Application: RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral

Madeleine Durand - mdurandrecherche@gmail.com
CTN+ Letter of Support Requests & Portfolio Study Submissions

Summary

ID: 0000000012
Status: In Review
Last submitted: Aug 26 2025 12:44 PM (PDT)
Labels: Fall 2025 Competition

Full Study Submission Form

Completed - Aug 26 2025

Full Study Submission Form

CIHR Pan-Canadian Network for HIV and STBBI Clinical Trials Research | Réseau pancanadien pour des essais cliniques sur le VIH et autres ITSS

Please read the CTN+ Portfolio Study Submission and Review Process Guidance document prior to completing your submission.

If you have received a CTN+ Letter of Support and secured funding for your project, please use the form below to submit your study for full CTN+ support. Your application will be reviewed by the CTN+ review committee panel before receiving final adjudication at the next CTN+ Steering Committee meeting. In the case of incomplete information, you may be contacted by a CTN+ administrator with a request to provide additional details or documents.

If you have any questions or concerns about this process, please send an email to submissions@hivnet.ubc.ca.

Principal Applicant

First and Last Name

Madeleine Durand

Email Address

madeleine.durand@gmail.com

Institutional Affiliation

CR CHUM

Is the Principal Applicant a CTN+ Researcher?

If you have not yet submitted the **CTN+ Researcher Application form**, please fill out the form via this link before submitting the Full Submission form.

Yes

Submitter

Leave blank if this form is being submitted by the Principal Applicant.

First and Last Name

Branka Vulesevic

Email Address

bvule091@uottawa.ca

Please upload the CTN+ Letter of Support you received for this project (if applicable).

Support Letter Durand LOI inflammation Team Grant_Updated Feb 2024-2.pdf

Filename: Support Letter Durand LOI inflammation Team Grant_Updated Feb 2024-2.pdf.pdf **Size:** 273.0 kB

Submission Details

Type of Submission

Final Submission

Regional Team Affiliation

Responses Selected:

Quebec Region

Think Tank Affiliation

Responses Selected:

Treatment & Management Think Tank

Study Details

Study Name

(Long and short versions)

RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy

Study Hypothesis

(In one sentence)

PLWH with undetectable viral load but detectable sgp120 are exposed to chronic inflammation, sustained immune dysfunction and increased risk of comorbidity. The addition of fostemsavir to their existing antiretroviral regimen will lead to decreased inflammation, improved immune function and decreased cardiovascular disease.

Lay Language Description

(300 words maximum)

At present, HIV is a chronic, manageable disease, but it remains incurable. In this context,
Aging well with HIV is a public health priority. The study population of this research project are people living with HIV with an undetectable viral load, and the overarching goal of this program is to close the prognostic gap for these people, so that they may have an optimal health-related quality of life.
Recognizing the complexity of aging with HIV, our study team includes researchers from
multiple domains of expertise, including general internal medicine, microbiology, and
immunology, cardiology, diagnostic radiology, virology, immunology, epidemiology and trial
experts, as well as a team of participants with diverse life experiences.
Briefly, this study is a randomized trial of fostemsavir to reduce inflammation in people living with HIV with undetectable viral load but detectable levels of HIV envelope protein subunit gp120 in plasma. It will establish whether treatment with fostemsavir can reduce inflammation and comorbidities such as cardiovascular disease in this population. At present, no intervention has been shown to be effective in reducing the risk of cardiovascular disease secondary to the chronic inflammation present in people living with HIV.

Number of Participants

(Total N, and N per Arm if applicable)

75 per arm - two arms (150)

Please list the participating sites.

(Use 1 row per Site. Leave any unused rows blank.)

	Investigator (total)	Institution	Target Enrolment
Site 1	Madeleine Durand	CHUM	90
Site 2	Cecilia Costiniuk	MUHC	40
Site 3	Melanie Murray	Oak Tree Clinic (UBC)	20
Site 4			
Site 5			
Site 6			
Site 7			
Site 8			
Site 9			

Background Information and Study Rational

(500 words maximum)

With more than 39 million people living with HIV (PWH), and 1.3 million new infections in 2023 alone, HIV remains a major public health issue. Under suppressive antiretroviral therapy, life expectancy for PWH is lengthening. However, PWH presently develop comorbidities 15 years earlier than their HIV-negative counterparts, with no signs of this gap closing in the past decade. The term inflammaging has been proposed to refer to accelerated aging caused by the chronic, low-level inflammation that persists in some people living with HIV despite suppressive antiretroviral therapy, affecting multiple organ systems.

One of the leading hypotheses for this gap is that ongoing antigenic stimulation from the virus itself contributes to the chronic inflammation. A potential mediator is a subunit of the HIV-1 entry mechanism: HIV-1 glycoprotein 120 (gp120). It has been shown that gp120 is shed from the viral membrane and can be detected in plasma, even when HIV itself is undetectable. Our team demonstrated that soluble gp120 (sgp120) is associated with the death of uninfected CD4 cells and a cytokine burst from monocytes, driving inflammation. Fostemsavir is a first-in-class entry inhibitor HIV antiretroviral, presently approved by Health Canada only in the context of drug-resistant HIV infection. Our group has shown that fostemsavir prevents the interaction of sgp120 with the CD4 receptor, preventing cytokine burst and CD4 cell death, therefore representing a potential treatment to reduce chronic inflammation and prevent comorbidity in PWH.

Our overarching goal is to close the prognostic gap in people with well-controlled HIV. We plan to do so in a large randomized controlled trial targeting chronic inflammation mediated by spg120 using fostemsavir to reduce cardiovascular diseases and other comorbidities.

Specific objectives:
1- conduct a randomized controlled trial of fostemsavir vs standard of care in adults with well-controlled HIV and detectable sgp120 in plasma, to reduce inflammation-associated comorbidities, most notably cardiovascular disease;
2- design, implement and support a trial-associated biobank and conduct biomarker analyses;
3- recruit a sample composed of 50% of women to the trial.

We have co-designed and will co-lead this trial with a diverse group of people with lived experience. From the inception, we have constituted two advisory bodies that will contribute to our research process, representing diverse gender identities, ethnic backgrounds and at-risk populations, including two members who self-identify as Indigenous. The addition of the Women's Advisory board (formed of six women living with HIV coming from diverse backgrounds) helped us plan our recruitment strategy, taking into account the intersecting vulnerabilities often experienced by women living with HIV. Both groups will have an ongoing active role throughout the study process.

Expected Results and Significance:
The standard of care for HIV treatment is the immediate institution of lifelong combination antiretroviral therapy for all, intending to obtain a suppression of HIV plasma viral load. Positive findings from the RESTART study would generate a paradigm shift in treatment goals. It would introduce a much-needed, HIV-specific, personalized approach to reducing the increased risk of comorbidities linked to enduring antigen stimulation for people aging with HIV.

Study Hypothesis and Design

(1000 words maximum)

This section must include:

1. the hypothesis;
2. the study design (methodology and statistical analysis, including the rationale for the sample size calculation);
3. the study population (including participant inclusion/exclusion criteria);
4. the specific study intervention details;
5. expected outcomes; and
6. expected results and implications for the field.

HYPOTHESIS: The addition of fostemsavir to their existing antiretroviral regimen will lead to decreased inflammation, improved immune function and decreased cardiovascular disease

STUDY DESIGN: Randomized Controlled Trial (RCT) evaluating the superiority of fostemsavir, compared with the standard of care, in reducing non-calcified coronary artery plaque volume in people living with well-controlled HIV.

COMPARISON AND RANDOMIZATION: In this Phase II RCT, randomization will be done in a 1:1 ratio, with allocation in parallel arms, stratified by sex and participant statin use at recruitment, through a computerized algorithm with permuted blocks of randomly varying size, to ensure allocation concealment. The intervention will be either the addition of fostemsavir to the current ART regimen, with the standard of care as comparison. Standard of care includes continuation of the ARV regimen and other medications prescribed by their physicians. This trial will be conducted as an open-label study; however, assessors of the primary outcome (based on two CCTA scans) and of the biobank analyses will remain blinded to treatment allocation, as well as statisticians.

Based on prior results of variation in total uncalcified coronary plaque volume measured on CCTA over 12 months in people with HIV, we estimated an expected mean change in the atorvastatin group of –7.67 mm^3, with a standard deviation of 17.59, and an expected mean change in the placebo group of 10.00 mm^3, with a standard deviation of 28.81. This corresponds to a Cohen's d effect size of 0.73. However, given that we expect statin use in both groups, we adopt a conservative approach for this study and assume a medium effect size (Cohen's d = 0.50) to account for potential attenuation of the fostemsavir effect due to concomitant statin therapy. This would translate to a decrease of 2.17 mm^3 in the fostemsavir group and an increase of 10.00 mm^3 in the group receiving standard of care, using standard deviations of 17.59 and 28.81, respectively. Based on this effect size, with 80% power and an alpha of 0.05, the estimated target sample size is 130 patients to detect a clinically meaningful difference. Allowing 10% incomplete CCTA or loss to follow-up, we aim to recruit a total sample size of 150 patients into the trial at three study sites (75:75). Statistical analysis will be conducted by CITADEL (part of the CRCHUM) after the closing of the study database, according to the statistical analysis plan, registered before the analysis is conducted. All analyses will be done by intention-to-treat; patients will be analyzed in the group they were randomized. Biobank analyses planned after 50% of participants completed the 12-month biobanking will be done by CITADEL after this part of the data collection is closed.

THE STUDY POPULATION:

Adults with well-controlled HIV who meet all the following inclusion criteria:

1. 40 years or older, or have lived with HIV for 25 years or more,
2. Undetectable HIV viral load (less than 50 copies/ml within the last 6 months);
3. Presence of at least one cardiovascular risk factor: longstanding HIV infection (>25 years), hypertension, diabetes, past or present smoking, dyslipidemia, family history of early onset cardiovascular disease (CVD) in a first-degree relative (younger than 55 in males or younger than 65 in females), known previous CVD (defined as past myocardial infarction, coronary revascularization, stroke, or

coronary artery atherosclerosis). Participants with past CVD must be in a stable clinical condition as judged by the study clinicians;
4. Evidence of detectable plasmatic HIV sgp120 levels at any point in the past 6 months, using the assay described previously and performed at CRCHUM in Dr Finzi's laboratory.
Exclusion Criteria:
1. Already on fostemsavir regimen
2. Hypersensitive to this drug or to any ingredient in the formulation,
3. Concomitant treatment with strong cytochrome P450 (CYP3A) inducers, including but not limited to: carbamazepine, phenytoin, mitotane, enzalutamide, androgen receptor inhibitor, rifampicin and St John's wort
4. Planning to become pregnant, pregnant, or breastfeeding
5. Contraindication for CT scan use (estimated glomerular filtration rate [eGFR] <40ml/min)
6. Known Congestive heart failure with NYHA class 3 or 4.
7. Elevated risk of prior ionizing radiation exposure outside clinical care exceeding 10 mSV over 3 years, per the investigator's judgement
8. Confirmed uncorrected QT value >500ms or confirmed QTcF >470 msec for women and >450 msec for men;
9. Acquired/ congenital long QT syndrome;
10. Current or anticipated treatment with any of the following medications: amiodarone, disopyramide, dofetilide, ibutilide, procainamide, sotalol, and quinidine;
11. Unstable liver disease (full details in the protocol)
12. Inability to provide informed consent;
13. Life expectancy less than 36 months;
14. Inability to attend study visits;
15. Participation in another interventional trial;
SPECIFIC STUDY INTERVENTION DETAILS: The intervention will be either the addition of fostemsavir (Rukobia 600 mg daily) to the patient's current ART regimen or the standard of care. The dose of the study drug (fostemsavir extended-release tablets - DIN 02520869) currently approved for use as an antiretroviral in people failing their ARV regimen is 600 mg orally twice daily. In the RESTART trial, we are using a once-daily dosage, with the agreement of ViiV Healthcare and Health Canada.
EXPECTED OUTCOMES
Primary Outcome: Change in total uncalcified plaque volume between baseline and month 24, contrasted between fostemsavir and standard of care.
Imaging Secondary Outcome: Perivascular fat attenuation index at month 24, adjusted for baseline values.
Clinical Secondary Outcome: time to and incidence of MACE, B-CAM and grip strength at month 24 (adjusted for baseline values).
Safety data will be collected at the first safety visit (one month after the beginning of treatment) and throughout the study through SUSAR and SAE reporting capture in the trial's CRF.
Biomarker Secondary Outcomes: Biomarkers identified in biobanking samples (virology, immunology, inflammation).
Safety Secondary Outcomes: Risk of serious adverse events and incidence of treatment discontinuation due to side effects.
EXPECTED RESULTS AND IMPLICATIONS FOR THE FIELD: Positive findings from the RESTART study would generate a paradigm shift in treatment goals. It would introduce a much-needed, HIV-specific, personalized approach to reducing the increased risk of comorbidities linked to enduring antigen stimulation for people aging with HIV.

Please list any barriers/potential risks that may impede the study and include mitigation strategies.

(100 words maximum)

1. COMPLIANCE – anticipated >80% treatment compliance due to the PLWH population's strong adherence, reflected by undetectable viral loads and consistent clinical care. Also, fostemsavir was well tolerated
2. LOSS TO FOLLOW UP – expected to be ≤10%, supported by high retention in participating sites, and efforts that will be made to limit loss to follow-up and missing data to a minimum (multiple recalls, visits outside of regular work hours and participant compensations).
3. LOW RECRUITMENT - Recruitment will occur at diverse, high-volume clinics in Montreal and BC well well-experienced in running RCT studies, aiming for 50% women for broad generalizability.

Estimated start date of recruitment/study start date

9/2025

Estimated final date of participant follow-up (if applicable)

9/2028

Estimated date of final study/project report

6/2029

Additional Documents

Please upload the Notice of Decision or Award Letter from your primary funding source.

Notice of decision-2.pdf

Filename: Notice of decision-2.pdf.pdf **Size:** 510.4 kB

Please upload the Reviewer Comments document related to the decision of funding (if applicable).

review CIHR.pdf

Filename: review CIHR.pdf.pdf **Size:** 177.5 kB

Please upload your Research Proposal document.

RESTART_proto_recherche_chum_v4.0_20250530.pdf

Filename: RESTART_proto_recherche_chum_v4.0_20250530.pdf.pdf **Size:** 1.7 MB

Please upload your Budget document.

budget final 2-2.pdf

Filename: budget final 2-2.pdf.pdf **Size:** 806.4 kB

Funding Source & CTN+ Service/Support Request

Confirmed funding source/agency/company name

CIHR

Is the study funded through a CIHR Project Grant?

Yes

If the study is *not* funded through a CIHR Project Grant, please list the type of grant or the type of agency/company support (e.g. Investigator-initiated grant in aid from a pharmaceutical company)

(If you responded "Yes" to the previous question, please leave this blank.)

(No response)

Please indicate which in-kind services you request from the CTN+ if your submission is approved.

You can find a full list of services on the resource page.

Responses Selected:

Basic Knowledge Mobilization services (plain language summary, recruitment materials, social media support)
Data Safety & Monitoring Committee (DSMC) - for interventional studies only
Regulatory – Health Canada Clinical Trial Application (CTA) Consultation, for Health Canada Regulated Trials only
Site Monitoring – for Health Canada Regulated Trials only

Please indicate which of the following service support estimates you requested in your CTN+ Letter of Support to conduct your study.

You can find a full list of services on the resource page.

Responses Selected:

Advanced Knowledge Mobilization support
Other, please specify...: Data Safety Monitoring Committee

Does your study include a Participant Informed Consent Form?

Yes (please attach the document via the upload function below)

Upload your Participant Informed Consent Form (if applicable)

RESTART ICF Version 6 _25.07.2025.docx

Filename: RESTART ICF Version 6 _25.07.2025.docx.docx **Size:** 155.6 kB

Have you created a Community Engagement Plan?

Yes (please attach the document via the upload function below)

Upload your Community Engagement Plan (if applicable)

Community Engagement Plan_MD.docx

Filename: Community Engagement Plan_MD.docx.docx **Size:** 114.6 kB

Have you created an Indigenous Engagement Plan?

No (please explain why): Within our CAB we are colaborating with 2 indigenouse memebrs. With their help we have identified ways to ensure that Indigenous participants in research can have their data reported back to them before any publication. We will also support the generation of Indigenous-led knowledge translation activities tailored to Indigenous participants.

Upload your Indigenous Engagement Plan (if applicable)

Do you have a Knowledge Mobilization Plan for your study?

Yes (please attach the document via the upload function below)

Upload your Knowledge Mobilization Plan (if applicable)

KM Plan.docx

Filename: KM Plan.docx.docx **Size:** 118.8 kB

BUDGET JUSTIFICATION

SUMMARY

	Year 1	Year 2	Year 3	Year 4
Research personnel	118,759$	118,759$	142,135$	142,135$
Benefits	32,007$	32,007$	37,751$	37,751$
Research trainees	0$	0$	60,000$	60,000$
Expendables	41,881$	32,981$	86,539$	80,539$
Services	857,550$	1,463,958$	1,158,886$	1,016,366$
Other/KTE cost	8,950$	3,250$	6,450$	11,950$
Travel	0$	4,000$	2,500$	2,500$
In-kind	-558,600	-1,174,575$	-984,232$	-842,200$
Total per year	**500,547$**	**480,380$**	**510,029$**	**509,041$**
Total requested to CIHR	**1,999,997$**			

RESEARCH PERSONNEL

COORDINATION TEAM

Branka Vulesevic, PhD, research coordinator 61,063$ + 17,223$ benefits per year

Dr. Vulesevic will be responsible for the logistics and the management of the study across all sites (ethical submissions, Health Canada communication, contracts, budget etc). Dr. Vulesevic will also be in charge of supervising enrollment at each site, she will overview the quality of data, audits, and execute overall supervision and monitoring of the study. She will coordinate all internal communications, schedules, meetings, study newsletters and coordinate logistics of the Investigator's meeting. Her base salary is 103K including 22% fringe benefits. She will devote 75% of her time to this project for a total of 3FTE over the 4 years period.

Marc Messier-Peet, Msc, Data management: 24,000$+5,280$ benefits per year

Data manager will be in charge of overseeing the data management and program periodical data output from the central database, and outputs adapted to every co-researcher's specific needs. He will also support sub-teams with data analysis and interpretation and participate in manuscript preparation and redaction. Mr Messier-Peet will devote a total of 1.25 FTE of his time on this project during the 4 years period.

RESEARCH ASSISTANTS

Halima Medjahed, research assistant: 33,696$ + 9,504$ benefits per year

She will be in charge of blood processing and storage for CHUM and Quartier Latin participants. She will also produce the antigens required for the different ELISAs and she will perform the ELISA and Luminex assays. Her annual salary is 60K. Fringe benefits are calculated at a rate of 22% of base salary, for a total annual salary of 72K. She will devote 60% of her professional effort on this project and consequently 60% of her salary is requested per year, for a total of 2.4 FTE.

Amélie Pagliuzza, MSc, research assistant: 13 547$ +2,973$ benefits (year 3-4)

Ms. Pagliuzza is a Research Assistant in the Chomont lab who is an expert in HIV reservoir measures. She will isolate CD4+ T cells from PBMCs by negative magnetic selection, extract genomic DNA and total RNA and will use our highly sensitive PCR-based approaches to measure HIV DNA and cell-associated HIV transcripts in all samples. She will be working on this project on years 3 and 4 for a total of 0.5 FTE

Mohamed Sylla, Msc, Research assistant: 9,828$ + 2,772$ benefits (year 3-4)

Mrs Sylla is a research assistant in Dr Tremblay's laboratory since 2004. He will be in charge of ELISA and PCR for the quantification of IL1/18/32/TRAIL. He will devote 0.4 FTE of his time on this project during year 3 and 4.

Cost for Research Personnel/year	**Year 1:**	**150,766$**
	Year 2:	**150,766$**
	Year 3:	**179,886$**
	Year 4:	**179,886$**

Total Research Personnel:	**661,304$**

RESEARCH TRAINEES

Manon Nayrac, Post doctoral 60,000$ per year (years 3-4)

Dr Nayrac is a post doctoral fellow in Dr Finzi's lab. She will conduct she will perform analysis on cells dysfunction such as ELISA, Luminex assays and flow cytometry measurement and analyze data generated by those assays. She will also prepare manuscripts and present results at study meetings, local and national conferences. Dr Nayrac applied to Mitacs grant for a total of 60,000$ per year for a total of 120,000$

Cost for Research Trainees	**Year 3-4:**	**120,000$**
Other funding (60,000$/2 years)		**-120,000$**

Total Research Trainees:	**0$**

MATERIALS, SUPPLIES AND SERVICES

EXPENDABLES

Team Finzi

- Tissue culture reagents and kits
  Blood collection (560 samples): tubes ACD, EDTA, Serum), Ficoll, HBSS, DMSO, FBS, RPMI, HEPES: **17,924$**
- Plasticware (50 mL Falcon tubes, ELISA plates, pipettes, microtubes, freezing microtubes, etc) : **17,900$**
- mAb anti-gp120 production and purification for sgp120 ELISA 293F, Freestyle medium, Prot A sepharose, Filters, etc): **4,500$**
- Mass Spec for TMR detection in plasma samples: **15,000$**
- Luminex kits to measure CCL2/JE/MCP-1, CCL4/MIP-1 beta, CCL20/MIP-3 alpha, sCD163, CXCL2/GRO, beta/MIP-2/CINC-3, CXCL13/BLC/BCA-1, IL-1 beta/IL-1F2, IL-6, IL-10, IL-18/IL-1F4, IL-23, IL-27, TNF-alpha, TSLP, sCD14.
  $5,000 / 40 samples in duplicate. For 600 samples **75,000$**
- Kits to isolate primary CD4 T cells (EasySep) **7,500$**
- BD anti-p24 KC57 for intracellular p24 staining required for FACS-based ADCC, (to identify uninfected bystander cells): **4,500$**

Total Finzi	**Year 1:**	**41,881$**
	Year 2:	**32,981$**
	Year 3:	**36,731$**
	Year 4:	**30,731$**
	Total:	**142,324$**

Chomont Lab

All experiments will be performed on samples collected at 3 visits (baseline, 24 and 27 months) from all participants (n=150). The total number of samples to be analyzed is 450.
Cost are span between Year 3 and Year 4.

