS events compared with those who did not interrupt ART,¹⁹ it also revealed that ATI can be done safely when the individual has suppressed plasma viraemia (pVL <50 copies/mL), high current CD4 count (>500 cells/ μ L) and high CD4 nadir (>200 cells/ μ L), in the context of a

carefully monitored trial.^{1 20–22} Therefore, participants in the HAVARTI trial will be screened for these inclusion criteria to decrease risks associated with ART interruption in a different context. Furthermore, successful re-initiation of ART and suppression of pVL is a priority, so prospective study participants will not have a history of drug-resistant HIV, treatment-refractory pVL response or non-adherence to ART. Certain HLA phenotypes have been shown to be protective and prevent viral rebound following ATI²³ and therefore HLA typing should be performed if any controller phenotypes emerge following vedolizumab treatment.

The rationale behind threshold criteria and judgement for re-initiation of ART stems from the rhesus macaque model, where ATI was followed by initial rebound of SIV pVL in most animals before subsequent sustained remission was achieved.³ If vedolizumab has the same effect in HIV-infected humans, it is hypothesised that there may be a similar short-term pVL rebound prior to SVR. Re-initiation of ART at first detection of pVL rebound would prevent detection of subsequent, perhaps immunologically mediated, SVR.

While the present trial is modelled on the macaque study,³ there are some notable differences in the dosing regimen. Primatised anti- $\alpha 4\beta 7$ mAb has Fc-receptor avid Fc-fragment, whereas vedolizumab is a masking antibody, without Fc-receptor avidity.^{24 25} Macaques were infused with 50 mg/kg of $\alpha 4\beta 7$ mAb; in this study, the highest vedolizumab dose is 300 mg per infusion, about 4 mg/kg for a 70 kg adult. Pharmacokinetic studies in humans showed saturation of peripheral blood lymphocyte target receptors at doses as low as 0.2 mg/kg,²⁶ with robust saturation at doses of 2 mg/kg.²⁷ Vedolizumab is shown to be clinically effective for IBD at doses of 0.5–2 mg/kg,^{28 29} with 300 mg per infusion being the recommended dose for patients with IBD.⁹ The half-life of vedolizumab is 18–25.5 days^{30 31} versus a half-life of 11.4 days for the $\alpha 4\beta 7$ mAb used in the macaque study; therefore, after initial loading of three doses over 5 weeks, the regular dosing interval is 4 weeks for this study as compared with 3 weeks in the macaque study. Finally, participants will receive seven infusions of vedolizumab instead of the eight received by macaques. In the macaque study, pVL suppression was evident by 6 weeks after ATI in all treated animals. Viral rebound occurred within 2 weeks in five of eight animals and was subsequently re-suppressed within 4 weeks.³ Virological control was therefore robust throughout the remaining $\alpha 4\beta 7$ mAb treatments and after its discontinuation. The number of necessary infusions is unclear; however, data from the macaque model suggest that immunological control developed early after withdrawal of ART, and that ongoing mAb therapy after viral suppression may not be necessary.

Another difference between the macaque study and our participant population is the chronicity of infection prior to ART treatment and duration of suppressive ART. Macaques were infected with SIV 5 weeks before initiation of ART,³ the equivalent of treatment during primary HIV infection

(PHI). For the present human trial, we are recruiting participants who are chronically infected with HIV and on suppressive ART for 2–10 years. Most people living with HIV (PLWH) are not diagnosed during primary infection. Meaningful impact in HIV cure research requires interventions accessible to this majority population who have chronic HIV infection on effective ART.

Design of the HAVARTI protocol aims to maximally protect study participants from developing ADA. In the macaque study, 3 of 11 animals developed antibodies against the $\alpha_4\beta_7$ mAb.³ However, these animals were excluded from analysis and the effect of ADA on HIV treatment efficacy remains uncertain. The GEMINI trials demonstrated a 4% immunogenicity rate for patients with IBD who received continuous vedolizumab treatment, with rates of persistent positive antibody and neutralising antibodies at 0.6% and 2.3%, respectively.^{32 33} However, the immunogenicity rate was 10% when patients were off vedolizumab treatment, suggesting the rate may have been underestimated due to decreased ability to detect low to moderate ADA titres during continuous treatment.^{10 31} Since ADA development is more likely for low-level and intermittent exposure, this study is designed with short dosing intervals to avoid recurrent prolonged periods of low mAb levels.

PLWH are required to take daily ART indefinitely. The SIV₂₃₉-infected rhesus macaques that were functionally cured by treatment with ART and a mAb against $\alpha_4\beta_7$ integrin give us hope that a similar functional cure could be possible for PLWH. This is the first study to employ a clinical trial design involving multiple dosing arms to assess safety, tolerability and best anti-HIV effect of vedolizumab in the context of chronic HIV infection. A licensed drug such as vedolizumab with a novel anti-HIV mechanism of action would be of great clinical interest in the pursuit of HIV cure.

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Contributors MM and DWC conceived and designed the study, drafted the pilot study grant and the protocol manuscript. MM will organise and manage the trial under the supervision of DWC. JBA, CC, JC and PAM provided input into study feasibility at the TOH HIV clinic. JBA and AK gave input into methods for sample collection and processing. SM and RS contributed their expertise related to collecting rectal biopsies and stool samples. MD and NT provided insight into participant inclusion/exclusion criteria and recruitment strategies. SNB contributed

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