- Isolation of CD4+ T cells by negative magnetic selection (StemCell)
  450 samples x 50$ = **22,500$**
- Dual extraction of genomic DNA and total RNA from isolated CD4+ T cells (Qiagen)
  450 samples x 20$ = **9,000$**
- Total HIV DNA quantification (nested PCR for LTR-gag)
  450 samples x 10$ = **4,500$**
- Cell-associated HIV RNA quantification (RT-nested PCR for LTR-gag)
  450 samples x 22$ = **9,900$**

Total Chomont	**Year 3:**	**22,950$**
	Year 4:	**22,950$**
	Total:	**45,900$**

Tremblay/El-Far Lab

- Human IL-1 beta/IL-1F2 Quantikine ELISA Kit, R&D Systems, DLB50, 800$ per kit x 9 = **7,200$**
- Human Total IL-18 DuoSet ELISA, R&D Systems, DY318-05 533$ per kit x 6 = **3,198$**
- Human IL-32 DuoSet ELISA, R&D Systems, DY3040-05, 533$ x 6=**3,198$**
- Human TRAIL/TNFSF10 Quantikine ELISA Kit, R&D Systems, DTRL00, 800$ per kit x 9= **7,200$**
- ELISA plates, VWR, Approx **1,500$**
- Ready to use primers for IL-32 isoforms and Ref, Invitrogen, = **1,000$**
- RNeasy Plus Micro Kit (50), Qiagen, 74034, 581$ per kit x 9, **15,687$**
- QuantiTect SYBR Green RT-PCR Kit (200), Qiagen, 204243, 1166$ x 6 = **6,996$**
- LightCycler 480 Multiwell Plate 96, white, Roche, 4729692001, 1,079$.box x 3 = **3,237$**
- Plasticware and Other reagents for the PCR, Approx **4,500$**
-

Total Tremblay/El-Far	**Year 3:**	**26,858$**
	Year 4:	**26,588$**
	Total:	**53,716$**

Cost for Expendables/year	**Year 1:**	**41,881$**
	Year 2:	**32,981$**
	Year 3:	**36,539$**
	Year 4:	**80,539$**

TOTAL EXPENDABLES:	**241,940$**

SERVICES

Patient recruitment, follow-up visit and compensation costs

Administration cost per patients visit include nurse/coordinator time for appointment booking, Informed consent administration, randomization, patient counseling, patient history, questionnaire, drug preparation and distribution by participating site pharmacy, specimens collection, CRF data collection/entry in RedCap and query resolution. We estimate that total cost for participant enrollment and follow-up will be 2,395$ per participant. This include participants compensations (60$ per visit and 120$ for randomization visit) and individual protection equipment. Costs per visit is as follow:

- Screening: **245$**
- Inclusion (phone call): **40$**
- Baseline/Randomization visist: **545$**
- Follow-up visits:
    - Month 1: **230$**
    - Month 6: **330$**
    - Month 12: **290$**
    - Month 18: **280$**
    - Month 24: **225$**
- End of study (Month 27): **210$**

We will also reimbursed sites for screen fail and unscheduled visist for an amount of **122.50$** per visit. This budget item also include start-up fees (**7,000$**), annual study cost (**1,250$**), study close-out and archiving (**7,000$**) for a total of 19,000$ per site.

We plan to enroll a total of 150 participants over a 12 months period. Therefore we are requesting funds for a total of **472,000$**. Expected cost per year are:

Year 1:	**156,092$**
Year 2:	**150,260$**
Year 3:	**110,432$**
Year 4:	**55,216$**
Total:	**472,000$**

Fostemsavir, (ViiV Healthcare Limited)

ViiV's contribution of fostemsavir for 75 participants at dosage of 600 mg/day over a 24-month period significantly enhances the feasibility and affordability of our study. With each month's supply valued at **1,883$** per participant, their in-kind donation represents a substantial investment in advancing medical research. This collaboration underscores ViiV's commitment to supporting innovative initiatives aimed at improving patient outcomes and underscores the importance of partnerships in advancing healthcare solutions. This represent a total of **3,389,607$**. See letter of support, partner applicant COI document and Partnership Details section.

Year 1:	**533,600$**
Year 2:	**1,167,705$**
Year 3:	**916,732$**
Year 4:	**772,200$**
Total (In-Kind)	**3,389,607$**

Fostemsavir encapsidation and Placebo preparation (Galenova inc)

Galenova Inc. will be are responsible for the encapsidation of fostemsavir, ensuring each capsule contains the precise dosage required for the trial. Additionally, Galenova will prepare the placebos, meticulously ensuring their composition aligns with the study's requirements. Beyond preparation, they also handle the distribution of both drugs to participating sites, ensuring timely and accurate delivery to support the progress of the trial. With their expertise and dedication, they will contribute significantly to the logistical and operational aspects of our research, facilitating the administration of fostemsavir and placebos to the 150 participants over the 24-month duration of the study. Cost for placebo preparation is estimated at 1.45$/capsule (total 78,259$) and fostemsavir encapsidation at 2.15$/capsule (total 105,941$). See Galenova quote attached in the application.

Year 1:	**33,156$**
Year 2:	**88,416$**
Year 3:	**62,628$**
Total:	**184,200$**

Laboratory services

This line include cost of blood tests for safety blood work (ALT, AST, Bilirubine, Chloride, CO2, Creatinine, complete blood work, blood smear, ALP Isoenzymes, Potassium, Sodium) and viral load for all participating sites. Prices are as follow

Safetely blood work (baseline, M1 and M12): 17.30$ x 3 x 150 = **7,785$**
Blook work Viral load (screening) 36.15$ x 450 (incl. screen fail) = **16,268$**

Year 1:	**13,959$**
Year 2:	**8,952$**
Year 3:	**1,142$**
Total:	**24,053$**

Cardiovascular imaging cost

Coronary CT angiography will be performed by using a 256-section CT scanner Cost for cardiovascular imaging include cost of Cardiac scans for 115 participants in Montreal (**250$ each**) and for the 35 women attending the Oak Tree clinic in Vancouver (**600$/unit**). This line also include funds for post-processing of images which will be done jointly at the end of the study. Images will be de-identified, and transferred to the CHUM core lab for post treatment at **500$/unit** (total 150,000$).

Total cardiovascular imaging and post –processing

Year 1:	**32,750$**
Year 2:	**17,000$**
Year 3:	**29,750$**
Year 4:	**170,000$**
Total:	**249,500$**

Laboratory services at BC Women's Research Laboratory

Laboratory at BC Women's research laboratory will be in charge of receiving and processing participant's sample during the study. They will be in charge of isolation of peripheral blood mononuclear cells (n= 400 samples), storage of samples and periodic shipping to Montreal central biobank. Service is **60$** for plasma preparation for sgp120 x 35 participants and **300$** for PBMCs processing x 35 participants x 7 visits for a total of 75,600$.

Year 1:	**25,873$**
Year 2:	**20,125$**
Year 3:	**22,102$**
Year 4:	**7,500$**
Total:	**75,600$**

CITADEL

CITADEL is a data infrastructure and biostatistics platform at the CHUM and is composed of data architects, data scientists, bioinformaticians, biostatisticians, physicians. They will be in charge of study preparation ie multicenter randomisation, eCRFs implementation (**4,995$**), support and validation in REDCap, audit trail, health care compliance and query and statistical analysis plan (**16,260$**). They will also be responsible for data base management, organization and analysis of research data generate from the study. They will carry out complex biostatical analysis (**$26,075**). The CHUM Research center authorized in-kind support of **12,000$** from CITADE (see letter of support).

Total:	**47,330$**
In-Kind	**-12,000$**
Total:	**35,330$**

Data Safety Monitoring Committee CIHR Canadian HIV Trials Network (CTN)

The Data Safety Monitoring Committee (DSMC) will conducts ongoing reviews of this clinical trial data to ensure participant safety and data integrity. They will assesses any adverse events, monitors efficacy, and may conduct interim analyses to evaluate the study's progress. The DSMC will provide recommendations regarding the trial based on its findings, contributing to the ethical conduct and validity of the research. Activities from the DSMC is valued at $5,000 per year for each year the trial is open and is supported by the CTN who have a vast and rich expertise in this field (see letter of support).

Year 1:	**5,000$**
Year 2:	**5,000$**
Year 3:	**5,000$**
Year 4:	**5,000$**
In-kind	**-20,000$**
Total:	**0$**

Flow cytometry facility platform at the CRCHUM ($45/hour)

Drs Finzi will use the equipment of the cytometry platform of the CRCHUM. More specifically his use the BD FACS Symphony, 6 lasers/31 parameters instrument usage for approximately 125 hours at **45$/hour** for a total of 5,625$

Total Y1-4 : 5,625$

NC3 utilisation cost:

Each research team (n=3) have a dedicated laboratory space in the NC3 which is under the CHUM management. This platform cost include real-time monitoring of temperature ATEK system (freezer, nitrogen tanks) and humidity (incubator), calibration and maintenance of equipment, biohazard autoclave sterilization service, cleaning products and all personal protection equipment (lab coats, N95 masks, face shield, gloves, shoes cover) for research staff.

Total Y1-4 : 8,000$

Annual equipment calibration

This line of cost is related to equipment calibration (NC2 space) to ensure optimal operation and storage of reagents in compliance with life science regulations. Refrigerators, -20 and -80 Freezer real-time temperature monitoring (ATEK), incubators, centrifuges, pipets etc). Real time pcr machine maintenance and calibration of dynamometer for grip strength.

Total Y1-4 : 2,400$

Courrier charge

Specimens shipping from Vancouver sites to Montreal (Globex, 175$ per shipment) and between clinics in Montreal and main laboratory (Courrier Plus, 33.76$).

Year 1:	**7,440$**
Year 2:	**4,030$**
Year 3:	**5,750$**
Year 4:	**1,225$**
Total:	**18,445$**

Cost for services/year	**Year 1:**	**857,550$**
	Year 2:	**1,463,958$**
	Year 3:	**1,158,886$**
	Year 4:	**1,016,366$**
	In-kind:	**-3,421,607$**

TOTAL SERVICES:	**1,075,153$**

OTHER/KNOWLEDGE TRANSLATION ACTIVITIES

Communication cost

Our knowledge translation and mobilization plan integrates a multi-faceted strategy that will develop tools to promote enrollment which will be tailored to special sub-populations, to ensure diverse and representative recruitment. All knowledge transfer and exchange material will be built using feedback from our Community Advisory Board and Women Advisory Group, to ensure it is adequately adapted. The Canadian HIV Clinical Trial Network (CTN) have a vast expertise in development of recruitment materials, social media posting, and trial document design and will support this project with staff and materials cost. In-kind value of this line of budget is of **18,000$** (see letter of support). This also include cost for scientific open access publications (**9,000$**).

Year 1:	**8,000$**
Year 3:	**2,500$**
Year 3:	**5,500$**
Year 4:	**11,000$**
In-Kind:	**-18,000$**
Total:	**9,000$**

Honoraria cost $

Honorarium will be paid to members (knowledge user, people with lived experience, patient partner, community member) for research-related activities such as steering committee, women advisory board, community consultation, team meetings and knowledge translation activities.

Total Y1-4:	**3,600$**

Total **OTHER/KNOWLEDGE TRANSLATION ACTIVITIES**	**12,060$**

TRAVEL

Funds are being requested for registration, travel and accommodations to attend international or national conference to share research findings and facilitating collaboration within the scientific community. Additionally, we request funding for attendance (principal applicants and principal knowledge user) of the CIHR mid-term meeting.

TOTAL TRAVEL	**9,000$**

TOTAL PROJECT COST	**5,559,604 $**
TOTAL IN-KIND VALUE	**-3 559 607$**
TOTAL REQUESTED TO CIHR	**1,999,997$**

Period	2024-2025	2025-2026	2026-2027	2027-2028	
RESEARCH STAFF					
Research Assistants (incl. 22% benefits)	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Total**
Research assistant Halima Medjahed, Finzi's team Total 2,4 FTE	43 200 $	43 200 $	43 200 $	43 200 $	172 800 $
Lab technician Amélie Pagliuzza, Chomont's team Total 0,5 FTE	0 $	0 $	16 520 $	16 520 $	33 040 $
Lab technician Mohamed Sylla, Tremblay-El-Far's team Total 0,4 FTE	0 $	0 $	12 600 $	12 600 $	25 200 $
Other Personnel-Cordination/Data mangement (incl. 22% benefits)					
Trial coordinator Branka Vulsevic Total 3 FTE	78 286 $	78 286 $	78 286 $	78 286 $	313 144 $
Data Manager, Marc Messier-Peet, Total 1,25 FTE	29 280 $	29 280 $	29 280 $	29 280 $	117 120 $
TOTAL RESEARCH STAFF	**150 766 $**	**150 766 $**	**179 886 $**	**179 886 $**	**661 304 $**
RESEARCH TRAINEES					
Post doctoral Manon Nayrac (Dr Finzi's team) 2 FTE	0 $	0 $	60 000 $	60 000 $	120 000 $
TOTAL RESEARCH TRAINEES	**0 $**	**0 $**	**60 000 $**	**60 000 $**	**120 000 $**
EXPENDABLES					
Dr Finzi's lab					
Blood collection: tubes ACD, EDTA, Serum, Ficoll, HBSS, DMSO, FBS, RPMI, HEPES	4 481 $	4 481 $	4 481 $	4 481 $	17 924 $
Plasticware Falcon tubes, ELISA plates, pipettes, microtubes, freezing microtube	17 900 $	0 $	0 $	0 $	17 900 $
mAb anti-gp120 production and purification for sgp120 ELISA	4 500 $	0 $	0 $	0 $	4 500 $
Mass Spec for TMR detection in 1050 plasma samples	1 875 $	4 375 $	4 375 $	4 375 $	15 000 $
Luminex kits	9 375 $	21 875 $	21 875 $	21 875 $	75 000 $
Kits to isolate primary CD4 T cells (EasySep)	3 750 $	0 $	3 750 $	0 $	7 500 $
D anti-p24 KC57 for intracellular p24 staining required for FACS-based ADCC	0 $	2 250 $	2 250 $	0 $	4 500 $
Total Finzi	**41 881 $**	**32 981 $**	**36 731 $**	**30 731 $**	**142 324 $**
Dr Chomont's Lab					
Isolation of CD4+ T cells by negative magnetic selection (450 samples x 50$)	0 $	0 $	11 250 $	11 250 $	22 500 $
Dual extraction of genomic DNA and total RNA from isolated CD4+ T cells (450 samples x 20 samples)	0 $	0 $	4 500 $	4 500 $	9 000 $
Total HIV DNA quantification (nested PCR for LTR-gag) 450 samples x 10$	0 $	0 $	2 250 $	2 250 $	4 500 $
Cell-associated HIV RNA quantification (RT- PCR for LTR-gag) 450 samples x 22$	0 $	0 $	4 950 $	4 950 $	9 900 $
Total Chomont	0 $	0 $	22 950 $	22 950 $	**45 900 $**

Drs Tremblay-El-Far's Lab					
Human IL-1 beta/IL-1F2 Quantikine ELISA Kit (800$/kit x 9)	0 $	0 $	3 599 $	3 601 $	7 200 $
Human Total IL-18 DuoSet ELISA (533$ per kit x 6)	0 $	0 $	1 599 $	1 599 $	3 198 $
Human IL-32 DuoSet ELISA (533$/ per kit x 6)	0 $	0 $	1 599 $	1 599 $	3 198 $
Human TRAIL/TNFSF10 Quantikine ELISA Kit (800$/kit x 9)	0 $	0 $	3 600 $	3 600 $	7 200 $
ELISA plates approx	0 $	0 $	750 $	750 $	1 500 $
Ready to use primers for IL-32 isoforms and Ref	0 $	0 $	500 $	500 $	1 000 $
RNeasy Plus Micro Kit (581$ per kit x 9)	0 $	0 $	7 844 $	7 843 $	15 687 $
QuantiTect SYBR Green RT-PCR Kit (1166$/kit x 6)	0 $	0 $	3 498 $	3 498 $	6 996 $
LightCycler 480 Multiwell Plate 96, white (1,079$/box x 3)	0 $	0 $	1 619 $	1 618 $	3 237 $
Plasticware and Other reagents for the PCR	0 $	0 $	2 250 $	2 250 $	4 500 $
Total Tremblay-El-Far	0 $	0 $	26 858 $	26 858 $	**53 716 $**
TOTAL EXPENDABLES	**41 881 $**	**32 981 $**	**86 539 $**	**80 539 $**	**241 940 $**
SERVICES					
Cost for participants visits (2395$/participants), screen fail, start-up, close out fees etc (see visist cost in justification file)	156 092 $	150 260 $	110 432 $	55 216 $	472 000 $
Pharmacy placebo/fostemsavir preparation and distributions services (2,15$/caplet or 1,45$/placebo x 150 pt x 24 months)	33 156 $	88 416 $	62 628 $	0 $	184 200 $
Fostemsavir, 600mg/day (1,950$ x 24 months x 75 participants)	533 600 $	1 167 075 $	916 732 $	772 200 $	3 389 607 $
Blood work-safetly analysis at 17,30$*3 visits (Baseline, M1, M12)*150 pt	3 114 $	3 529 $	1 142 $	0 $	7 785 $
Blook work Viral load 36,15$ at screening x 450 (including screen fail)	10 845 $	5 423 $	0 $	0 $	16 268 $
Cardiac scan MTL (250$*115 particpants x 2 time point)	17 750 $	11 000 $	14 750 $	14 000 $	57 500 $
Cardiac scan BC (600$*35 participants x 2 time point)	15 000 $	6 000 $	15 000 $	6 000 $	42 000 $
Post processing Cardiac imaging (500$ x150 particpants x 2 time-point)				150 000 $	150 000 $
PBMCs processing Vancouver (300$ x 35 participants x 7 time point)	25 873 $	20 125 $	22 102 $	7 500 $	75 600 $
Randomisation, Statistical analysis, eCRF implementation	12 000 $	0 $	0 $	0 $	12 000 $
eCRF creating in RedCap data base management entry, querries, data preparation from CRCHUM CITADEL	35 330 $	0 $	0 $	0 $	35 330 $
Data Safety Monitoring Committee (CTN in-Kind)	5 000 $	5 000 $	5 000 $	5 000 $	20 000 $
BSL3 Acces and personal protection equipment-Finzi, Chomont, El-Far/Tremblay	1 000 $	1 000 $	3 000 $	3 000 $	8 000 $
Flow cytometry facility $45/hour (estimated need of 125 hours)-Finzi	750 $	1 500 $	1 750 $	1 625 $	5 625 $
Equipment calibration, real-time temperature monitoring (freezers, refrigirators)	600 $	600 $	600 $	600 $	2 400 $
Samples shipment BC to MTL (175$/unit) and between MTL sites (33,76$/unit)	7 440 $	4 030 $	5 750 $	1 225 $	18 445 $
TOTAL SERVICES	**857 550 $**	**1 463 958 $**	**1 158 886 $**	**1 016 366 $**	**4 496 760 $**

OTHER/KNOWLEDGE TRANSLATION ACTIVITIES					
Honoraria Steering and DSMB commitee (100$/meeting x 3 meetings x 2 patient representative and KU)	200 $	0 $	200 $	200 $	600 $
Honoraria Community and Women group representative at team meeting (50$/meeting x 3 meeting per year x 5 representatives)	750 $	750 $	750 $	750 $	3 000 $
Developement of material for enrollement, knowledge mobilization, dissemination	8 000 $	2 500 $	2 500 $	5 000 $	18 000 $
Open access Publicatioons	0 $	0 $	3 000 $	6 000 $	9 000 $
TOTAL KNOWLEDGE TRANSLATION ACTIVITIES	**8 950 $**	**3 250 $**	**6 450 $**	**11 950 $**	**30 600 $**
TRAVEL					
Travel to national/international conferences	0 $	0 $	2 500 $	2 500 $	5 000 $
Travel to mid-term CIHR workshop (Durand/Finzi/Margolese)	0 $	4 000 $	0 $	0 $	4 000 $
TOTAL TRAVEL	**0 $**	**4 000 $**	**2 500 $**	**2 500 $**	**9 000 $**
In-Kind support from CTN, CRCHUM, ViiV			**In-Kind value**		
CITADEL contribution authorized by the CRHUM (see letter of support)	-12 000 $	0 $	0 $	0 $	-12 000 $
CTN support -Communications team support for development of recruitment materials, social media posting and trial document design (see letter of support)	-8 000 $	-2 500 $	-2 500 $	-5 000 $	-18 000 $
Data Safety Monitoring Committee (CTN)	-5 000 $	-5 000 $	-5 000 $	-5 000 $	-20 000 $
Mitacs grant for post doc salary Manon Nayrac	0 $	0 $	-60 000 $	-60 000 $	-120 000 $
ViiV supply of Fostemsavir (1,950$ per month per participant)*24 months*75 participants (see partner section and associated documents)	-533 600 $	-1 167 075 $	-916 732 $	-772 200 $	-3 389 607 $
Total In-Kind from CTN & CITADEL	**-558 600 $**	**-1 174 575 $**	**-984 232 $**	**-842 200 $**	**-3 559 607 $**
TOTAL OPERATING COST	**1 059 147 $**	**1 654 955 $**	**1 494 261 $**	**1 351 241 $**	**5 559 604 $**
TOTAL FUND REQUESTED TO CIHR	**500 547 $**	**480 380 $**	**510 029 $**	**509 041 $**	**1 999 997 $**

Canadian Institutes of Health Research
160 Elgin Street, 9th Floor
Address Locator 4809A
Ottawa, Ontario K1A 0W9

Instituts de recherche en santé du Canada
160, rue Elgin, 9e étage
Indice de l'adresse 4809A
Ottawa (Ontario) K1A 0W9

Institute of Aging
Institute of Cancer Research
Institute of Circulatory and Respiratory Health
Institute of Gender and Health
Institute of Genetics
Institute of Health Services and Policy Research
Institute of Human Development and Child and Youth Health
Institute of Indigenous Peoples' Health
Institute of Infection and Immunity
Institute of Musculoskeletal Health and Arthritis
Institute of Neurosciences, Mental Health and Addiction
Institute of Nutrition, Metabolism and Diabetes
Institute of Population and Public Health

Institut du vieillissement
Institut du cancer
Institut de la santé circulatoire et respiratoire
Institut de la santé des femmes et des hommes
Institut de génétique
Institut des services et des politiques de la santé
Institut du développement et de la santé des enfants et des adolescents
Institut de la santé des Autochtones
Institut des maladies infectieuses et immunitaires
Institut de l'appareil locomoteur et de l'arthrite
Institut des neurosciences, de la santé mentale et des toxicomanies
Institut de la nutrition, du métabolisme et du diabète
Institut de la santé publique et des populations

Le 8 juillet 2024

Docteure Madeleine Durand
CHUM research Center
room S01-134
850, rue Saint-Denis
Montreal, Québec H2X 0A9

Bonjour Madeleine Durand,

Au nom des Instituts de recherche en santé du Canada (IRSC) et de l'Initiative de recherche sur le VIH/sida et autres infections transmissibles sexuellement et par le sang (ITSS) des IRSC, j'ai le plaisir de vous informer que votre demande intitulée «The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy», présentée au concours de subvention d'équipe : Essai interventionnel sur l'inflammation et maladies chroniques, a été approuvée pour du financement.

Les évaluations et les résultats de votre demande sont accessibles dans RechercheNet. Si vous ne pouvez accéder aux documents, veuillez communiquer avec nous à support-soutien@cihr-irsc.gc.ca. Votre autorisation de financement vous sera envoyée par courriel.

Étant donné que les IRSC n'informent pas les cocandidats de leur décision, nous vous prions de communiquer le résultat de cette demande aux personnes concernées et à leurs établissements de recherche (s'ils diffèrent du vôtre).

Pour toute question, n'hésitez pas à communiquer avec le centre de contact par téléphone au 613-954-1968 ou par courriel à support-soutien@cihr-irsc.gc.ca.

Nous vous félicitons pour votre réussite à ce concours.

Sincères salutations,

Tiffany Richards

Tiffany Richards
Deputy Director, Program Design and Delivery
Research Programs Portfolio

517111-202403II2-ITI-524614-161823-DLPJT

Review Type/Type d'évaluation:	Committee Member 1/Membre de comité 1
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

Competition: Team grant intervention trial in inflammation for chronic conditions

A randomized controlled trial of fostemsavir versus placebo to curb comorbidity in people with well controlled HIV and detectable soluble glycoprotein 120

nPI: Dr Madeline Durant

Background: Despite the success of HIV antiretroviral therapy there continues to be chronic low level inflammation in some individuals living with HIV which is thought to have negative long term consequences on multiple organ systems. This research group proposes that HIV-1 glycoprotein 120 (gp120), a subunit of HIV involved with cellular entry, is a major contributor to chronic inflammation. gp120 is shed from the viral membrane and can be detected in plasma even when plasma HIV RNA levels are undetectable. Fostemsavir is a first in class entry inhibitor which prevents soluble gp120 from interacting with CD4 T cell receptors. This research group has demonstrated that this interaction prevents cytokine burst and CD4 T cell death which could potentially reduce chronic inflammation and prevent cardiovascular disease in people living with HIV.

This group proposes to conduct a randomized clinical trial to assess fostemsavir in reducing cardiovascular disease and other comorbidities. They believe that this intervention could reduce the risk of co-morbidities linked to enduring antigen stimulation in people aging with HIV.

They will conduct a RCT in adults with fully suppressed HIV on antiretroviral therapy and detectable soluble gp120.

Key objectives include:

1) assessment of fostemsavir to reduce inflammation-associated co-morbidities

2) conduct biomarker analysis

3) recruit a study population that is composed equally of women and men

Primary outcome - change in uncalcified coronary artery plaque volume as measured by CCTA
Secondary outcomes include assessment of perivascular fat attenuation ratio (this radiological tool evaluates the fat surrounding coronary arteries). Grip strength at 24 months will be assessed. A brief cognitive ability measure score will be obtained at 24 months and adjusted for baseline. A wide range of biological markers

Review Type/Type d'évaluation:	Committee Member 1/Membre de comité 1
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

of inflammation and immune deficiencies will be evaluated.

The target sample size is 150 individuals recruited at four sites. They anticipate screening 450 to 500 potential participants to reach this target. They will recruit individuals who are 40 years or older (or have lived with HIV for at least 25 years), have undetectable HIV viral load on HIV antiretroviral therapy, have at least one cardiovascular risk factor and have detectable plasma gp120.

Fostemsavir 600 mg PO OD or placebo will be dosed for 24 months followed thereafter by three months of follow-up. The standard dose is 600 mg po twice daily. The group is confident to this reduced daily dose exposure will not contribute to the development of resistance - I think this is a reasonable assumption as long as participants remain fully adherent to HIV antiretroviral therapy.

Issues of Concern:

1) The research group reports the soluble gp120 is detectable in the plasma of 28% of people living with HIV with suppressed viral loads. It would be valuable to have information related to the reproducibility of this finding and details pertaining to quantification. Any preliminary in vivo data demonstrating that the proposed intervention reduces soluble gp120 levels and/or the interaction with CD4 T cells would be of value in support of the hypothesis.

2) As the primary outcome, they will evaluate change in uncalcified coronary artery plaque volume from baseline to month 24 as measured by coronary CT angiography (CCTA). This is not an easily accessible device which raises feasibility questions related to implementation if this intervention is found to be successful. Additional background information as to if and how CCTA findings are influenced by sex would be valuable.

3) The applicants state that they wish to assess the time to major cardiovascular event as a secondary outcome. It seems that the sample size is insufficient given what can be anticipated as a low event rate.

4) Grip strength at 24 months will be assessed. It would be useful to provide additional detail on the impact of sex and aging on this measure.

5) Details on smoking and alcohol use will be gathered but will not be considered in the randomization process. There is a clinically relevant impact of smoking and alcohol and cardiovascular disease risk. It is unclear how these confounding variables will be addressed in the analysis.

Review Type/Type d'évaluation:	Committee Member 1/Membre de comité 1
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

6) The post intervention follow up is only three months. I am concerned that this is an insufficient duration.

7) The research group aims to recruit 3 to 4 patients per week per site which seems optimistic given the complexity of the study and the challenges in recruiting for clinical trials in those living with HIV.

8) It is plausible that some individuals will change or discontinue antiretrovirals over the course of this study. The management of this contingency is not considered. It would not be desirable for a patient to continue on low dose Fostemsavir monotherapy in the event of HIV ARV interruption.

9) It is not stated how an HIV viral load breakthrough will be addressed if it occurs.

This is a relatively long and complex study. Strategies to ensure adherence between visits should be discussed.

Research Team: The study team is led by a successful, mid career clinical investigator. I am confident that Dr Durant has the ability to lead this study as described. There is a compliment of talented and experienced investigators who will contribute their expertise over the course of this study. The sites that will contribute to recruitment and perform the various investigations listed in the protocol are well versed in the conduct of HIV clinical trial and translational research. I am confident that there are no gaps in the areas of expertise required for successful conduct of this study. There is an experienced Community Advisory Board who have been involved with the development of this study proposal. The Canadian HIV Clinical Trials Network has pledged their support for data safety monitoring.

Knowledge Mobilization: There is an excellent knowledge mobilization and exchange plan that is well articulated within the proposal.

Sex/EDI: There is a serious and convincing commitment to equity diversity and inclusion as represented by the composition of the research group and the plan to recruit equally in terms of participant sex.

Budget: The budget is approximately $2,000,000. I am concerned that the request for research coordinator funding is underestimated given that the sample size is 150 individuals, the study protocol is relatively complex, and will be conducted over multiple years at four sites. I believe that the funding requests for supplies and laboratory testing are appropriate.

Impact of Research: The hypothesis itself is interesting, original and reasonably well supported by

Review Type/Type d'évaluation:	Committee Member 1/Membre de comité 1
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

preliminary work. Successful conduct of this study could be valuable in informing future studies related to this intervention. There a several concerns that are not fatal flaws but should be addressed. The sample size is likely insufficient to provide hard secondary outcomes such as impact on cardiovascular disease outcomes.

Review Type/Type d'évaluation:	Committee Member 2/Membre de comité 2
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

In this study Dr Durand proposes to study fostemsavir, an approved ARV used for highly treatment experienced PWH, as a means of reducing inflammation and CVD progression in PWH. This study aim is directly responsive to the RFA objectives.

1. Research Approach

-The study is responsive to the aims of the RFA

-The study design, a RCT, is appropriate to the stated research goals. The research proposal addresses important potential limitations such as the impact of statins in PWH. Patients have been meaningfully integrated in the study design and will be involved in its execution, having had 2 patient advisory board meetings, providing input on study inclusion criteria, endpoints, as well as opportunities and mechanisms to enhance recruitment of women.

-Sex and gender are clearly considered in the design of the study with a supporting rationale for why sex should be included as an analytic variable. The investigators will seek to "over enroll" women and have a separate "womens advisory group" in addition to the PAB

-EDI plan does not provide much detail beyond the hiring of a diverse team and the engagement of a diverse PAB; this is a weakness

2. Originality of the Proposal

-This proposal addresses a critical unmet need among PWH and proposes a novel intervention.

-The investigators are using coronary artery plaque on CTA instead of MACE as the outcome; this enables them to recruit a smaller sample size, however the CTA score is only a surrogate for the outcome of interest.

-Use of sgp120 – they have used registry data to bolster their in vitro findings of sgp120 having a pro-inflammatory effect and linked sgp120 to CVD outcomes in CHACS

-Based on their past data only 30% of the cohort would be anticipated to have detectable sgp120. Their recruitment plan anticipates screening 450- 500 but this number does not account for those who may decline to participate. The recruitment time frame of 42 weeks also seems overly optimistic. I did not see any

Review Type/Type d'évaluation:	Committee Member 2/Membre de comité 2
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

mention of how large the base population of PWH they can potentially recruit from is; while they cite prior studies with rapid enrollment the intervention proposed here is different from say a COVID vaccine study.

-Details surrounding the DSMB were lacking

-Power calculation and sample size derived from study of statin on CTA score – hard to know if fostemsavir will have the same effect if any on the CTA score. Therefore the study is at risk of being underpowered to detect a difference, acknowledging that there is not much published data upon which to base a power calculation. I am wondering if they might consider a power calculation based upon what they would consider a clinically meaningful change in score instead.

-The investigators do state that all CTA will be done at CHUM or St Paul's; as there can even be inter machine variation it is important that they specify that preset parameters will be established for machine settings and ideally the same machine used each time; central analysis by same investigators is good.

-The investigators address the main challenge which is the possibility that statin use will become widespread and it may be hard to tease out the relative contributions of fostemsavir vs statin. Ideally with the RCT design statin use should be equal between groups; they may wish to consider stratifying their analysis by statin use

-They do not comment specifically on other factors that could influence progression of plaque such as actual lipid levels, smoking, DM etc – the investigators should plan to collect these data so they can be accounted for within the analysis

-The proposed budget appears appropriate and justified by the work outlined in the research strategy.

3. Team Composition

-Team leadership by Drs Durand and Finzi, who are both well established mid-later career individuals with a track record of successful funding and research publications. They are supported by a diverse group of investigators with experience in internal medicine, infectious diseases, radiology and cardiology. The roles of team members are clearly specified.

-They plan to train a PhD student in Dr Finzi's lab and recruit a MD scientist to work with Dr. Durand but do not specifically address EDI in trainee recruitment.

Review Type/Type d'évaluation:	Committee Member 2/Membre de comité 2
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

-Patients are well and fully incorporated into the research team as members of the steering committee, advisory committees, results dissemination group and as peer researchers.

-lack of EDI specifications is a weakness

4. Environment for the Research

-the environment is suitable to the proposed research in terms of access to the required materials to perform the CTAs, analyze the data, process and store biospecimens. CHUM has a long history of academic research.

5. Impact of the Research

-This study focuses on PWH who are acknowledged to be at disproportionately high risk of CVD; the mechanism of this risk is attributed to chronic inflammation and this study proposes an intervention that will directly mitigate this risk. In specific, women among PWH are at even higher risk of CVD events, so this study targets 2 high risk groups while considering the effect of sex.

6. Knowledge Mobilization

-KM strategy lead is well positioned to disseminate study findings to the medical community (leads HIV and Aging Research Development group of HIV CTN). The research team has liaised with community groups to further disseminate results to the larger patient community. PAB will be actively involved in KM activities. Role and responsibilities of the KM Liaison were clearly described. Appropriate stakeholders engaged.

-investigators propose to train 2 individuals in addition to 2 peer researchers; likelihood of increased capacity for inflammation research is moderate.

Review Type/Type d'évaluation:	Committee Member 2/Membre de comité 2
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

Review Type/Type d'évaluation:	Committee Member 3/Membre de comité 3
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

HIV remains a significant global health challenge, affecting millions and leading to early onset of comorbidities despite advances in treatment. The research highlights that people living with HIV (PLWH) experience accelerated aging, termed "inflammaging," due to chronic inflammation caused by the virus, even when treated with antiretroviral therapy. This inflammation contributes significantly to an increased risk of cardiovascular disease (CVD), which is notably higher in PLWH compared to the general population. Existing treatments reduce cardiovascular risks but do not address the persistent inflammation.

The proposal aims to undertake a randomized controlled trial using fostemsavir, an HIV antiretroviral drug, to target inflammation-associated comorbidities in PLWH who continue to show signs of chronic inflammation despite effectively managed viral loads.

Fostemsavir, a first-in-class attachment inhibitor, blocks the interaction of sgp120 with the CD4 receptor, thereby preventing cytokine release and CD4 cell death. As demonstrated in the BRIGHTE study, fostemsavir leads to a prolonged decrease in inflammation biomarkers in PLWH. Fostemsavir is well-tolerated and compatible with other antiretroviral regimens. However, due to its high cost, its use may be best targeted to a specific sub-population of PLWH identified through the detection of sgp120 levels, who would most benefit from its anti-inflammatory effects.

1. Research Approach

a. Strength of the study design, methods and research plan developed.

This is a quadruple-blind, multicentric, randomized controlled trial comparing fostemsavir versus placebo. Eligibility is determined by detectable sgp120 levels, with participants randomized in a 1:1 ratio across parallel arms, ensuring blinding of participants, staff, and evaluators to treatment allocation.

Participants will take fostemsavir 600 mg or a matching placebo daily for 24 months, alongside their existing HIV therapy, followed by a 3-month follow-up off treatment.

Review Type/Type d'évaluation:	Committee Member 3/Membre de comité 3
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

Careful consideration of fostemsavir dose. Fostemsavir is administered once daily at 600 mg, a dosage approved by ViiV Healthcare, primarily for its anti-inflammatory effects rather than antiviral actions. This decision is based on Phase 2B findings that showed no significant differences in safety or efficacy between various doses, including a once-daily 600 mg dose. This dosage has demonstrated reductions in the inflammatory biomarker sCD14, and enhances compliance alongside existing single-pill antiretroviral regimens, reduces medication costs, and minimizes side effects.

Fostemsavir is well tolerated in treatment-experienced people living with HIV, with gastrointestinal issues being the most common side effect. It has no interactions with other antiretroviral drugs and does not require dosage adjustments for liver or kidney conditions.

While inclusion criteria include individuals with risk factors for cardiovascular disease, it's not clear if those with clinical disease will be included. The response to anti-inflammatory treatment may be different in these folks compared to those without disease.

Sufficient description given of randomization, blinding and unblinding procedures.

b. The extent to which barriers and requirements are anticipated, and risk management plan and mitigation strategies are established.

The primary outcome of the study is the change in uncalcified coronary artery plaque volume from baseline to 24 months, assessed via cardiac computed tomography angiography (CCTA). This measure is significant as uncalcified plaque is more closely associated with major cardiovascular events and has been validated in the context of HIV infection.

Sufficient detail provided around image acquisition and CCTA post-processing.

Secondary outcomes include:

Review Type/Type d'évaluation:	Committee Member 3/Membre de comité 3
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

i. Perivascular fat attenuation ratio (P-FAI); at 24 months; novel imaging biomarker; attenuation of fat around coronary arteries associated with major adverse cardiovascular events.

ii. Time to major cardiovascular events (defined as myocardial infarction, coronary revascularization through percutaneous intervention or surgery, peripheral artery revascularization, stroke, hospitalization due to heart failure or unstable angina, or death from cardiovascular causes). Will analysis include efforts to stratify effect of drug treatment on individual cardiovascular events since each have unique underlying immunopathologies?

The recruitment plan and timelines seem realistic. Authors present evidence of similar enrollment kinetics (450-500 participants within 1 year) in other HIV-focused studies performed at proposed sites.

Participant compliance: previous trial (BRIGHTE) saw only 7% discontinuance due to drug toxicity at twice the dose. That study participants must have undetectable viral load speaks to compliance around antiretroviral regimens.

Loss to follow up: predicted at 10%; possible mitigation strategies include home visits, visits outside of work hours and participant compensations. Are these guaranteed to be followed through with if loss exceeds 10%?

Authors acknowledge that much larger participant cohort (and longer study duration) is required to draw definitive conclusions around the effect of fostemsavir on adverse clinical events.

Will be important to determine if fostemsavir has added benefits to statin treatment which is standard of care for PLWH with cardiovascular disease risk.

c. Strength, feasibility and clarity of the strategies to meaningfully engage/integrate participating KUs and PWLE in the research process.

For this project, the co-applicants with lived experience actively participate in the research team and sit on

Review Type/Type d'évaluation:	Committee Member 3/Membre de comité 3
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

the trial steering committee, and have recruited a diverse group of seven peers to form the Community Advisory Board (CAB).

The CAB actively participates during full team meetings (grant preparation) and have demonstrated significant input in recruitment, secondary outcomes, visit procedures.

d. Strength of EDI plan to ensure equitable and inclusive recruitment of diverse patients and/or samples.

Women living with HIV constitute 23% of people living with HIV (PLWH) in Canada and 54% of PLWH globally.

Goal is to ensure 50% of study participants are women to assess sex differences in outcomes.

To address the complexities of recruiting women, a Women's Advisory Group has been established, led by co-applicant and sex and gender expert E. King. Composed of women with lived HIV experience, this group aims to identify barriers and propose strategies to enhance the recruitment of women living with HIV into the trial. This group has already met and identified several strategies which are being implemented to encourage recruitment of women into the study. WAG meets every 6 months.

e. Extent to which the budget is appropriate and justified in relation to the proposed activities.

Budget is appropriate.

f. For projects that include activities with Indigenous communities, the project must: i. be conducted by, grounded in, or engage with First Nations, Inuit and/or Métis communities, societies and/or individuals and their wisdom, cultures, experiences and/or knowledge systems, as expressed in their dynamic forms, past and present. ii. demonstrate appropriate consideration of TCPS 2: Chapter 9 - Research Involving the First Nations, Inuit and Métis Peoples of Canada and of meaningful and culturally safe practices, plans and activities throughout the project.

Review Type/Type d'évaluation:	Committee Member 3/Membre de comité 3
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

2. Team Composition and Strength of Plan for Collaborative Teamwork

a. Clarity of roles and contributions of all team members, partners, KUs and PWLE to carry out the proposed research, training, mentoring and knowledge mobilization activities of the research program.

The principal clinical investigator is M Durand, who leads the Canadian HIV and Aging Cohort Study (CHACS) is experienced in heading large research teams, has served as a site investigator for several major randomized controlled trials and co-leads the Clinical Care Management core of the Canadian HIV Clinical Trial Network.

A. Finzi, a global authority on HIV-1 envelope glycoprotein conformation and Fc-effector functions, has developed the assay to measure sgp120 in plasma, linking it to systemic inflammation reversible by temsavir. He will oversee all biomedical aspects of this trial.

Other co-applicants include folks with specialties in randomized controlled trials, clinical researchers, cardiovascular disease specialists (this team published cardiovascular results from CCTA on the CHACS cohort; have a track record of successfully working together). There is a biomedical team which includes immunologists and virologists with backgrounds in HIV research. Will provide viral load reservoir measurements.

In addition to the Community Advisory Board, other PWLE include the principal knowledge user S. Margolese, who is also a researcher involved with CHACS.

b. Strength of plan for collaborative teamwork, including strategies for communication and collaboration between interdisciplinary members, the KM Hub, partners and KUs, and geographical sites, and sharing of resources as required.

Not explicitly outlined how members of different teams (clinical researchers, cardiovascular disease

Review Type/Type d'évaluation:	Committee Member 3/Membre de comité 3
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

specialists, biomedical teams) will interact with each other.
Are there planned team meetings for discussing results across platforms, challenges, next steps, etc.?

c. Strength of EDI plan to manage recruitment and integration of trainees and meaningful inclusion of ECRs to benefit from the full pool of talent in the system.

EDI plan includes the Community Advisory Board and Women's Advisory Group to address issues around participant inclusion and study design.

The research team consists of 16 women and 19 men, including 6 early-career, 8 mid-career, and 12 senior investigators. Additionally, 17 team members are non-native English speakers.

Not a lot of detail provided regarding EDI recruitment strategies for trainees.
d. Strength of the plan to realize EDI goals through concrete and appropriate initiatives and measures, and through adequate team composition that will foster the representation of a variety of identity dimensions and groups historically underrepresented in science (including but not limited to those marginalized by gender, Indigenous Peoples, racialized communities, persons with disabilities, and members of LGBTQIA/2S+ communities), and a diversity of experiences on the research team including a plan to reduce systemic barriers and mitigate biases.

The team emphasizes involving self-identifying Indigenous people, adhering to the Ownership, Control, Access, and Possession (OCAP) principles. Through community consultations for the RESTART Trial, C. Cardinal and E. Hennie have guided the application of OCAP within the constraints of a randomized controlled trial. Although it is a continuing effort, strategies have been developed to ensure Indigenous participants can review their data prior to publication.

3. Impact of the Research

a. Likelihood that the proposed research training and mentoring environments for trainees and ECRs will increase capacity in interdisciplinary inflammation research.

Review Type/Type d'évaluation:	Committee Member 3/Membre de comité 3
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

The RESTART study aims to target a persistent viral antigen in PLWH with controlled HIV to reduce inflammation-related comorbidities. Successful outcomes could shift current standards, introducing a personalized approach to mitigate the higher comorbidity risks in aging HIV populations.

The proposed research increases capacity in interdisciplinary inflammation research.

4. Knowledge Mobilization and Engagement Plan

a. Clarity, appropriateness and adequacy of the proposed knowledge mobilization plan and how it will support the path to translation of research outcomes.

Much of the knowledge transfer is focused on liaising with the knowledge mobilization Hub, which has also submitted an application with this funding opportunity. However, not clear what the status/fate of the activities associated with knowledge HUB are if not funded. The contribution to the Knowledge Hub is high level without much granularity (i.e., communicating with them, sharing material with them, participating in their planned activities). Little mention of a path to translation of research outcomes.

b. Originality/description of the proposed KM and dissemination plan activities in terms of solutions and /or repurposing or optimization of existing KM products and activities.

Considerable attention given to engagement of PWLE. Most of these activities are around recruitment (Community Advisory Board and Women Advisory Group) and study design (i.e., some contribution to secondary endpoints).

c. Potential to successfully and appropriately mobilize research findings and accelerate uptake of evidence, as demonstrated by a clear translation path and planned KM activities through early, sustained,

Review Type/Type d'évaluation:	Committee Member 3/Membre de comité 3
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

authentic and meaningful collaboration of KUs, PWLE, partners and inflammation researchers across disciplines.

Not a lot of detail provided regarding how research findings will be mobilized within multidisciplinary team.

d. Clear roles and responsibilities for the Team's KM Liaison and how this person will coordinate activities with the KM Hub.

J. McMillan, an early-career HIV researcher and geriatrician, will serve as the knowledge translation liaison. She is a geriatrician and the site lead for Alberta in the Canadian Longitudinal Study on Aging. She will develop knowledge transfer and exchange (KTE) materials and activities for the community of people aging with HIV. Additionally, she is the scientific co-lead of the HIV and Aging Research Development group within the HIV Clinical Trial Network and chairs its quarterly meetings, which include a mix of HIV researchers, trainees, and community members.

e. Appropriateness of description of key stakeholders for knowledge mobilization.

Key stakeholders identified as PWLE. Little mention of how either knowledge mobilization hub (if funded) or liaison will be involved with knowledge mobilization to the study team.

Review Type/Type d'évaluation:	Committee Member 4/Membre de comité 4
Name of Applicant/Nom du chercheur:	Durand, Madeleine
Application No./Numéro de demande:	520812
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2024-03-06 Team Grant: Intervention Trial in Inflammation for Chronic Conditions - Evidence to Impact/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques - Des données aux retombées
Committee/Comité:	Team Grant : Intervention Trial in Inflammation for Chronic Conditions/Subvention d'équipe : Essai interventionnel sur l'inflammation et les maladies chroniques
Title/Titre:	The RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.

Assessment/Évaluation:

Dr. Durand is an internist, clinician-investigator at University Laval (Faculty since 2011) and HIV expert. Her research salary is supported by a FRQS (due for renewal in 2024?). In this application, she proposes a RCT to determine whether treatment with fostemsavir (blocks HIV gp120 soluble secretion that induces chronic monocyte and T cell stimulation can reduce coronary plaque formation and inflammation in patients with HIV (with a negative viral load).

The clinical problem addressed is well explained – people living with HIV have reduced life expectancy, increased risk of cardiovascular disease (despite statin treatments – as current standard of care).

The team is strong and well experienced with this type of studies.

Inclusion criteria: >=40 years-old with HIV for >=25 years, undetectable viral load, risk factors for CVD.

The proposal plan includes sufficient measures to include vulnerable/under-represented sex and socio-economic groups, with a compelling plan for patient representation.

The intervention (dose) is well justified (fostemavir 600 mg orally once daily for 24 months).

The outcome measures seem relevant and acceptable from a risk point of view (CT scans under metoprolol), capturing also relevant clinical outcomes, inflammation, etc, including the time to cardiovascular events, is clever and important despite that some of these events may be infrequent.

Sample size appears achievable (130 patients over 27 months).

The trial structure and DSMB is planned, appropriately.

Sample size may or may not be sufficient. At this point there are no data on the expected effect from fostemsavir. This sample size seems in line with studies that have used similar outcomes. Investigators hope that the effect may be like the effect of statins, on plaque progression (Lo, Lancet HIV). However, since most eligible participants will also be on statins, it is unclear whether this argument is valid. The projected study sample size is speculative, but the study is likely to provide important information, with meaningful clinical and CT outcomes.

KT engagement plan is satisfactory.

February 22, 2024

Madeleine Durand, MD, MSc, FRCPC
l'Université de Montréal, CHUM Research Centre
850, rue Saint-Denis Montréal,
QC H2X 0A9
Tour Saint-Antoine - 1er étage local SO1-134

RE: Collaboration with Letter of Support for Dr. Madeleine Durand for her application "RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy.."

Dear Review Committee Members:
On behalf of the CIHR Canadian HIV Trials Network (CTN), I am pleased to confirm our support as a collaborator with Dr. Madeleine Durand for her application titled "**RESTART Trial: Reducing Systemic inflammation for people on AntiRetroviral Therapy. A randomised, controlled, double-blind trial of fostemsavir versus placebo to curb comorbidity in people with well-controlled HIV",** responding to the funding opportunity: *Team Grant - Intervention Trial in Inflammation for Chronic Conditions* from the Canadian Institutes of Health Research, due March 6, 2024.

Established in 1990, the CTN has pioneered 30 years of practice-changing clinical studies and trials to prevent, treat and manage HIV, hepatitis C, other sexually transmitted and blood-borne infections (STBBIs) and, more recently, COVID-19. The CTN is a Canada-wide collaborative and inclusive partnership of researchers, people living with HIV and their caregivers, governments, health advocates and the pharmaceutical and biotechnology industry. Since our inception, the Network has trained over 100 postdoctoral fellows, enrolled over 24,000 study participants and conducted more than 330 clinical studies. For example, our work has shaped the current Canadian guidelines on HIV pre-exposure (PrEP) and post-exposure prophylaxis (PEP). With our research excellence, community engagement and robust infrastructure, we pursue an integrated approach across the continuum of prevention, testing, initiation of care and treatment, and ongoing care and support. Comorbidity for people aging with HIV is a research priority for the Network.

Our long-standing Community Advisory Committee is integrated within the Network's decision-making process to ensure the research is relevant and responsive to the community's needs and has served as a model for major initiatives like the CIHR Strategy for Patient-Oriented Research. Comprised of Canadians with lived experience and other community members, this committee reviews all study protocols and informed consent, joins research teams, provides critical equity and diversity considerations, and highlights community concerns. In addition, our newly formed Community Engagement Team creates additional opportunities to strengthen a community-informed and centred research model.

Since completing her CTN Postdoctoral Fellowship in 2014, Dr. Durand has continuously contributed and collaborated with the CTN. Upon completing her fellowship, Dr. Durand became a CTN Investigator. As an Investigator she became the co-principal investigator of CTN 272 – Canadian HIV and Aging Cohort: discovering pathways to successful aging with HIV infection, of which she subsequently became the nominated principal applicant after receiving CIHR team grant funding to add new sites and endpoints to the cohort. Nominated by her peers within the

Funded by the Canadian Institutes of Health Research and sponsored by the University of British Columbia and St Paul's Hospital (Providence Health Care).
Subventionné par les Instituts de recherche en santé du Canada et commandité par l'Université de la Colombie Britannique et de l'Hôpital Saint Paul (*Providence Health Care*).

CTN, in 2022, she was appointed Co-Lead of the Clinical Care and Management scientific core. Numerous co-applicants on this grant are also CTN investigators with a longstanding history of contributing to the network and promoting community engagement (Melanie Murray, Cecilia Costiniuk, Cécile Tremblay) as well as young investigators who have recently joined the network (Elizabeth King, Jacqueline McMillan), with specialties in women centred care and geriatrics, respectively.

We look forward to collaborating with Dr. Durand and her team to maximize the impact of research and accelerate solutions that will improve the health of people living with HIV as they age. As the CTN is currently in the renewal process, the submission for support will only be available if the CTN receives a successful Notice of Decision in June 2024. Upon receiving her CIHR grant, as a CTN Investigator, Dr. Durand will be eligible to submit the project for CTN review. With CTN approval, we may provide the following:

- Communications team support for the development of recruitment materials, social media posting, and trial document design for the duration of the trial is estimated to be $18,000 (staff time and materials).
- Oversight by the CTN's Data Safety Monitoring Committee valued at $5,000 per year for each year the trial is open.

We are pleased to join efforts with this proposal as it aligns with our vision to treat, prevent, manage and cure HIV and STBBIs in Canada and globally, by potentially providing an impactful solution for reducing chronic inflammation in people living with HIV and thereby helping to prevent co-morbidities. The focus on recruitment of women, as well as the strong commitment to community partnership by the team are also aligned with CTN's priorities.

Kind regards,



Aslam Anis, Ph.D., FCAHS
National Director, CIHR Canadian HIV Trials Network
Director, Centre for Advancing Health Outcomes
Professor and Director pro tem, School of Population and Public Health, University of British Columbia
T: 604.806.8712, E-mail: aslam.anis@ubc.ca

Funded by the Canadian Institutes of Health Research and sponsored by the University of British Columbia and St Paul's Hospital (Providence Health Care).
Subventionné par les Instituts de recherche en santé du Canada et commandité par l'Université de la Colombie Britannique et de l'Hôpital Saint Paul (*Providence Health Care*).

The RESTART Trial: Reducing Systemic Inflammation for People on Antiretroviral Therapy
A randomized, controlled trial of fostemsavir versus standard of care to curb comorbidity in people with well-controlled HIV and detectable soluble glycoprotein 120.

Chercheur (euse) responsable

Madeleine Durand, Université de Montréal

Co-chercheurs (euses)

Andrés Finzi, Université de Montréal
Shari Margolese, Community consultant
Cécile Tremblay, Université de Montréal
Cecilia Costiniuk, McGill University
Jean-Pierre Routy, McGill University
Alexandra de Pokomandy, McGill University
Jacqueline McMillan, University of Calgary
Elizabeth King, Simon Fraser University
Melanie Murray, University of British Columbia
Mona Loutfy, Women's College Research Institute
Emmanuelle Duceppe, Université de Montréal
Michael Chassé, Université de Montréal
Valérie Martel Laferrière, Université de Montréal
Julian Falutz, McGill University
Samer Mansour, CHUM
Jean-Guy Baril, Clinique Médicale Urbaine du Quartier Latin
Daniel Kaufmann, Université de Montréal
Frank Maldarelli, National Institutes of Health
Patrick Bourgouin, Université de Montréal
Carl Chartrand-Lefebvre, Université de Montréal
Jonathon Leipsic, Providence Health Care
Kevin Boczar, University of Ottawa

Collaborateurs (trices)

Joel Singer, HIV Clinical Trial Network
Mohamed El-Far, Université de Montréal
Nicolas Chomont, Université de Montréal
Jonathan Richard, Université de Montréal
Brenda Gagnier, Women's College Research Institute and Peer Research Associate
Claudette Cardinal, BC Centre for Excellence in HIV/AIDS and Indigenous Peer Research Associate
Noemi Tshinkenke, Peer Research Associate
Inoua Haoua, AIDS Committee of Ottawa
Kenneth Monteith, COCQ-SIDA Director
Sylvain Beaudry, Community consultant
Mehdi Benlarbi, Université de Montréal, PhD (A. Finzi)
Manon Nayrac, Université de Montréal, Post-Doc (A. Finzi)

Isabelle Hardy, ViiV Healthcare
Jean-François Fortin, ViiV Healthcare
Andrew Clark, consultant
Dana Nohynek, CIHR Canadian HIV Trials Network
Annie Chamberland, Université de Montréal
Mehdi Benlarbi, PhD student
Branka Vulesevic, McGill University – study manager (coordinatrice de recherche)

Version du protocole

Version 4.0

Date

30 Mai 2025

Financement

Institute de Recherche en Santé du Canada (IRSC) / Canadian Institutes of Health Research (CIHR)

PROTOCOL NUMBER: MP-02-2025-12725

Table des matières (Table of Content)

INVESTIGATOR AGREEMENT 5
SPONSOR APPROVAL 7
APPROBATION DU PROMOTEUR 8
0. Synopsis (English) 9
1. Résumé du protocole de recherche (français) 16
2. Introduction (*Introduction*) 24
2.1 Raison d'être de la recherche *(Study rationale)* 24
2.1 Recension des écrits (Background) 25
2.3 Bénéfices et risques (Benefits and risks) 26
3. Objectifs et critères d'évaluation *(Objectives and endpoints)* 28
3.1 Objectif primaire *(Primary objective)* 28
3.2 Objectifs secondaires (secondary objectives) 28
3.2.1 Objectif secondaire d'imagerie *(Secondary imaging objective)* 28
3.2.3 Objectifs secondaires de biomarqueurs *(Secondary biomarker objectives)* 28
3.4 Critère d'évaluation primaire *(Primary endpoint, primary outcome measure)* 29
3.5 Critères d'évaluation secondaires *(Secondary Outcomes)* 29
4. Méthodes *(Methods)* 32
4.1 Devis et contexte de l'étude *(Study design and context)* 32
4.2 Population à l'étude *(Study population)* 33
4.2.1 CRITÈRES D'INCLUSION *(Inclusion criteria)* 33
4.2.2 CRITÈRES D'EXCLUSION *(Exclusion criteria)* 34
4.3 Recrutement des participants (*Participant recruitment*) 35
4.4 Collecte de données: variables et mesures *(Data collection: variables and measurements)* 36
4.4.1 PROCEDURES ET DEROULEMENT DE L'ETUDE *(Study procedures and execution)* 36
4.4.2 Variable d'intervention ou d'exposition *(Intervention or exposure variable)* 38
4.4.5 MESURE DU CRITÈRE D'ÉVALUATION PRIMAIRE (*Primary outcome measurement)* 41
4.4.7 VARIABLES DEMOGRAPHIQUES ET CLINIQUES *(Clinical and demographic variables)* 44
4.4.8 CONDUITE DE L'ETUDE ET STRATEGIES SPECIFIQUES DE MINIMISATION DES BIAIS *(Study conduct and specific strategies for minimizing biases)* 45
4.5 Aspects statistiques *(Statistical aspects)* 46

4.5.1 TAILLE D'ECHANTILLON *(Sample size)* 46
4.5.2 ANALYSE STATISTIQUE *(Statistical analysis)* 47
5. Surveillance et sécurité *(Surveillance and safety)* 51
5.6 Les Événements Indésirables (*Adverse events*) 53
5.7 Événements indésirables d'intérêt particulier et autres sujets liés à la sécurité (Adverse Events of Special Interest (AESIs) and other safety topics) 55
5.7 Grossesse (Pregnancy) 57
5.8 Critères d'arrêt et de suivi des tests de fonction hépatique (Liver Chemistry Stopping And Follow-Up Criteria) 59
6. Considérations éthiques *(Ethical considerations)* 61
6.1 Processus d'identification et de recrutement (*Identification and recruitment process*) 61
6.2 Processus de consentement (*Informed consent process*) 61
6.3 Risques et inconvénients (*Risks and inconveniences*) 62
6.4 Plateforme de collecte de données (*Data collection platform*) 62
6.5 Compensation des participants 63
6.6 Confidentialité et conservations des données, et des échantillons biologiques si applicable 63
6.7 Utilisation secondaire des données (et des échantillons biologiques si applicable) et science ouverte (Secondary use of data) 64
6.8 Diffusion des résultats généraux de la recherche (Results dissemination) 64
6.9 Conflit d'intérêt (*Conflict of interst*) 65
7. Références (References) 66
8. Annexe (Appendix) 73
Appendix 1: Fostemsavir risk tables 73
Appendix 2: Highly Effective Methods for Avoiding Pregnancy in Individuals of childbearing Potential 79
Appendix 3: Follow Up Assessments for Any Liver Stopping Event 81
Appendix 4: List of Abbreviations 82

INVESTIGATOR AGREEMENT

Protocol Title:	**The RESTART Trial: Reducing Systemic Inflammation for People on Antiretroviral Therapy**
Protocol No.:	MP-02-2025-12725
Version No.:	4.0
Date:	

This clinical study will be conducted in accordance with applicable Health Canada regulations, ICH guidelines on current GCP, and the Declaration of Helsinki.

I confirm that I have read and understood this protocol, and I agree to conduct this clinical trial in accordance with its design and specific provisions, with the exception of a change intended to eliminate an immediate hazard to participants. Any deviation from the study protocol will be documented in a separate protocol deviation form and reported to the applicable REB.

I agree to promptly report to the applicable ethics boards any deviations, changes in the research activity, and all unanticipated problems involving risks to human participants or others. Additionally, I will not make any changes in the research without prior ethics and sponsor approval, except where necessary to ensure the safety of study participants.

Name	Signature	Date (dd-mmm-yyyy)

ACCORD AVEC L'ENQUÊTEUR

Protocol Title:	**Essai RESTART : Réduire l'inflammation systémique chez les personnes sous traitement antirétroviral**
Protocol No.:	MP-02-2025-12725
Version No.:	4.0
Date:	

Cette étude clinique sera menée conformément à la réglementation applicable de Santé Canada, aux lignes directrices de l'ICH sur les BPC en vigueur et à la déclaration d'Helsinki.

Je confirme que j'ai lu et compris ce protocole, et j'accepte de mener cet essai clinique conformément à sa conception et à ses dispositions spécifiques, à l'exception d'une modification visant à éliminer un risque immédiat pour les participants. Tout écart par rapport au protocole de l'étude sera consigné dans un formulaire distinct d'écart par rapport au protocole et signalé au CÉR compétent.

J'accepte de signaler rapidement aux comités d'éthique compétents toute déviation, tout changement dans l'activité de recherche et tout problème imprévu impliquant des risques pour les participants humains ou d'autres personnes. En outre, je n'apporterai aucune modification à la recherche sans l'accord préalable du comité d'éthique et du promoteur, sauf si cela est nécessaire pour assurer la sécurité des participants à l'étude.

Nomme	Signature	Date (jj-mm-aaaa)

SPONSOR APPROVAL

Study Title:	The RESTART Trial: Reducing Systemic Inflammation for People on Antiretroviral Therapy
Protocol No.	MP-02-2025-12725
Version No.	4.0
Date:	30-May-2025

I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol comply with scientific principles, the guidelines of Good Clinical Practice, the Declaration of Helsinki in the latest relevant version and applicable legal and regulatory requirements.

Sponsor Representative:

Name: Madeleine Durand, MD MSc FRCPC

Signed:  Date: 30 May 2025

APPROBATION DU PROMOTEUR

Titre de l'étude: L'essai RESTART: **Réduire l'inflammation systémique chez les personnes sous traitement antiretroviral**

Protocole n° MP-02-2025-12725

Version n° 4.0

Date: 30-Mai-2025

Je soussigné(e) ai lu et approuvé ce protocole et je suis d'accord avec son contenu. Il est confirmé que les informations et les conseils donnés dans ce protocole sont conformes aux principes scientifiques, aux lignes directrices des bonnes pratiques cliniques, à la Déclaration d'Helsinki dans sa dernière version pertinente et aux exigences légales et réglementaires applicables.

Représentant du sponsor :

Name: Madeleine Durand, MD MSc FRCPC

Signed:  Date: 30 May 2025

0. Synopsis (English)

Protocol Number	MP-02-2025-12725
Title of Study	**The RESTART Trial**: Reducing Systemic Inflammation in People on Antiretroviral Therapy. A randomized, controlled trial of fostemsavir versus standard of care to curb comorbidity in people with well-controlled HIV
Phase of Clinical Trial	Phase II
Study Hypothesis:	People living with HIV with undetectable viral load but detectable soluble HIV gp120 (sgp120) are exposed to chronic inflammation, sustained immune dysfunction, and increased risk of comorbidity. The addition of fostemsavir to their existing antiretroviral regimen will lead to decreased non-calcified coronary artery plaque volume, decreased inflammation, and improved immune function.
Study Objectives	This study aims to examine the efficacy of an HIV-specific intervention against glycoprotein 120 (a subunit of HIV-1 entry machinery implicated in sustained inflammation and immune dysfunction) in reducing the inflammation-associated comorbidity risk in people living with HIV. **Primary Objective:** Estimate the efficacy of fostemsavir to decrease cardiovascular disease in the study population, as measured by change in uncalcified coronary artery plaque volume between baseline and month 24 /measured by CCTA **Secondary Imaging Objective**: Estimate the efficacy of fostemsavir to decrease peri-coronary inflammation, measured by Pericoronary Fat attenuation ratio (P-FAI) by analysis of CCTAs taken at baseline and month 24. **Secondary Clinical Objective:** Estimate the efficacy of fostemsavir to favorably impact clinical outcomes such as cardiovascular disease, frailty and cognition. **Secondary Biomarker Objective:** Estimate the impact of study treatment on inflammation and immune dysfunction, measured using biomarkers of

	systemic inflammation and biomarkers associated to CVD, HIV reservoirs, immuno-serology and levels of HIV soluble gp120. **Secondary Safety Objective:** Estimate safety and tolerability of study treatment
Study Design	Multi-centre, open-label, randomized controlled trial of fostemsavir versus standard of care. Randomization will be done in a 1:1 ratio with allocation in parallel arms, stratified by sex and participant statin use at recruitment, through a computerized algorithm with permuted blocks of randomly varying size, to ensure allocation concealment. The intervention will be either the addition of fostemsavir (Rukobia 600 mg daily) to the patient's current ART regimen, or the participant receiving the standard of care. The standard of care for people living with HIV includes the continuation of the ARV regimen and other medications prescribed by their physicians. Changes in ARV regimens or concurrent medications as indicated by treating physicians are allowed. This trial will be conducted as an open-label study; however, assessors of the primary outcome (based on two CCTA scans) and of the biobank analyses will remain blinded to treatment allocation, as well as statisticians. **Screening visit**: Written informed consent will be obtained, and then a blood test will be done for measurement of HIV sgp120 to establish eligibility (unless prior data on HIV sgp120 levels, not older than six months are already available), viral load (unless prior data is available in the last 6 months), and contribution to the biobank. Limited data collection necessary for inclusion/exclusion criteria assessment (age, sex at birth, self-declared gender, CVD risk factors, duration of HIV and current HIV regimen) will be collected. A log of all screening visits and screen fails will be kept. **Inclusion visit**: This visit will take place by phone. All participants will be notified of their plasma HIV sgp120 results. For those who meet the inclusion criteria, an appointment will be made for the baseline visit. For those who do not meet inclusion criteria, their participation will end at this visit. **Baseline visit:** The baseline study visit will be scheduled within six months of the inclusion visit. During that visit, baseline measurements for each outcome measure will be performed: CCTA, B-CAM and grip strength, and the baseline CRF will be filled. A blood draw will be taken for biobanking, viral load, CD4 and CD8 cell count and percentages, and safety. A physical examination will be performed. Medical history, medications and ARV regimen will be reviewed and demographic data will be collected. Randomization and

medication dispensing will also take place. Pregnancy testing and ECGs will be performed and the results known prior to dispensing study medication. Vital signs will be checked. If an appointment for the CCTA is not available on the same day as the other procedures, the baseline visit may be split in two, and randomization will happen on the date of the CCTA, to ensure all randomized participants have baseline CCTA.

Safety visit: The safety visit will take place at month 1 (+/- 2 weeks), during which blood tests will be done for safety (Complete blood count, creatinine, eGFR, sodium, potassium and liver function tests [ALT, bilirubin, alkaline phosphatase]) as well as viral load, CD4 and CD8 cell count and percentages. Medications and ARV regimen will be reviewed, along with treatment adherence and adverse events. Vital signs will be checked. Pregnancy testing and ECGs will be performed. Additionally, clinical results from the enrollment CCTA will be discussed with the participants, and referrals will be planned as clinically indicated. All clinical results of CCTA will be available to participants' treating physicians.

Follow-up visits: Follow-up visits will take place at months 6, 12, and 18 (+/- one month). At each follow-up visit, study CRF will be filled; clinical outcomes ascertainment will be done; compliance will be assessed by pill counts; and study medication will be dispensed. At each visit, blood drawn for safety, viral load, CD4 and CD8 count and percentages, and the biobank will be collected. Medications and ARV regimen will be reviewed, along with treatment adherence and adverse events. Vital signs will be checked. Pregnancy testing and ECGs will be performed.

End of treatment visit: At month 24 (+/- 1 month), the end of treatment visit will be conducted, with measures of B-CAM, Grip Strength, CCTA, collection of clinical endpoints as well as biobanking. Medications and ARV regimen will be reviewed, along with treatment adherence and adverse events. Vital signs will be checked. Pregnancy testing and ECGs will be performed. Blood will be drawn for safety, viral load, CD4 and CD8 count and percentages, and the biobank A final assessment of pill counts and reconciliation will be done. All unused pills returned by the participant will be destroyed.

Post-treatment visit: The last study visit will happen at month 27 (3 months after the end of treatment), where the last blood test for biobanking will be collected and clinical endpoints will be collected along with safety, viral load, CD4 and CD8 count and percentages. At this visit the ARV regimen will also be reviewed and vital signs measured.

Study sites	Canada 4 sites
Study Duration	Screening: up to 24 weeks (6 months) Treatment period: 2 years (24 months) Follow-up period: 12 weeks (3 months) The total duration of participation is **27 months**, plus screening.
Study Endpoint s	**Primary Outcome**: Change in total uncalcified plaque volume between baseline and month 24, contrasted between fostemsavir and standard of care. **Imaging Secondary Outcome**: Perivascular fat attenuation index at month 24, adjusted for baseline values. **Clinical Secondary Outcome**: Clinical events – time to MACE, B-CAM and grip strength at month 24 (adjusted for baseline values), incidence of MACE. Safety data will be collected at the first safety visit (one month after the beginning of treatment) and throughout the study through SUSAR and SAE reporting capture in the trial's CRF. **Biomarker Secondary Outcomes:** Biomarkers identified in biobanking samples (virology, immunology, inflammation). **Safety Secondary Outcomes:** Risk of severe and serious adverse events and incidence of treatment discontinuation due to side effects.
Biomarker interim analysis	A biomarker interim analysis will be performed when 50% of the planned samples size will have completed 1 year of follow-up. Pre-specified biomarker outcomes will be measured using the study-associated biobank.
Study Treatment	The intervention will be either the addition of fostemsavir (Rukobia 600 mg daily) to the patient's current ART regimen, or the participant receiving the standard of care. The dose of the study drug (Rukobia (fostemsavir extended-release tablets - DIN 02520869) used in the BRIGHTE trial and currently approved for use as an antiretroviral in people failing their ARV regimen is 600 mg orally twice daily. In RESTART trial, we are using a once-daily dosage, with the agreement of ViiV Healthcare.
Control	Standard of care (SOC)

Dosing and Administration	Arm 1 (active): • Once daily oral administration (600 mg extended-release tablet) for 24 months Arm 2 (Standard of care) • Participants will continue to follow their current ART regimen, as well as other medications prescribed by their treating physician throughout the trial
Eligibility Criteria	Individuals must meet all following inclusion criteria • 40 years or older, or have lived with HIV for 25 years or more, any sex; • Undetectable HIV viral load (defined as last viral load measurement less than 50 copies/ml within the last 6 months); • Presence of at least one cardiovascular risk factor among the following: longstanding HIV infection (25 years or more), hypertension, diabetes, past or present smoking, dyslipidemia, family history of early onset CVD in a first-degree relative (defined as younger than 55 in males or younger than 65 in females (80)), known previous cardiovascular disease (defined as past myocardial infarction, coronary revascularization, stroke, or coronary artery atherosclerosis with >= 50% stenosis demonstrated on coronary angiography or CCTA); • Participants with past cardiovascular disease must be in a stable clinical condition as judged by the study clinicians; • Past cardiovascular events are defined as having occurred at least 3 months before screening; • Evidence of detectable plasmatic HIV sgp120 levels at any point in the past year, using the assay described priorly and performed at CRCHUM in Dr Andrés Finzi's laboratory. Exclusion Criteria: • Already on fostemsavir regiment • Hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container; • Concomitant treatment with strong cytochrome P450 (CYP3A) inducers, including but not limited to: carbamazepine, phenytoin (anticonvulsants), mitotane (antineoplastic), enzalutamide

(androgen receptor inhibitor), rifampicin (antimycobacterial) and St John's wort (Hypericum perforatum, herbal supplement);

- Planning to become pregnant, pregnant, or breastfeeding (as requested per product monography (55)). Females of childbearing potential must have a negative pregnancy test at **baseline visit**, and follow contraception requirements **throughout** the treatment;
- Contraindication for CT scan use (estimated glomerular filtration rate [eGFR] less than 40ml/min using the Modification of Diet in Renal Diseases [MDRD] formula or iodine allergy);
- Elevated risk of prior ionizing radiation exposure outside clinical care exceeding 10 mSV over 3 years, per the investigator's judgement (eg. a participant with occupational ionizing radiation exposure, prior participation in clinical trials with multiple CT scans)
- Confirmed uncorrected QT value >500ms or confirmed QTcF >470 msec for women and >450 msec for men;
- Acquired/ congenital long QT syndrome;
- Current or anticipated treatment with any of the following medications: amiodarone, disopyramide, dofetilide, ibutilide, procainamide, sotalol, and quinidine;
- Unstable liver disease (as defined by any of the following: presence of ascites, encephalopathy, coagulopathy (INR > 2.0), hypoalbuminemia (<30 mg/ml), untreated esophageal or gastric varices, or persistently elevated bilirubinemia (>1.5x upper limit of normal [ULN]), known biliary abnormalities (except Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment);
- ALT >=5 times the ULN, OR ALT >=3xULN and bilirubin >=1.5xULN with >35% direct bilirubin;
- History of liver cirrhosis with CHILD-PUGH classification C;
- Inability to provide informed consent;
- Life expectancy of less than 36 months;
- Inability to present to study visits;
- Participation in another interventional trial;
  Known Congestive heart failure with NYHA class 3 or 4.

Sample Size N=150

- Arm 1 (active): n= approx. 75
- Arm 2 (standard of care): n= approx.75

	Based on prior results of variation in total uncalcified coronary plaque volume measured on CCTA over a period of 12 months in people with HIV, we estimated an expected mean change in the atorvastatin group of –7.67 mm³, with a standard deviation of 17.59, and an expected mean change in the placebo group of 10.00 mm³, with a standard deviation of 28.81 (Lo et al. 2015; Wan et al. 2014). This corresponds to a Cohen's d effect size of 0.73, which is relatively large (Cohen 1988). However, given that we expect statin use in both groups, we adopt a conservative approach for this study and assume a medium effect size (Cohen's d = 0.50) to account for potential attenuation of the fostemsavir effect due to concomitant statin therapy. This would translate to a decrease of 2.17 mm^3 in the fostemsavir group and an increase of 10.00 mm^3 in the group receiving standard of care, using standard deviations of 17.59 and 28.81, respectively. Based on this effect size, with 80% power and an alpha of 0.05, the estimated target sample size is 130 patients to detect a clinically meaningful difference. Allowing 10% incomplete CCTA or loss to follow-up, we aim to recruit a total sample size of 150 patients into the trial at four study sites
Statistical Analysis	Statistical analysis will be conducted by CITADEL after the closing of the study database, according to the statistical analysis plan, which will be registered before the analysis is conducted. All analyses will be done by intention-to-treat; patients will be analyzed in the group they were randomized to. Biobank analyses planned after 50% of participants completed the 12 months biobanking will be done by CITADEL after this part of the data collection is closed. Details can be found in the protocol

1. Résumé du protocole de recherche (français)

Numéro de protocole	MP-02-2025-12725
Titre de l'étude	**Essai RESTART** : Réduire l'inflammation systémique chez les personnes sous traitement antirétroviral Essai randomisé et contrôlé du fostemsavir par rapport à la norme de soins pour réduire la comorbidité chez les personnes dont le VIH est bien contrôlé.
Phase de l'essai clinique	Phase II
Hypothèse de l'étude	Les personnes vivant avec le VIH ayant une charge virale indétectable mais dont la gp120 soluble du HIV est détectable dans le plasma sont exposées à une inflammation chronique, un dysfonctionnement immunitaire persistant et un risque accru de comorbidité. L'ajout de fostemsavir à leur traitement antirétroviral actuel entraînera une diminution du volume de la plaque coronaire non calcifiée, une diminution de l'inflammation et une amélioration de la fonction immunitaire.
Objectifs de l'étude	Cet essai vise à examiner l'efficacité d'une intervention ciblée contre la gp120 du VIH (une sous-unité de la machinerie d'entrée du VIH-1 impliquée dans l'inflammation persistante et le dysfonctionnement immunitaire) pour réduire le risque de comorbidité associée à l'inflammation chez les personnes vivant avec le VIH. <u>Objectif primaire:</u> Estimer l'efficacité du fostemsavir à diminuer la maladie cardiovasculaire dans la population à l'étude, telle que mesurée par le changement de volume de plaque coronarienne non calcifiée entre le début de l'étude et 24 mois, mesurée par angiographie coronarienne par tomographie couplée par ordinateur. <u>Objectif secondaire radiologique</u> : Estimer l'efficacité du fostemsavir à diminuer l'inflammation peri-coronarienne, mesuré avec l'indice d'atténuation du gras péri-coronarien. <u>Objectif secondaire clinique :</u> Estimer l'efficacité du fostemsavir à améliorer les évènements cliniques tels que les évènements cardiovasculaire, le déclin cognitif et la fragilité.

	Objectif secondaire de biomarqueurs : Estimer l'impact du fostemsavir sur l'inflammation et la dysfunction immunaitaire, les reservoirs du VIH et les niveaux de gp120 soluble. Objectifs secondaires de sécurité : Estimer la sécurité et la tolérance du traitement.
Conception de l'étude	Essai multicentrique, ouvert, randomisé et contrôlé comparant le fostemsavir aux soins standards. La randomisation sera effectuée selon un ratio 1:1 avec une répartition en bras parallèles, stratifiée selon le sexe et l'utilisation de statines au moment du recrutement, grâce à un algorithme informatisé utilisant des blocs permutés de taille variable afin de garantir la dissimulation de l'allocation. L'intervention consistera à ajouter le fostemsavir (Rukobia 600 mg par jour) au schéma antirétroviral (ARV) actuel du patient, ou à continuer les soins standards. Les soins standards incluent la poursuite du traitement ARV et autres médicaments prescrits par leur médecin. Les changements dans le schéma ARV ou les traitements concomitants selon l'indication du médecin traitant sont autorisés. Cet essai sera conduit en mode ouvert ; cependant, les évaluateurs du critère principal (basé sur les deux scans CCTA), le personnel responsable des analyses de la biobanque, ainsi que les statisticiens resteront à l'aveugle quant à l'allocation du traitement. **Visite de sélection** : Un consentement éclairé écrit sera obtenu. Un test sanguin sera effectué pour mesurer la HIV sgp120 afin de déterminer l'éligibilité (sauf si des données sur le niveau de gp120 de moins de six mois sont disponibles), ainsi que la charge virale (sauf si disponible dans les 6 derniers mois) ainsi que pour la contribution à la biobanque. Seules les données uniquement nécessaires à l'évaluation des critères d'inclusion/exclusion (âge, sexe à la naissance, genre auto déclaré, facteurs de risque cardiovasculaires, durée du VIH, traitement ARV actuel) seront collectées. Un registre de toutes les visites de sélection et des échecs de sélection sera tenu à jour. **Visite d'inclusion** : Réalisée par téléphone. Les résultats de HIV sgp120 seront communiqués à tous les participants. Ceux qui répondent aux critères

d'inclusion seront invités à la visite de référence. Les autres termineront leur participation à ce stade.

Visite de référence : Planifiée dans les six mois suivant la visite d'inclusion. Les mesures de base suivantes seront effectuées : CCTA, B-CAM, force de préhension, et le formulaire CRF sera complété. Un prélèvement sanguin sera obtenu pour la biobanque, la mesure de la charge virale, le décompte des CD4, CD8, et pour la surveillance de la sécurité du participant. Un examen physique sera réalisé, ainsi qu'une revue de l'historique médical, des médicaments et du traitement anti rétroviral pris par le participant. Des données démographiques seront également collectées. La randomisation et la distribution du traitement seront faites lors de cette visite. Un test de grossesse et ECG seront réalisés à cette visite et la distribution du traitement ne pourra se faire qu'après que les résultats de ces tests soient obtenus. Les signes vitaux seront vérifiés. Si la CCTA ne peut pas être réalisée le même jour, la visite pourra être divisée en deux et la randomisation reportée au jour de la CCTA, afin de s'assurer que tous les participants randomisés aient une CCTA de référence.

Visite de surveillance : Réalisée au mois 1 (+/- 2 semaines). Des tests sanguins de surveillance seront effectués (formule sanguine, créatinine, eGFR, sodium, potassium, fonction hépatique (ALT, bilirubine, phosphatase alcaline)) ainsi que la mesure de la charge virale, le décompte et pourcentage CD4/CD8. Révision des médicaments concomitants, des antirétroviraux. Révision de l'adhérence au traitement et des événements indésirables. Prise des signes vitaux, test de grossesse, ECG. De plus, les résultats cliniques de la CCTA seront discutés avec les participants et un suivi planifié selon l'indication clinique. Tous les résultats cliniques des CCTTA seront disponibles pour les médecins traitants.

Visites de suivi : Les visites de suivi auront lieu aux mois 6, 12 et 18 (+/- un mois). Lors de chaque visite de suivi, le formulaire de collecte de données (CRF) de l'étude sera rempli; les indicateurs de résultats cliniques seront évalués; l'observance du traitement sera vérifiée par le décompte des comprimés; et le médicament de l'étude sera remis. À chaque visite, des prélèvements sanguins seront effectués pour les analyses de surveillance, la charge virale, le dénombrement et les pourcentages des cellules CD4 et CD8, ainsi que pour la biobanque. Les médicaments et le schéma antirétroviral seront révisés, de même que l'adhérence au traitement et les événements indésirables. Les signes vitaux seront contrôlés. Un test de grossesse et un électrocardiogramme (ECG) seront réalisés.

	Visite de fin de traitement : Au mois 24 (+/- 1 mois), la visite de fin de traitement sera réalisée. Elle comprendra les mesures B-CAM, la force de préhension, la CCTA, la collecte des indicateurs de résultats cliniques ainsi que des prélèvements pour la biobanque. Les médicaments et le schéma antirétroviral seront révisés, de même que l'adhérence au traitement et les événements indésirables. Les signes vitaux seront vérifiés. Un test de grossesse et un électrocardiogramme (ECG) seront effectués. Un prélèvement sanguin sera réalisé pour les analyses de surveillance, la charge virale, les taux et pourcentages de CD4 et CD8, ainsi que pour la biobanque. Un décompte final des comprimés pris sera effectué. Tous les comprimés non utilisés, retournés par le participant, seront détruits. **Visite post-traitement** : La dernière visite de l'étude aura lieu au mois 27 (3 mois après la fin du traitement). Les procédures réalisées lors de cette visite comprennent le prélèvement sanguin pour biobanque, et l'évaluation des indicateurs de résultats. Le prélèvement sanguin permettra également la surveillance, le décompte des CD4/CD8, et la mesure de la charge virale. Revue du traitement ARV et prise des signes vitaux.
Sites d'étude	Canada 4 sites
Durée de l'étude	Période de sélection : jusqu'à 24 semaines (6 mois) Période de traitement : 2 ans (24 mois) Période de suivi : 12 semaines (3 mois) Durée totale de participation : 27 mois, plus la période de sélection
Indicateurs de résultats	**Critère principal** : Variation du volume total de plaques non calcifiées entre le début de l'étude et la fin du traitement (mois 24), entre le groupe fostemsavir versus celui des soins standards. **Critère secondaire d'imagerie**: Indice d'atténuation de la graisse péri vasculaire au mois 24, ajusté aux valeurs de base. **Critères secondaires cliniques**: Événements cliniques – délai avant un événement cardiovasculaire majeur (MACE), B-CAM, force de préhension au mois 24 (ajusté aux valeurs de base), incidence des MACE. Données de surveillance collectées dès la première visite de surveillance (un mois après le début du traitement) et pendant toute l'étude via les rapports SUSAR et SAE dans le CRF.

	Critères secondaires de biomarqueurs : Des anlayses pré-spécifiées de biomarqueurs effectuées dans les échantillons de la biobanque (virologie, immunologie, inflammation). **Critères secondaires de sécurité** : Risque d'effet secondaires sévère et sérieux et incidence de discontinuation de traitement en raison d'effets secondaires.
Analyse intérimaire des biomarqueurs	Une analyse intérimaire sera effectuée pour les critères secondaires de biomarqueurs lorsque 50% de la population de l'étude aura complété 1 an de suivi. Les biomarqueurs spécifiques inclus dans cette analyse sont un sous-groupe de l'ensemble des biomarqueurs prévus dans les critères secondiares de biomarqueurs.
Traitement à l'étude	L'intervention consiste à ajouter le fostemsavir (Rukobia 600 mg une fois par jour) au schéma ARV actuel du patient, ou à poursuivre les soins standards. Le médicament d'étude (Rukobia, (fostemsavir comprimés à libération prolongée - DIN 02520869)) a déjà été utilisé dans une étude (BRIGHTE) et est approuvé pour les patients en échec thérapeutique à raison d'un comprimé de 600 mg pris deux fois par jour. Dans l'essai RESTART, une prise unique quotidienne est utilisée avec l'accord de ViiV Healthcare.
Contrôle	Standard de soins
Posologie et administration	Bras 1 (actif) : Administration orale une fois par jour (comprimé à libération prolongée de 600 mg) pendant 24 mois. Bras 2 (Soins standards) : Les participants poursuivront leur schéma ARV actuel ainsi que tout traitement prescrit par leur médecin traitant pendant l'essai.
Critères d'éligibilité	Critères d'inclusion (tous doivent être remplis) : • Être âgé de 40 ans ou plus, ou vivant avec le VIH depuis 25 ans ou plus, tous sexes confondus. • Charge virale VIH indétectable (moins de 50 copies/ml au cours des 6 derniers mois). • Présence d'au moins un facteur de risque cardiovasculaire parmi : VIH de longue date (≥ 25 ans), hypertension, diabète, tabagisme passé ou actuel, dyslipidémie, antécédents familiaux de MCV précoce (avant 55 ans chez les hommes ou 65 ans chez les femmes), maladie cardiovasculaire avérée (infarctus du myocarde, revascularisation coronaire, accident vasculaire cérébral, ou athérosclérose des artères coronaires avec une sténose ≥ 50%, démontrée par CCTA)

- Toute maladie cardiovasculaire antérieure doit être stable selon le jugement du médecin de l'étude. (événements ≥ 3 mois avant la sélection).
- Présence documentée de gp120 du VIH plasmatique détectable dans l'année passée (analyse faite au CRCHUM, laboratoire du Dr Andrés Finzi).

Critères d'exclusion :

- Traitement déjà en cours avec fostemsavir
- Hypersensibilité au médicament ou à un de ses composants y compris tout ingrédient non médicinal
- Traitement concomitant avec inducteurs puissants du cytochrome P450 (CYP3A) ex : carbamazépine, phénytoïne, mitotane, enzalutamide, rifampicine, millepertuis...
- Grossesse, projet de grossesse, allaitement. Les femmes en âge de procréer doivent présenter un test de grossesse négatif lors de la visite initiale et respecter les exigences en matière de contraception pendant toute la durée du traitement.
- Contre-indication à l'utilisation du scanner (eGFR < 40 ml/min ou allergie à l'iode)
- Risque élevé d'exposition antérieure aux rayonnements ionisants en dehors des soins cliniques dépassant 10 mSV sur 3 ans, selon le jugement de l'investigateur (par exemple, un participant exposé aux rayonnements ionisants dans le cadre de son travail, une participation antérieure à des essais cliniques avec de multiples tomodensitométries).
- QT > 500 ms ou QTcF > 470 ms chez la femme ou > 450 ms chez l'homme
- Syndrome du QT long (congénital ou acquis)
- Traitement actuel ou prévu avec certains médicaments prolongeant le QT (ex : amiodarone, disopyramide, dofetilide, ibutilide, procainamide,sotalol, and quinidine.
- Maladie hépatique instable (définie par l'un des éléments suivants : présence d'ascite, encéphalopathie, coagulopathie (INR > 2,0), hypoalbuminémie (< 30 mg/ml), varices œsophagiennes ou gastriques non traitées, ou bilirubinémie élevée persistante (> 1,5 fois la limite supérieure de la normale [LSN]), anomalies biliaires connues (à

l'exception du syndrome de Gilbert ou de calculs biliaires asymptomatiques ou d'une maladie hépatique chronique par ailleurs stable selon l'évaluation de l'investigateur).

- ALT >=5 fois la LSN, OU ALT >=3x LSN et bilirubine >=1,5xLSN avec >35% de bilirubine directe ;
- Maladie hépatique instable ou cirrhose selon la classification de CHILD-PUGH C
- Incapacité à donner un consentement éclairé ou à participer aux visites
- Espérance de vie < 36 mois
- Participation à un autre essai interventionnel
- Insuffisance cardiaque congestive New York Heart Association (NYHA) classe 3 ou 4

Taille de l'échantillon

N=150

- Bras 1 (active): n= approx.75
- Bras 2 (soins standards): n=approx. 75

Sur la base des résultats antérieurs concernant la variation du volume total de plaques coronaires non calcifiées mesuré par CCTA sur une période de 12 mois chez des personnes vivant avec le VIH, nous avons estimé un changement moyen attendu dans le groupe atorvastatine de –7,67 mm^3, avec un écart-type de 17,59, et un changement moyen attendu dans le groupe placebo de 10,00 mm^3, avec un écart-type de 28,81 (Lo et al., 2015 ; Wan et al., 2014). Cela correspond à une taille d'effet de Cohen (Cohen's d) de 0,73, ce qui est considéré comme relativement élevé (Cohen, 1988).

Cependant, étant donné que nous prévoyons l'utilisation de statines dans les deux groupes, nous adoptons une approche prudente pour cette étude en supposant une taille d'effet moyenne (Cohen's d = 0,50), afin de tenir compte d'une possible atténuation de l'effet du fostemsavir due à la prise concomitante de statines. Cela correspondrait à une diminution de 2,17 mm^3 dans le groupe fostemsavir et à une augmentation de 10,00 mm^3 dans le groupe recevant les soins standards, en utilisant les écarts-types de 17,59 et 28,81 respectivement.

Sur la base de cette taille d'effet, avec une puissance statistique de 80 % et un seuil alpha de 0,05, la taille d'échantillon cible estimée est de 130 patients pour détecter une différence cliniquement significative. En tenant compte d'un taux

	de CCTA incomplètes ou de pertes au suivi de 10 %, nous prévoyons de recruter un total de 150 participants pour cet essai, répartis sur quatre sites d'étude.
Analyses statistiques	L'analyse statistique sera réalisée par CITADEL après la fermeture de la base de données de l'étude, conformément au plan d'analyse statistique, lequel sera enregistré avant le début de l'analyse. Toutes les analyses seront effectuées selon le principe de l'intention de traiter ; les participants seront analysés dans le groupe auquel ils ont été randomisés. Les analyses intérimaire de biomarqueurs prévues après que 50 % des participants auront complété les 12 mois de collecte pour la biobanque seront également effectuées par CITADEL, une fois cette phase de collecte terminée. De plus amples détails sont disponibles dans le protocole.

2. Introduction (*Introduction*)

2.1 Raison d'être de la recherche *(Study rationale)*

CONTEXTE (*Background*): While tremendous progress in life expectancy has been achieved with antiretroviral therapy (ART) for People Living with HIV (PWH),[1,2] healthy aging remains an elusive goal for many living with the infection: comorbidity occurs on average 15 years earlier for PWH, and this gap has shown no signs of closing in the past two decades.[3] Cardiovascular disease (CVD) is among the leading causes of non-AIDS morbidity and mortality in PWH.[4] In addition to the risk attributable to the traditional cardiovascular risk factors, PWH are exposed to toxicity from antiretroviral drugs, and, even when the infection is well controlled, to a chronic state of inflammation.[4,5] HIV-1 glycoprotein 120 (gp120), a subunit of HIV-1 entry machinery, may be causally implicated in this sustained inflammation and immune dysfunction leading to increased comorbidity in PWH.

PROBLÈME DE RECHERCHE (*Research problem*): Our group has shown that soluble gp120 (HIV sgp120) is detectable in plasma in 28% of PWH with suppressed viral load – using a novel assay developed by Dr. Finzi's group that measures HIV sgp120 in plasma specifically. We measured HIV sgp120 in 386 participants with undetectable viral load selected from CHACS and found that HIV sgp120 was detectable in the plasma of 107/386 (28%).[6] To further support the hypothesis that HIV sgp120 is damaging, we measured its association with known markers of chronic inflammation and comorbidity. In CHACS participants with detectable CVD (measured by coronary computed tomography angiography [CCTA]) and detectable spg120, HIV sgp120 levels correlated positively with the volume of atherosclerotic plaque.[6] Our group has also shown that temsavir (the active metabolite of fostemsavir BMS-663068; GSK3684934), a first-in-class attachment inhibitor, prevents the interaction of HIV sgp120 with the CD4 receptor, preventing the cytokine burst and CD4 cell death.[7,8] Furthermore, *in vivo* measurements from the BRIGHTE study show that in the randomized group, treatment with fostemsavir was associated with a sustained decrease in biomarkers of inflammation for up to 5 years of treatment.[9,10]

RAISONS JUSTIFIANT LA TENUE DE CETTE ÉTUDE (*Study rationale*): Based on our preliminary results, Fostemsavir, the prodrug of temsavir, is a potential treatment to reduce HIV sgp120-associated chronic inflammation leading to comorbidity in PWH. However, while fostemsavir's potential to curb inflammation and comorbidity for PWH is promising, it cannot be offered to everyone with an undetectable HIV viral load, as it is a costly drug. The detection of HIV sgp120 levels in plasma may identify the sub-population that will benefit most from the addition of fostemsavir to their therapeutic regimen, and our study can pave the way for a larger study looking into the benefits of HIV sgp120 reduction in PWH and the effects of this reduction on CVD as one of the resulting comorbidities.

HYPOTHÈSE (*Hypothesis*)

PWH with undetectable viral load but detectable soluble HIV gp120 are exposed to chronic inflammation, sustained immune dysfunction, and increased risk of comorbidity. The addition of fostemsavir to the ARV regimen of PWH will improve their immune function and lead to a reduction in the size of non-calcified coronary plaque and inflammation.

2.1 Recension des écrits (Background)

HIV continues to be a major public health issue, with more than 39 million living with the disease worldwide. In 2022 alone, 1.3 million acquired the infection, 630,000 died from the disease, and there is still no existing cure or vaccine.[11] Tremendous progress in life expectancy has been achieved with ART for PWH,[1,2] but healthy aging remains an elusive goal for many living with the infection: comorbidity occurs on average 15 years earlier for PWH, and this gap has shown no signs of closing in the past two decades.[3] One of the leading hypotheses for this prognostic gap is the enduring antigenic stimulation from HIV, leading to chronic inflammation.[12-14] The term "inflammaging" has been proposed to refer to accelerated aging caused by the chronic, low-grade inflammation that persists in PWH despite suppressive ART, affecting multiple organ systems.[13-19]

DONNÉES PRÉLIMINAIRES PERTINENTES (*Relevant preliminary data*)

Cardiovascular disease (CVD) is among the leading causes of non-AIDS morbidity and mortality in PWH.[4] We [20] and others [4,21,22] have shown that PWH are at increased risk of CVD compared to the general population. While proportionate mortality from CVD has decreased for the general US population from 1999 to 2018, for PWH, it has increased from 1.9 to 6.7% during the same period.[23] A modelling study based on the Netherlands' HIV population structure (which is similar to Canada's) estimates that in 2030, based on increases in age and prevalence of CVD risk factors, 78% of PWH will have been diagnosed with CVD.[24] In addition to the risk attributable to the traditional cardiovascular risk factors, PWH are exposed to toxicity from antiretroviral drugs, and, even when the infection is well controlled, to a chronic state of inflammation.[4,5] While cardiovascular toxicity is notably decreased with integrase-inhibitors-based treatment regimens compared to protease inhibitor-based regimen,[25-28] enduring antigenic stimulation from HIV, leading to chronic inflammation, remains one of the leading hypotheses for the increased risk of CVD observed in PWH.[12-14] Chronic states of inflammation have long been recognized as a risk factor for CVD.[29,30]

ÉTUDES CLINIQUES, BASES POPULATIONNELLES ET OUTILS D'ÉVALUATION (*Clinical studies, population data and evaluation tools)*

As part of the Canadian HIV and Aging cohort study (CHACS), our group has shown that in a cohort of people, 40 years and older living with HIV and non-infected controls,[31] coronary atherosclerotic plaques measured by cardiac computed tomography angiography (CCTA) differed in PWH compared to non-infected individuals and these plaques are less likely to be calcified and exhibit more high-risk features.[32]

Recently, the REPRIEVE study became the first study to show the efficacy of a pharmacological intervention (pitavastatin) to reduce cardiovascular risk for PWH at low to moderate risk of cardiovascular disease.[33] However, no HIV-specific treatment exists to curb the remaining chronic inflammation that endures in PWH, even when plasma viral load is undetectable.

Recent data show that even while current antiretroviral regimens are very effective at blocking HIV replication, they do not prevent the expression of viral products from a subset of reservoir cells (spontaneously active reservoirs, sometimes colloquially termed "leaky reservoirs").[34-37] One of these products, soluble HIV-1 glycoprotein 120 (HIV sgp120) acts as a toxin driving chronic

inflammation *in vitro*. Gp120, a subunit of HIV-1 entry machinery, may be causally implicated in the sustained inflammation and immune dysfunction leading to increased comorbidity in PWH. It has been shown that gp120 is shed from infected cells (becoming soluble) [38,39] and can accumulate in tissues.[40,41] Soluble gp120 has been associated with HIV-induced immune dysfunction in several studies.[41-45] This is further illustrated by findings from our group that HIV sgp120 can bind to the CD4 receptor on uninfected cells, thus exposing vulnerable epitopes targeted by anti-cluster A antibodies (which are non-neutralizing antibodies present in the serum of PWH), leading to their elimination via antibody-dependent cellular cytotoxicity.[7,8,46] We also demonstrated that HIV sgp120 can trigger a cytokine burst from monocytes.[47]

HIV sgp120 is detectable in plasma in 28% of PWH with suppressed viral load. One of the hurdles to studying spg120 is that its conformational flexibility makes it analytically challenging to measure in plasma.[48] Dr. Finzi has developed a novel assay to measure HIV sgp120 in plasma specifically. As a proof of concept that HIV sgp120 is found in the plasma of PWH with undetectable viral load, we measured HIV sgp120 in 386 participants selected from CHACS and found that HIV sgp120 was detectable in the plasma of 107/386 (28%).[6] To further support the hypothesis that HIV sgp120 is damaging, we measured its association with known markers of chronic inflammation and comorbidity. We showed high levels of HIV sgp120 correlated with increased IL-6.[6] We also demonstrated that the negative associations between levels of anti-cluster A Abs and CD4 cell counts depended on the levels of HIV sgp120.[6] Moreover, in CHACS participants with detectable CVD (measured by CCTA) and detectable HIV sgp120, anti-cluster A Abs and their combination with HIV sgp120 levels correlated positively with the volume of atherosclerotic plaque.[6] These novel findings suggest that people with detectable HIV sgp120 constitute a distinct, at-risk group of individuals.[6]

Our group has shown that temsavir (the active metabolite of fostemsavir BMS-663068; GSK3684934), a first-in-class attachment inhibitor, prevents the interaction of HIV sgp120 with the CD4 receptor, and prevents the cytokine burst from monocytes and CD4 cell death.[7,8] Furthermore, *in vivo* measurements from the BRIGHTE study show that in the randomized group, treatment with fostemsavir was associated with a sustained decrease in biomarkers of inflammation (sCD14, sCD163) for up to 5 years of treatment.[9,10] Fostemsavir, the prodrug of temsavir, is, therefore, a potential treatment to reduce HIV sgp120-associated chronic inflammation leading to comorbidity in PWH. Fostemsavir is well-tolerated and has no interactions with other antiretroviral regimens.[49]

2.3 Bénéfices et risques (Benefits and risks)

The standard of care for HIV treatment is the immediate institution of lifelong combination antiretroviral therapy for all, intending to obtain a suppression of HIV plasma viral load. Once this is achieved, with the exclusion of statin therapy for low to moderate cardiovascular risk, there is no additional, HIV-specific treatment recommended to address the 15-year gap in comorbidity-free life expectancy.

BÉNÉFICES POTENTIELS (*Potential benefits*)

The RESTART study will target a persistent HIV viral antigen, found in plasma in a substantial fraction of PWH with controlled HIV, to reduce inflammation-associated comorbidities. Our study

represents the necessary first step to establish whether targeting HIV sgp120 specifically may lead to decreased inflammation-associated comorbidities in PWH.

The fostemsavir dosage used in the BRIGHTE trial and currently approved for use as an antiretroviral in people failing their ARV regimen is 600 mg orally twice daily.[50] In the RESTART trial, we are using a once-daily dosage, with the agreement of ViiV Healthcare, for the following reasons:

1. in this trial, this drug is intended for its anti-inflammatory effect (by blocking HIV sgp120-induced inflammation) rather than its anti-viral effect. Data from Phase 2B evaluated four fostemsavir doses, including 600 mg once daily, and found no safety/efficacy differences. Importantly, in a subsequent analysis looking at the inflammatory biomarker sCD14 (which is associated with CVD), the dose of 600 mg daily showed similar reductions to doses of 1200 mg.[51]
2. the pharmacokinetics data are in favour of a once-daily dosage for our purposes, with a plasmatic half-life of 7-14 hours for fostemsavir.[52]
3. a once-daily dosage will bolster compliance, in particular as most participants will already have one pill a day for their complete antiretroviral regimen.
4. this will cut down medication costs by half, greatly improving the chances that this intervention, if shown effective, may also be cost-effective.
5. side effects of QTc interval prolongation have been described mostly with a higher dosage, so a reduced dose is expected to be associated with increased safety on this front.[52]

PRISE EN CONSIDÉRATION DES RISQUES (*Risks assessment*)

It should also be mentioned that as this will be administered to people with undetectable HIV plasma viral load exclusively, the use of a reduced dose does not raise concerns for emerging drug resistance. Fostemsavir is safe and well tolerated in treatment-experienced PWH, with the most frequently reported side effects being gastrointestinal.[50,52] There are no interactions with other antiretroviral drugs, and no dosage adjustments are necessary with liver disease (including severe) or kidney failure (including late stages or hemodialysis).[52-54] Fostemsavir side effects are mostly mild and non-specific.[55] Most of our participants are expected to receive concomitant statin therapy, as our inclusion criteria will result in higher cardiovascular risk.

In case the participants do not tolerate the addition of fostemsavir to their regular AVR regimen, they will discontinue the additional therapy after consultation with the study doctor but will continue with the follow-up visits, unless they choose to completely withdraw from the study. Please refer to Appendix 1 for the table of risks with a potential clinical significance and associated risk mitigation strategy.

3. Objectifs et critères d'évaluation *(Objectives and endpoints)*

3.1 Objectif primaire *(Primary objective)*

The primary objective of this study is to determine the effectiveness of fostemsavir in decreasing the risk of cardiovascular disease in PWH, with undetectable viral load and detectable plasmatic HIV sgp120 levels, by comparing randomized groups of fostemsavir (Rukobia 600 mg daily) versus standard-of-care after 24 months of treatment.

3.2 Objectifs secondaires (secondary objectives)

3.2.1 Objectif secondaire d'imagerie *(Secondary imaging objective)*

A secondary imaging biomarker, Pericoronary Fat attenuation ratio (P-FAI), will be measured by analysis of CCTAs taken at baseline and month 24. Incidence of major cardiovascular events will be reported throughout the 27-month follow-up period.

3.2.2 Objectifs secondaires cliniques *(Secondary clinical objectives)*

Secondary clinical objectives of this study include: evaluating the effects of fostemsavir on frailty and cognition, by comparison of outcomes between groups of fostemsavir versus standard of care, after 24 months of treatment. Grip strength and B-CAM score will be measured via a dynamometer and a web-based measurement tool, respectively. A key secondary objective is the assessment of a possible interaction between sex and treatment.

3.2.3 Objectifs secondaires de biomarqueurs *(Secondary biomarker objectives)*

This trial includes pre-specified biomarker outcomes, which will confirm/infirm that our strategy of including a sub-population of people with well-controlled HIV and detectable HIV sgp120 identifies a key sub-population benefiting from fostemsavir. It will also inform the biological plausibility of reducing CVD and inflammation with fostemsavir and is a necessary step before designing a large-scale trial powered to look at clinical outcomes.

Table 1. Summary of study objectives

Objectives	Definition / Measurement methods
Primary	Estimate the efficacy of fostemsavir to decrease cardiovascular disease in the study population, as measured by change in uncalcified coronary artery plaque volume between baseline and month 24 /measured by CCTA
Secondary Imaging	Estimate the efficacy of fostemsavir to decrease peri-coronary inflammation, measured by Pericoronary Fat attenuation ratio (P-FAI) by analysis of CCTAs taken at baseline and month 24.
Secondary Clinical	Estimate the efficacy of fostemsavir to favorably impact clinical outcomes such as cardiovascular disease, frailty and cognition.

Secondary Biomarkers	Estimate the impact of study treatment on inflammation and immune dysfunction, measured using biomarkers of systemic inflammation and biomarkers associated to CVD, HIV reservoirs, immuno-serology and levels of HIV soluble gp120.
Secondary Safety	Estimate safety and tolerability of study treatment

3.4 Critère d'évaluation primaire *(Primary endpoint, primary outcome measure)*

The primary endpoint will be change in uncalcified coronary artery plaque volume between baseline and 24 months, measured by CCTA. Measure of uncalcified coronary artery plaque volume is a robust, well-established method that has been shown to predict major cardiovascular events,[56,57] as it is more related to major events than calcified volume. It has been well validated in the context of HIV infection, including in the CHACS cohort.[32,58-60]

3.5 Critères d'évaluation secondaires *(Secondary Outcomes)*

3.5.1 CRITÈRES D'ÉVALUATION SECONDAIRES RADIOLOGIQUES (*Imaging Secondary Outcomes*)

i) Perivascular fat attenuation ratio (P-FAI) on cardiac CT at month 24, adjusted for baseline values.

3.5.2 CRITÈRES D'ÉVALUATION SECONDAIRES CLINIQUES (*Clinical Secondary Outcomes*)

i) Time to major cardiovascular events (defined as myocardial infarction, coronary revascularization by percutaneous coronary intervention or surgery, peripheral artery revascularization, stroke, hospitalization for heart failure or unstable angina, or cardiovascular death).

ii) Grip strength at 24 months, adjusted for baseline values.

iii) Brief Cognitive Ability Measure (B-CAM) scores at 24 months, adjusted for baseline.

3.5.3 CRITÈRES D'ÉVALUATION SECONDAIRES de BIOMARQUEURS (*Biomarker Secondary Outcomes*)

i) Biomarker outcomes (using biobanked blood samples): A comprehensive panel of biomarkers exploring systemic inflammation and comorbidities, as well as immune-serologies, HIV reservoirs, immune cells profiling, levels of HIV sgp 120 and plasmatic concentration of fostemsavir will be measured. This comprehensive panel (listed in Table 2) will ensure that we can capture any anti-inflammatory effect associated with the study treatment.

3.5.4 CRITÈRES D'ÉVALUATION SECONDAIRES de SÉCURITÉ (*Secondary safety outcomes*)

i) Risk of severe and serious adverse events.

ii) Incidence of treatment discontinuation for side effects.

Table 2 : Summary and definitions of study outcomes	
Outcomes	**Definition / Measurement methods**
Primary Outcome	
Change in size of uncalcified coronary artery plaque volume between baseline and 24 months	The effectiveness of fostemsavir in decreasing uncalcified coronary artery plaque volume between baseline and 24 months will be measured by CCTA
Secondary Imaging Outcome	
Pericoronary Fat Attenuation Ratio (P-FAI)	Pericoronary Fat attenuation ratio (P-FAI), will be measured by analysis of CCTAs taken at baseline and month 24.
Secondary Clinical Outcomes	
Time to major cardiovascular events	Defined as myocardial infarction, coronary revascularization by percutaneous coronary intervention or surgery, peripheral artery revascularization, stroke, hospitalization for heart failure or unstable angina, or cardiovascular death.
Grip strength	Grip strength at 24 months adjusted for baseline values.
Brief Cognitive Ability Measure (B-CAM)	Defined as a change in B-CAM score between 24 months and baseline.
Secondary Biomarker Outcomes	
Biomarkers of systemic inflammation and biomarkers associated to CVD	IL-1β, IL-6, IL-10, IP-10, IL-15, TSLP, IFNg, TNF-α, sCD14, sCD163, hs-CRP, d-dimers, VCAM-1 A-FABP and BDNF I-FABP IL 32, TRAIL
HIV reservoirs	HIV-integrated DNA and cell-associated HIV RNA, single copy-HIV viral load.
Immunoserology and ADCC activity	Anti-cluster A levels, Anti-CD4i antibodies, Anti-p24 antibodies, Anti-CD4 binding sites antibodies Antibody-dependent Cellular Cytotoxicity (ADCC) activity
Immune cells profiling	Peripheral blood leukocyte subset profiling (CD3, CD4, CD8, CD11b, CD14, CD16, CD19, CD25, CD33, CD56, CD66, CD127, CCR6, CXCR5, HLA-DR, CD38, Ki67, PD-1, CTLA-4, Tim-3, TIGIT, LAG-3, CCR7, CD45RA, CCR5, CXCR3, CCR2) and gut (integrin B7, CD103) markers. CD4:CD8 ratio NK cell phenotype and profiling (CD3, CD56, CD16, Siglec-7, KLRG1, NKp30, NKp44, NKp46, KLRG1,CD38, HLA-DR, NKp44.
HIV sgp120 levels	Plasmatic HIV sgp120 levels.
Plasma fostemsavir concentration	Plasmatic concentration of fostemsavir
Secondary Safety Outcomes	

Adverse events	Incidence of adverse events, serious en severe adverse events
Treatment discontinuation	Incidence of treatment discontinuation due to side effects

3.5.5 ANALYSE INTÉRIMAIRE DES BIOMARQUEURS (*Biomarker Interim Analysis*)

There will be an interim analysis of the biomarker outcomes, which will take place when 50% of the planned sample size has completed one year of follow-up. (e.g.: When the 75th enrolled participant will have completed their one year visit, which means that there will be approximately 37 or 38 participants per group available for the biomarker interim analysis.) The biomarker interim analysis will be conducted using biobanked samples, and will include a subset of all pre-planned biomarker analyses, which is presented in Table 3 below. No pre-planned stopping rule is associated to the biomarker interim analysis.

Table 3 - Scope of secondary biobank outcomes included in the biomarker interim analysis

Outcomes	Measurements / responsibility for measurement
Biomarkers of systemic inflammation and biomarkers associated to CVD	IL-1β, IL-6, IL-10, IP-10, IL-15, TSLP, IFNg, TNF-α, sCD14, sCD163, , d-dimers, VCAM-1 A-FABP, and BDNF will be measured in A Finzi's lab hs-CRP, CD4:CD8 ratio will be extracted from the clinical labs
Immuno-serology	Anti-cluster A levels, anti CD4 bs antibodies ADCC activity will be measured in A. Finzi lab
Presence of HIV soluble gp120	Soluble gp120 will be measured in A. Finzi Lab
Plasma fostemsavir concentration	Plasmatic concentration of fostemsavir by mass spectrometry will be measured by the Finzi Lab

4. Méthodes *(Methods)*

4.1 Devis et contexte de l'étude *(Study design and context)*

TYPE D'ESSAI CLINIQUE (*Type of clinical trial*)
This study is a Randomized Controlled Trial (RCT) comparing fostemsavir, with the standard of care, in reducing non-calcified coronary artery plaque volume in people living with well-controlled HIV.

MODE DE COMPARAISON ET RANDOMISATION (*Comparison and Randomization*)
In this Phase II RCT, randomization will be done in a 1:1 ratio, with allocation in parallel arms, stratified by sex and participant statin use at recruitment, through a computerized algorithm with permuted blocks of randomly varying size, to ensure allocation concealment. The intervention will be either the addition of fostemsavir (Rukobia 600 mg daily) to the patient's current ART regimen, or the participant receiving the standard of care. Standard of care for people living with HIV includes continuation of the ARV regimen and other medications prescribed by their physiciants. Changes in ARV regimens or concurrent medications as indicated by treating physcians are allowed. This trial will be conducted as an open-label study; however, assessors of the primary outcome (based on two CCTA scans) and of the biobank analyses will remain blinded to treatment allocation, as well as statisticians.

LISTE DES CENTRES, NOMBRE DE PATIENTS PROJETÉS ET DURÉES (*Study centres, projected number of patients and timeline*)
Data collection will take place at four sites: CHUM, McGill University Health Center, Clinique Médicale Urbaine du Quartier Latin in Montreal, and Oak Tree Clinic in Vancouver. We aim to recruit 150 participants (N=150) over the course of 12 months. Once the recruitment period is over, the follow-up of participants will span the course of 32 months.
After randomization, each participant will follow an intervention treatment for 24 months (end of treatment visit at month 24) and will be followed for 27 months in total (post-treatment follow-up visit three months after the end of medication). Additional follow-up visits are scheduled at months 1, 6, 12, and 18. In total, this RCT will take place over 48 months.

Table 4 - Study design and timeline

Site initiation visits	Recruitment (N=150)		Follow-up					Biobank and data analysis
4 m - 12 m	**4 m - 16 m**		**4 m - 36 m**					**37 m - 48 m**
Montreal: *CHUM, *McGill University Health Center, *Clinique Médicale Urbaine du Quartier Latin; **Vancouver**: *Oak Tree Clinic	**Screening visit** Up to T0 - 6 m HIV viral load HIV sgp120 levels Biobank	**Inclusion visit** Up to T0 - 4 w Ineligible patients exit the trial	**Baseline visit** T0 Study visit CCTA Biobank Grip strength B-CAM CRF Randomization	**Follow-up visits** +1 m Safety visit CRF	+6 m +12 m +18 m Study visit CRF Biobank	**End of treatment visit** +24 m Study visit CCTA Biobank Grip strength B-CAM	**Post-treatment visit** +27 m Study visit Biobank	The biomarker interim analysis will be carried out when 50% of participants in both groups have completed one year of follow-up. Other analyses, including for the primary outcome, will start once all patients' visits are done

4.2 Population à l'étude *(Study population)*

The population studied consists of people with virologically-suppressed HIV and detectable HIV sgp120 levels, and of any sex. Recruitment will be done at two large hospital-based HIV clinics and one community-based clinic in Montreal, as well as in a women-centred clinic in British Columbia, who cater to an ethnically and gender-diverse population of PWH. Thus, the population served by those clinics is a good representation of PWH in Canada.[61]

4.2.1 CRITÈRES D'INCLUSION *(Inclusion criteria)*

Individuals must meet all following inclusion criteria

1. 40 years or older, or have lived with HIV for 25 years or more, any sex;
2. Undetectable HIV viral load (defined as last viral load measurement less than 50 copies/ml within the last 6 months);
3. Presence of at least one cardiovascular risk factor among the following: longstanding HIV infection (25 years or more), hypertension, diabetes, past or present smoking, dyslipidemia, family history of early onset CVD in a first-degree relative (defined as younger than 55 in males or younger than 65 in females (80)), known previous cardiovascular disease (defined as past myocardial infarction, coronary revascularization, stroke, or coronary artery atherosclerosis with >= 50% stenosis demonstrated on coronary angiography or CCTA);
4. Participants with past cardiovascular disease must be in a stable clinical condition as judged by the study clinicians;

5. Past cardiovascular events are defined as having occurred at least 3 months before screening;
6. Evidence of detectable plasmatic HIV sgp120 levels at any point in the past year, using the assay described priorly and performed at CRCHUM in Dr Andrés Finzi's laboratory.

4.2.2 CRITÈRES D'EXCLUSION *(Exclusion criteria)*

1. Already on fostemsavir regiment
2. Hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container
3. Concomitant treatment with strong cytochrome P450 (CYP3A) inducers, including but not limited to: carbamazepine, phenytoin (anticonvulsants), mitotane (antineoplastic), enzalutamide (androgen receptor inhibitor), rifampicin (antimycobacterial) and St John's wort (Hypericum perforatum, herbal supplement);
4. Planning to become pregnant, pregnant, or breastfeeding (as requested per product monography (55)). Females of childbearing potential must have a negative pregnancy test at **baseline visit**, and follow contraception requirements **throughout** the treatment;
5. Contraindication for CT scan use (estimated glomerular filtration rate [eGFR] less than 40ml/min using the Modification of Diet in Renal Diseases [MDRD] formula or iodine allergy);
6. Elevated risk of prior ionizing radiation exposure outside clinical care exceeding 10 mSV over 3 years, per the investigator's judgment (eg. a participant with occupational ionizing radiation exposure, prior participation in clinical trials with multiple CT scans).
7. Confirmed uncorrected QT value >500ms or confirmed QTcF >470 msec for women and >450 msec for men;
8. Acquired/ congenital long QT syndrome;
9. Current or anticipated treatment with any of the following medications: amiodarone, disopyramide, dofetilide, ibutilide, procainamide, sotalol, and quinidine;
10. Unstable liver disease (as defined by any of the following: presence of ascites, encephalopathy, coagulopathy (INR > 2.0), hypoalbuminemia (<30 mg/ml), untreated esophageal or gastric varices, or persistently elevated bilirubinemia (>1.5x upper limit of normal [ULN]), known biliary abnormalities (except Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment);
11. ALT >=5 times the ULN, OR ALT >=3xULN and bilirubin >=1.5xULN with >35% direct bilirubin;
12. History of liver cirrhosis with CHILD-PUGH classification C;
13. Inability to provide informed consent;
14. Life expectancy of less than 36 months;

15. Inability to present to study visits;
16. Participation in another interventional trial;
17. Known Congestive heart failure with NYHA class 3 or 4.

4.3 Recrutement des participants (*Participant recruitment*)

4.3.1 POPULATION SOURCE (*Source of participants*)

This is a prospective study that will recruit participants at four study sites using the inclusion/exclusion criteria described above. Participation will be offered to suitable patients of the study clinics, namely CHUM, McGill University Health Center, Clinique Médicale Urbaine du Quartier Latin in Montreal, and Oak Tree Clinic in Vancouver. This trial will also recruit patients of the CHACS cohort, as they are already retained in follow-up and have known levels of HIV sgp120. Additionally, particular efforts will be made to enroll more women, who tend to be underrepresented in HIV clinical trials (see the section below on women recruitment). Additionally, advertisements on social media and through community-based organizations will take place.

4.3.2 STRATÉGIE DE RECRUTEMENT (*Recruitment strategy*)

All clinic lists will be screened by research personnel to identify potential participants, who will be approached for participation at the time of their clinical visit. Participants from the CHACS cohort (who have consented to be recontacted for research) will be reached by phone to inquire if they are interested in participating in the study. For participants agreeing to take part in the study, informed consent will be sought, and the screening visit will take place immediately. HIV viral load and HIV sgp120 levels (as needed) will be measured in each prospective participant to verify their eligibility to enter this trial, as outlined in Figure 1. Blood samples for measurement of HIV sgp120 will be processed using common standard operating procedures (for centrifugation and freezing of plasma) in all study sites and will be shipped to A. Finzi's core lab, where testing for HIV sgp120 will be done every week during the recruitment phase of the trial. Following the screening visit, an inclusion visit will take place by phone, during which participation of patients who do not meet the inclusion criteria will end. Randomization will occur after completion of the CCTA during the baseline visit, unless both cannot happen on the same day, in which case randomization will be done on the day of the CCTA.

4.3.3 CALENDRIER DU RECRUTEMENT (*Recruitment timeline*)

We aim to recruit 3-4 patients per week per site (8-16/week total for screening). We expect to need to screen for eligibility between 450 and 500 participants to reach our target sample size of 150 randomized participants. At this rate, recruitment should be complete in 40-60 weeks. We allocated 1 ½ years for recruitment. For a detailed expected timeline of study procedures, refer to Table 5.

Table 5 - Expected timeline of study procedures												
	Year 1			Year 2			Year 3			Year 4		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
Site initiation visits		X	X									
Recruitment		X	X	X	X	X						
Follow-up		X	X	X	X	X	X	X	X			
Data analysis										X	X	X

4.4 Collecte de données: variables et mesures *(Data collection: variables and measurements)*

4.4.1 PROCEDURES ET DEROULEMENT DE L'ETUDE *(Study procedures and execution)*

Galenova, a pharmaceutical company based in Saint-Hyacinthe, Québec, will be used as a third party to handle drug reception from ViiV and distribution to site pharmacies following guidelines such as temperature-controlled shipments. Galenova will also be responsible for drug conservation and storage during the study and will plan regular shipments to sites as required. Upon receipt of the study drug to the site delegated pharmacy personnel, will conduct a complete inventory of the shipment received and assume responsibility for storage and dispensing to participants. Dispensation and return of unused study drugs will be appropriately documented and will be done by the pharmacy. Upon completion or termination of the study, all unused products should be returned to the clinic in their original containers. A complete accountability will be required at the end of the study. Any unused or expired product will be destroyed on-site by the research pharmacy and appropriately documented.

4.4.2 DÉROULEMENT DE L'ÉTUDE (*Study execution*)

Screening visit: Written informed consent will be obtained, and then a blood test will be done for measurement of HIV sgp120 to establish eligibility (unless prior data on HIV sgp120 levels, not older than six months are already available), viral load (unless prior data is available in the last 6 months), and contribution to the biobank. Limited data collection necessary for inclusion/exclusion criteria assessment (age, sex at birth, self-declared gender, CVD risk factors, duration of HIV and current HIV regimen) will be collected. A log of all screening visits and screen fails will be kept.

Inclusion visit: This visit will take place by phone. All participants will be notified of their plasma HIV sgp120 results. For those who meet the inclusion criteria, an appointment will be made for the baseline visit. For those who do not meet inclusion criteria, their participation will end at this visit.

Baseline visit: The baseline study visit will be scheduled within six months of the inclusion visit. During that visit, baseline measurements for each outcome measure will be performed: CCTA, B-CAM and grip strength, and the baseline CRF will be filled. A blood draw will be taken for

biobanking, viral load, CD4 and CD8 cell count and percentages, and safety. A physical examination will be performed. Medical history, medications and ARV regimen will be reviewed and demographic data will be collected. Randomization and medication dispensing will also take place. Pregnancy testing and ECGs will be performed and the results known prior to dispensing study medication. Vital signs will be checked. If an appointment for the CCTA is not available on the same day as the other procedures, the baseline visit may be split in two, and randomization will happen on the date of the CCTA, to ensure all randomized participants have baseline CCTA.

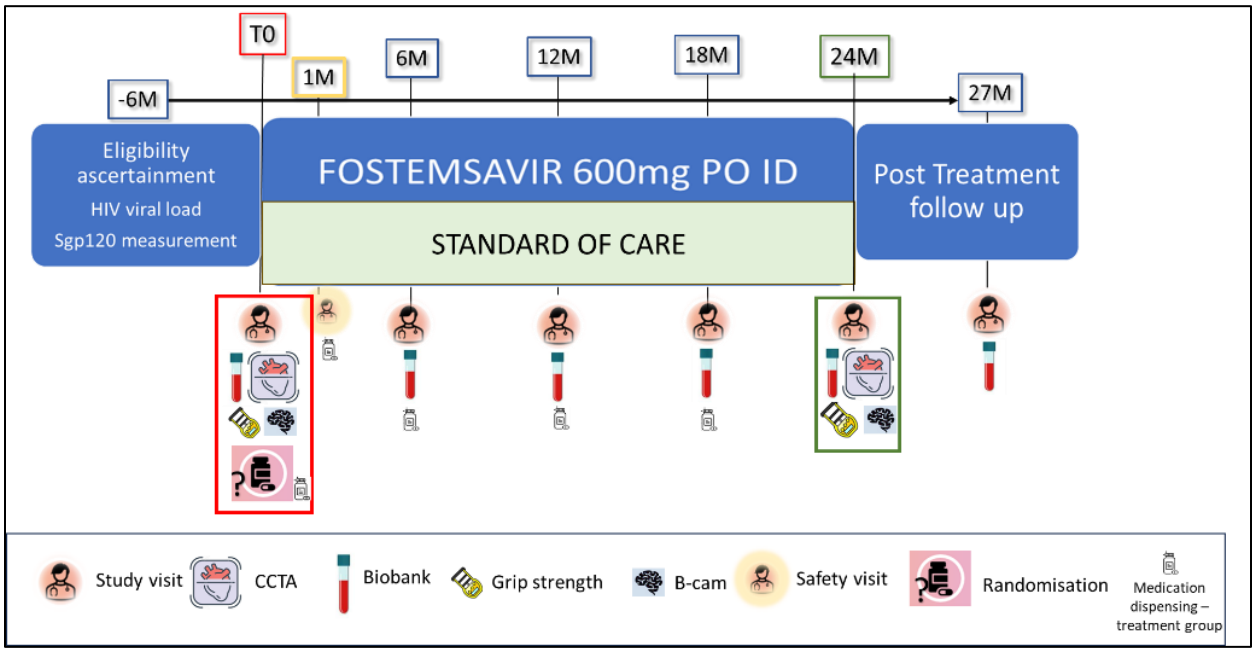


Figure 1. Overview of study procedure and timelines

Safety visit: The safety visit will take place at month 1 (+/- 2 weeks), during which blood tests will be done for safety (Complete blood count, creatinine, eGFR, sodium, potassium and liver function tests [ALT, bilirubin, alkaline phosphatase]) as well as viral load, CD4 and CD8 cell count and percentages. Medications and ARV regimen will be reviewed, along with treatment adherence and adverse events. Vital signs will be checked. Pregnancy testing and ECGs will be performed. Additionally, clinical results from the enrollment CCTA will be discussed with the participants, and referrals will be planned as clinically indicated. All clinical results of CCTA will be available to participants' treating physicians.

Follow-up visits: Follow-up visits will take place at months 6, 12, and 18 (+/- one month). At each follow-up visit, study CRF will be filled; clinical outcomes ascertainment will be done; compliance will be assessed by pill counts; and study medication will be dispensed. At each visit, blood drawn for safety, viral load, CD4 and CD8 count and percentages, and the biobank will be collected. Medications and ARV regimen will be reviewed, along with treatment adherence and adverse events. Vital signs will be checked. Pregnancy testing and ECGs will be performed.

End of treatment visit: At month 24 (+/- 1 month), the end of treatment visit will be conducted, with measures of B-CAM, Grip Strength, CCTA, collection of clinical endpoints as well as biobanking. Medications and ARV regimen will be reviewed, along with treatment adherence and

adverse events. Vital signs will be checked. Pregnancy testing and ECGs will be performed. Blood will be drawn for safety, viral load, CD4 and CD8 count and percentages, and the biobank A final assessment of pill counts and reconciliation will be done. All unused pills returned by the participant will be destroyed.

Post-treatment visit: The last study visit will happen at month 27 (3 months after the end of treatment), where the last blood test for biobanking will be collected and clinical endpoints will be collected along with safety, viral load, CD4 and CD8 count and percentages. At this visit the ARV regimen will also be reviewed and vital signs measured.

Table 6 Blood Draw summary per visit

Visit	Screening visit	Inclusion visit	Baseline visit	Follow-up visits		End of treatment visit	Post-treatment visit
Time point	Up to T0 - 3 m	Up to T0 - 4 w	T0	+1 m (Safety)	+6 m +12 m +18 m	+24 m	+27 m
HIV SGP120 screening test and biobank - The cell portion of the blood will be saved for biomarker outcomes analysis (Volume: 10ml/1 tube)	**X**						
Clinical tests: (Volume: 40ml/4 tubes)			**X**	**X**	**X**	**X**	**X**
Biobank – For biomarker outcomes analysis (Volume: 110ml/11 blood tubes)			**X**	**X**	**X**	**X**	**X**

4.4.2 Variable d'intervention ou d'exposition *(Intervention or exposure variable)*

Fostemsavir treatment is the exposure of interest. However, to maintain the benefits of randomization, all participants will be analyzed in the group they have been allocated to, regardless of the quantity of fostemsavir they have been exposed to.

Table 7 – Overview of study visits and procedures

Table 7. Overview of study procedures at each study visit										
Procedures	**Screening**	**Inclusion**	**Baseline**	**Follow-up**				**End of treatment**	**Post-treatment**	**Premature discontinuation**
	Up to 6 m before T0	Until 6m before T0	T0	1 m ± 2w	6m ±1m	12m ± 1m	18m ±1 m	24 m± 1 m	27 m± 1 m	
Informed consent	X									
Eligibility assessment	X	X								
Pregnancy test*			X	X	X	X	X	X		
Urine dipstick test			X#					X#		
ECG***			X	X	X	X	X	X		
Blood draw for sgp120	X									
Randomization			X**							
Blood draw for biobank	X		X		X	X	X	X	X	
Blood draw for safety			X	X	X	X	X	X	X	
Physical examination			X					x		
Compliance assessment				X	X	X	X			X
Medication dispensation			X**	X	X	X	X			
CCTA			X**					X		X****
Outcome ascertainment (MACE)				X	X	X	X	X		X
Grip strength			X					X		X
B-CAM			X					X		X

CCTA: Cardiac Computed Tomography Angiography; B-CAM: Brief Cognitive Ability Measure
*(blood or urine) refer to the section on Pregnancy for details on pregnancy testing (section 5.3)
**in cases where the baseline visit cannot take place on the same day as the CCTA, randomization and medication dispensation will happen on the day of the CCTA
*** To prevent false positives and participants' stopping unnecessarily, ECGs with QT prolongation will be evaluated by a cardiologist. To enable this to be practically implemented, the cardiologist will be consulted within 24-48 hours.
# To be performed on the day of CCTA as an additional confirmation of no pregnancy
**** CCTA will be offered at premature discontinuation if the participant after ≥ 1-year follow-up, decides to withdraw from the study. To avoid any possible risk of fetal exposure, in case of pregnancy, the exit CCTA will be done after delivery.

4.4.3 ATTRIBUTION DES INTERVENTIONS *(Allocation of interventions)*

Participants will be randomized in a 1:1 ratio, with allocation in parallel arms, stratified by sex and use of statins at recruitment, through a computerized algorithm with permuted blocks of randomly varying size, to ensure allocation concealment. The randomization procedure will be generated by the Centre d'intégration et d'analyses en données médicales (CITADEL), a data science, biostatistics and trial support platform of the Centre Hospitalier de l'Université de Montréal (CHUM) research center.

Open-label study **:** This trial will be conducted as an open-label study, as no placebo is available. Nonetheless, assessors of the primary outcome (based on two CCTA scans) and of the biobank analyses as well as statistician, will remain blinded to treatment allocation.

Intervention**:** Fostemsavir 600 mg orally once daily for 24 months or standard of care. Participants randomized to the fostemsavir arm will take the study medication in addition to their current HIV suppressive therapy and other medications, as prescribed by their treating physician throughout the trial. Each RUKOBIA extended-release tablet contains 600 mg of fostemsavir (equivalent to 725 mg of fostemsavir tromethamine). The tablets are beige, oval, film-coated, biconvex tablets, debossed with "SV 1V7" on one side. Additional information (all prescribing info) is available at Rukobia Medical Information - Our HIV Medications - ViiV Medical Information. The intervention will cease in participants experiencing low tolerability to the drug. No dosage adjustment is envisioned. At the baseline visit participants will receive only one bottle of RUKOBIA, two bottles at the safety visit and three bottles on consequent visits - this way we will reduce the extra dispensing and possible waste at the beginning of the study. Usually, AEs will be observed rapidly so drop-out for these reasons will happen within the first month. The study nurse or coordinator will collect the unopened bottles from a participant at their home if needed, if participant decides to drop out of the study.

4.4.4 INTERUPTION DU TRAITEMENT A L'ÉTUDE *(Study Drug Discontiuation)*:

The study drug will be discontinued if any of the following situations arise.

i)Participant no longer meets the study entry criteria.

ii)Participant requires use of a strong CYP3A4 inducer or any prohibited prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St. John's Wort).

iii) Participants meet criteria for QTc interval prolongation listed in the safety section, namely, QTcF interval >500 msec OR on treatment , triplicate averaged QTcF value > 60 msec over baseline, regardless of sex.

iv) Participant meets the Liver Chemistry Stopping rules defined in section

v) Intolerance to study medication or other reasons to stop, according to the study physician's expertise.

vi) Participants withdraw consent

Participants who stop medication due to one of the criteria above will not start it again during the study period. All participants will be kept in follow-up even if the study drug is discontinued.

4.4.5 MESURE DU CRITÈRE D'ÉVALUATION PRIMAIRE (*Primary outcome measurement)*

Result variable definition: The primary outcome variable is the change in uncalcified coronary artery plaque volume between baseline and month 24, measured by CCTA. This variable was chosen as it is a robust, well-established measure that has been shown to predict major cardiovascular events,[56,57] as uncalcified volume is more related to major events than calcified volume. The total uncalcified plaque volume (expressed in cubic millimetres) will be measured by CCTA at baseline and at month 24, and the baseline value will be subtracted from the same parameter at the end of the treatment, to assess the evolution in volume from baseline.

Image acquisition: CCTA will be performed during the baseline and the end of treatment visit (month 24) by using a 256-section CT scanner (Brilliance iCT; Philips Healthcare) and 370 mg/mL iopamidol contrast media (Bracco Imaging). Image acquisition protocols will be the same in our two imaging sites - CHUM core lab and Vancouver St Paul's Hospital (see the section below on primary outcome variable measurement).

We have used and validated our CCTA image acquisition and post-processing methods in the past in the CHACS.[32,62] Before undergoing CT, participants will be administered metoprolol 50–75 mg orally if their heart rate is greater than 60 beats per minute, and 0.4 mg nitroglycerin sublingually unless contraindicated. Coronary CT angiography will be performed by using a 256-section CT scanner (Brilliance iCT; Philips Healthcare) and 370 mg/mL iopamidol contrast media (Bracco Imaging) infused at a rate of 5 mL/sec. Prospective electrocardiographic gating will be used when the heart rate is 70 beats per minute or less, and retrospective electrocardiographic gating when the heart rate is more than 70 beats per minute. Gantry rotation time will be 270 msec, axial section thickness 0.625 mm, and section interval 0.45 mm. Imagine acquisition protocols will be the same in our two imaging sites (CHUM core lab and Vancouver St Paul's Hospital). ECG-gated CT scan will be used, ensuring that ionizing radiation dose is decreased to a minimum.

Risks associated with radiation are discussed in the ICF, which reads: "A tomodensitometry examination involves exposure to x-rays. There is a risk of inducing cancer, although this risk is relatively low. Cardiac tomodensitometry is done using a technology called prospective ECG synchronization, which lessens the exposure to the X-rays. A thyroid shield is placed in front of the thyroid gland to reduce the gland's exposure to radiation. If the examination is done on a woman of child bearing age, a breast shield is used. The total effective radiation dose from this CT scan will be 2.87 mSv (or 5.8 over the period of two years). The average annual global background radiation dose is 2.4 mSv and therefore the total estimated dose from one study procedure is equivalent to approximately one year of background radiation. The additional risk of developing a fatal malignancy as a result of this radiation exposure is around 1 in 20,000 (~0.005%) for 18-year-old females and around 1 in 12,500 (~0.008%) for 18-year-old males. To avoid any possible risk of fetal exposure to X-rays, pregnancy tests will be performed at baseline and at the end of the study visit before the CT scan. In case of pregnancy at the baseline, participants will be referred to inquire about the study after delivery. In case of pregnancy during the study, participants will discontinue the treatment and the exit CCTA will be done after

delivery. For participants of child-bearing potential, the pregnancy test will be performed at most seven days before the CT scan. Repeat scans will be given if there is technical failure (one additional).

CCTAs are likely to yield results that are of clinical significance for participants and their healthcare providers, such as the presence of subclinical coronary artery disease, or incidental findings such as lung nodules. It would be unethical to withhold those results for the duration of the study, so a clinical interpretation of each CCTA will be performed and added to the clinical file. Adequate clinical management will be instituted according to standard clinical practice.

CCTA Post-processing: All post-processing of images will be done jointly at the end of the study. All image assessors (radiologists, technicians) will remain blinded to treatment allocation, sex and cardiovascular risk factors. Images will be de-identified and transferred to the CHUM core lab for images post-processing. First, plaques will be identified on the CCTA by two board-certified radiologists (Co-applicants C. Chartrand-Lefebvre and P. Bourgouin), and then plaque quantification will be performed by a technician. Each coronary plaque will be classified as calcified, mixed, or noncalcified. Calcified and noncalcified plaques are defined as hyper- and hypoattenuating lesions, with values greater than or equal to 150 Hounsfield units and less than 150 Hounsfield units, respectively.[63,64] Plaque volume will be assessed by using semiautomated software (Aquarius iNtuition 4.4.6; TeraRecon).[65] The analysis will be performed in multiplanar reformat. Proximal and distal plaque boundaries will be established visually. Segmentation will be made by using the software, with manual adjustment if plaque delimitation is inaccurate. The uncalcified volume of plaque will be expressed as the total volume of plaques of < 150 Hounsfield units. We previously established an excellent inter- and intraobserver agreement for plaque volume with this technique (intraclass correlation coefficient, 0.95 and 0.93, respectively).[62] The same post-processing methods will be used for both CCTA (baseline and end of treatment). The total uncalcified plaque volume (expressed in cubic millimetres) at baseline will be subtracted from the same parameter at the end of treatment, which will yield a change in uncalcified plaque volume.

4.4.6 MESURE DES CRITÈRES D'ÉVALUATION SECONDAIRES (*Secondary Outcomes measurements*)

Measurements for Imaging secondary outcome :

Perivascular fat attenuation ratio (P-FAI): P-FAI is a novel imaging biomarker, in which the attenuation of fat surrounding coronary arteries is measured (in Hounsfield units).[66] This biomarker was associated with major adverse cardiovascular events, even after adjustment for coronary artery plaque size, in a derivation cohort of 1872 and a validation cohort of 2040 participants, with the prospective assessment of clinical events.[67] It has also been shown to be associated with a higher burden of noncalcified plaque [68] and higher levels of circulating inflammatory markers in PWH.[69]

P-FAI will be obtained from the same images used for the primary outcome, using TeraRecon software designed to measure P-FAI. P-FAI is quantified by first delimiting a three-dimensional cylindrical volume around the proximal 10-50 mm segment of the right coronary artery, and measuring the attenuation (in Hounsfield units) of this volume.[70] Results for P-FAI typically range between -190 and -30 Hounsfield units, with more negative values (closer to -190) associated with

less peri-vascular inflammation and better prognosis, and larger values (closer to -30) associated with higher inflammation and poor prognosis.[67] A cut-off of -70 or higher has been associated with increased cardiovascular and all-cause mortality.[67] For this outcome, P-FAI will be modelled as a continuous value, adjusted for baseline values. P-FAI is a continuous variable that is normally distributed.

Measurements for Clinical secondary outcomes :

Time to major cardiovascular events: Events will be assessed at each study visit by patient interview and chart review. Events will be captured in specific case report forms, supporting documentation (e.g: doctor's notes, ECGs, imaging and laboratory data) will be uploaded to case report form. All events will be reviewd and adjudicated by an independent two-doctor committee.

Grip strength is a marker of sarcopenia. Grip strength will be measured at baseline and month 24, and the measurement of interest will be the final value (month 24), adjusted for baseline. Measurement will be taken using a dynamometer, according to the standard operating procedures of the CHACS cohort and Women's Interagency HIV Study (WHIS).[71]

Brief Cognitive Ability Measure (B-CAM) scores will be determined for the cognitive assessment of participants. [72] B-CAM scores will be measured at baseline and month 24 using a web-based measurement tool.[72] It can be administered in 30 minutes, has been shown to be superior to the Montréal Cognitive Assessment score (MoCA) to assess cognition in PWH, and remains valid when used repetitively in the same individual, with no need to adjust for practice effects.[72] The measurement of interest will be the final value (month 24), adjusted for baseline.

Measurements for Biomarker secondary outcomes :

Biomarker outcomes overall and biobank: The biomarkers (listed in table 2) will be measured longitudinally at six-time points: baseline, months 6, 12, 18, 24 and 27, and their dynamic will be contrasted overall and at each time point between fostemsavir and the standard of care. Participants in the trial will be asked to contribute to a biobank at each study visit (see blood draw table for details), allowing the conduct of both pre-specified (below) and potential additional yet unforeseen post-hoc analyses. Plasma and Peripheral Blood Mononuclear Cell (PBMC) samples will be processed and stored respectively at -80°C and in liquid nitrogen in A. Finzi's laboratory at CRCHUM. The CRCHUM biobanking platform will provide storage space, fully equipped with alarms to prevent equipment failure and samples' loss.

Biomarkers of systemic inflammation associated with CVD: Measures of soluble inflammatory markers will be done by Luminex, as we recently reported.[73], and I-FABP measurement will be done by ELISA. Total IL-32 protein will be measured by regular ELISA. Individual IL-32 isoforms will be quantified at the transcriptional level by RT-qPCR in stored PBMCs using standardized protocols as we previously reported.[74] IL-18 and TRAIL (biomarkers that together with IL-32 represented a specific subclinical CVD signature that we identified in PWH receiving ART [75]) will be quantified by the highly sensitive Meso Scale technology from the plasma of all participants from the same visits.

HIV viral load and reservoirs: We will measure integrated HIV DNA as well as cell-associated HIV RNA using the assay developed by co-applicant N. Chomont.[76-79] CD4+ T cells will be isolated from cryopreserved PBMCs by negative magnetic selection and DNA/RNA will be dlly

extracted (Qiagen). We will use our well-established ultrasensitive assays to measure total HIV DNA (LTR-gag) and HIV RNA (LTR-gag) by nested-real time PCR.

Immunoserology and ADCC activity: The level of anti-cluster A Abs will also be measured by ELISA using an engineered stabilized gp120 inner domain protein (ID2) only exposing the cluster A region as previously reported.[80] The measurement of anti-CD4i antibodies, anti-p24 antibodies and anti-CD4BS antibodies, which target the CD4 binding site on gp120, will be measured using ELISA. Levels of anti-CD4-induced (CD4i) antibodies targeting gp120 and gp41 will be measured by ELISA against an engineered stabilized gp120 core or a gp41 cluster I peptide respectively.[81] Levels of antibodies targeting the recombinant HXB2 p24 protein will be measured by ELISA as previously reported.[82] This family of antibodies will serve as a control, as it is not expected to be affected by the presence of Fostemsavir in PWH with no viremia. Anti-CD4BS Abs measurement Levels of antibodies targeting the gp120 CD4 binding site (CD4BS) will be measured by ELISA using a gp120 recombinant stabilized core 3 (RSC3) as previously reported.[6] The ADCC activity of participant plasma against HIV-1-infected CD4 T cells and uninfected bystander cells will be also measured over time using an established flow cytometry-based ADCC assay, as previously reported.[7,8,46]

Immune cells profiling: We will conduct cell-based assays by high-parameter flow cytometry on PBMC, which will allow us to quantitatively and qualitatively characterize multiple subtypes of immune cells, including T cells, B cells, monocytes and macrophages, and deeply phenotype their functional statuses in terms of immune activation, exhaustion and/or inflammation. Peripheral blood leukocyte subset profiling will be done by high-parameter flow cytometry using panels of lineage (CD3, CD4, CD8, CD11b, CD14, CD16, CD19, CD25, CD33, CD56, CD66, CD127, CCR6, CXCR5), activation/proliferation (HLA-DR, CD38, Ki67), exhaustion (PD-1, CTLA-4, Tim-3, TIGIT, LAG-3), memory (CCR7, CD45RA), inflammatory (CCR5, CXCR3, CCR2) and gut (integrin B7, CD103) markers. The CD4 and CD8 absolute counts and ratio will be also measured. NK cell phenotype and profiling will be measured by high-parameter flow cytometry based on surface subset markers (CD3, CD56, CD16, Siglec-7, KLRG1), activating/inhibitory receptor expression (NKp30, NKp44, NKp46, KLRG1) and activation marker (CD38, HLA-DR, NKp44), while their cytolytic activities will be measured (CD107a) upon stimulation with sensitive target cells as previously reported.[83,84] Panels were designed to study 10 to 13 colours simultaneously in high-quality panels on a 5-laser BD FACS FORTESSA.

HIV sgp120 levels: Sgp120 will be measured in plasma using a previously reported sandwich ELISA.[6]

Plasmatic concentration of fostemsavir :will Plasmatic levels of fostemsavir will be measured by mass spectrometry using a previously described method.[8]

4.4.7 VARIABLES DEMOGRAPHIQUES ET CLINIQUES *(Clinical and demographic variables)*

Data will be collected at the baseline visit on the date of birth (month/year), sex, gender identity and ethnicity of the participant. Clinical baseline covariates include HIV duration, nadir CD4,

duration of antiretroviral therapy treatment, baseline CD4 and CD4:CD8 ratios, cardiovascular risk according to ASCVD risk score, reproductive history (obstetrical history and menopause status), lifestyle (smoking, quantity of alcohol consumed, recreational and illicit drug use), traditional cardiovascular risk factors (high blood pressure, diabetes, sedentary lifestyle, waist circumference, family history of premature cardiovascular disease), past medical history and concurrent medical conditions including co-infections with hepatitis C or B, prior exposure to antiretrovirals drugs (by drug class) and present pharmacological therapy. Any change in medical conditions or pharmacological therapy will be updated at every study visit.

4.4.8 CONDUITE DE L'ETUDE ET STRATEGIES SPECIFIQUES DE MINIMISATION DES BIAIS *(Study conduct and specific strategies for minimizing biases)*

Plans for retention and follow-up of participants **:**

Over the course of the study, we expect a loss to follow-up of 10% or less because PWH are retained into care at a very high proportion in the participating clinics, and study sites are experienced with randomized controlled trials. All efforts will be made to limit loss to follow-up and missing data to a minimum (including multiple recalls, the possibility of doing home visits, visits outside of regular work hours and participant compensations). If participants do decide to leave the study, they will be asked if they agree to take the end-of-study tests (CCTA, BCAM, Grip strength) and fill out the end-of-study CRF, which includes clinical outcome ascertainment, as well as reasons for dropping out.

Strategies to improve compliance and monitoring procedures **:**

We expect compliance of >80% to the study treatment. The population of PWH is extremely sensitive to the importance of adherence, which is discussed routinely at every clinical visit. The inclusion criteria of having an undetectable viral load is an indication that participants are already adherent to their antiretroviral regimens and retained in care. Fostemsavir was well tolerated in a cohort of people with highly resistant viruses, and drug discontinuation for side effects was 7% (BRIGHTE trial).[50,55] Therefore, we expect that compliance with the study treatment, which is only once daily and at half the dose received in BRIGHTE, will be high. The importance of compliance will be underlined at every study visit, and pill counts will be performed to assess it. The risk of treatment discontinuation for side effects will be measured as a secondary outcome.

Permitted/excluded concomitant treatments**:**

Participants will continue to follow their current ART regimen, as well as other medications prescribed by their treating physician throughout the trial, and according to standards of care. However, concomitant treatment with strong cytochrome P450 (CYP3A) inducers including but not limited to: carbamazepine, phenytoin (anticonvulsants), mitotane (antineoplastic), enzalutamide (androgen receptor inhibitor), rifampicin (antimycobacterial) and St John's wort (Hypericum perforatum, herbal supplement) constitutes an exclusion criterion to the study and is prohibited throughout the duration of the study

Strategies to improve protocol compliance and minimize biases **:**

No deviations from the protocol will be permitted without approval from the REB or the Sponsor. To ascertain data quality, the conduct of the study will be monitored by representatives of the Sponsor, inspections or on-site audits may be carried out by Health Canada or by the Sponsor, and records of all data collection and corrections will be kept. In addition, the Trial Steering Committee will be tasked with approving the study protocol, case report forms, data analysis plan, and all study-related documentation. It will oversee the progress of the trial (recruitment rates, loss to follow-up, completeness of data and visits participation) and the communication of the results (manuscripts, knowledge translation material). It will review all recommendations from the Data Safety and Monitoring Board (DSMB). Members of the steering committee will be expert trialist E. Duceppe, M. Durand and A. Finzi, as clinical and biomedical principal investigators, respectively, together with site leads and patient partners. Additional members will be the trial-assigned biostatistician from CITADEL, as well as a representative from CHUM's research pharmacy.

4.4.9 INTERRUPTION DE L'ETUDE (Study discontinuation)

Sponsor reserves the right to discontinue the study early in case of:

- Safety concerns – Unacceptable adverse events, SAEs, or SUSARs emerge.
- New scientific evidence – External data renders the trial scientifically unnecessary or unethical to continue.
- Poor recruitment/enrollment – Not enough participants enrolled to meet sample size targets.
- High dropout rate – Too many participants withdraw, affecting study integrity.
- Protocol violations – Frequent or severe deviations from the study protocol.
- Regulatory authority request – Health Canada or other regulators halt the study.
- Ethical concerns – Ethics committees or institutional review boards raise significant concerns.
- Protocol amendments not approved – Critical changes to the study cannot be implemented.

Exit and post-treatment follow-up visits will be executed for all the remaining participants before study closure.

Participant discontinuation

- Participants may withdraw consent at any time and discontinue study follow-up.
- In case of safety concerns and interruption of study treatment, study follow-up will be completed whenever possible.

4.5 Aspects statistiques *(Statistical aspects)*

4.5.1 TAILLE D'ECHANTILLON *(Sample size)*

Sample size calculation based on primary outcome

Based on prior results of variation in total uncalcified coronary plaque volume measured on CCTA over a period of 12 months in people with HIV, we estimated an expected mean change in the atorvastatin group of –7.67 mm³, with a standard deviation of 17.59, and an expected mean change in the placebo group of 10.00 mm³, with a standard deviation of 28.81 (Lo et al. 2015; Wan et al. 2014). This corresponds to a Cohen's d effect size of 0.73, which is relatively large (Cohen 1988). However, given that we expect statin use in both groups, we adopt a conservative approach for this study and assume a medium effect size (Cohen's d = 0.50) to account for potential attenuation of the fostemsavir effect due to concomitant statin therapy. This would translate to a decrease of 2.17 mm^3 in the fostemsavir group and an increase of 10.00 mm^3 in the group receiving standard of care, using standard deviations of 17.59 and 28.81, respectively. Based on this effect size, with 80% power and an alpha of 0.05, the estimated target sample size is 130 patients to detect a clinically meaningful difference. Allowing 10% incomplete CCTA or loss to follow-up, we aim to recruit a total sample size of 150 patients into the trial at four study sites

Sample size and secondary outcomes

Power calculations for biomarker outcomes: For the secondary biomedical outcomes, a power analysis by simulation (focusing on the IL-6 biomarker) was conducted to determine the detectable effect size with 130 participants (i.e. accounting for 10% attrition) and alpha of 0.05, under different assumptions for the within-subject correlation between the baseline and 12 months measures. IL-6 was assumed to follow a log-normal distribution. The model used for the power calculations is an an analysis of covariance, where the outcome is IL-6 at 12 months, and the independent variables are the randomization group and the IL-6 at baseline. We used available data on 73 participants similar to our population of interest (living with HIV, 40 years or older, with undetectable viral load) from the Canadian HIV and Aging cohort study [75] to estimate the mean and standard deviation of log(IL-6) to be used in our simulation algorithm. We varied the within-subject correlations (ρ) from 0.5 to 0.9 (0.5 represents a conservatively low range, as much higher correlations have been reported for our biomarkers of interest in people living with HIV).[85] Depending on the ρ, the detectable effect size varied between 24% (ρ = 0.9) and 41% (ρ = 0.5) reduction in IL-6 from baseline to 12 months, which represent both plausible [86,87] and clinically significant [88] reductions. Expressed as the standardized effect measure generalized eta-squared (η^2) as recommended by Olejnik and Algina,[89] the median detectable effect size varied between 0.02 and 0.05, which is in the range of small to medium effect sizes.[89-91] This range of detectable effect size can be reasonably extrapolated to other biomarkers with normal or log-normal distributions, as a function of their within-subject correlations (ρ), given that similar ranges of effect sizes are biologically plausible. Therefore, our sample size is adequate to detect effect sizes ranging from small (for biomarkers with high within-subject correlations) to medium (for biomarkers with lower within-subject correlations).

4.5.2 ANALYSE STATISTIQUE *(Statistical analysis)*

Generalities of statistical analysis

Statistical analysis will be conducted by CITADEL after the closing of the study database, according to the statistical analysis plan, which will be registered before the analysis is conducted.

All analyses will be done by intention-to-treat; patients will be analyzed in the group they were randomized to. Biobank analyses planned after 50% of participants completed the 12 months biobanking will be done by CITADEL after this part of the data collection is closed.

Analysis plan for primary outcome

The primary outcome is the change in uncalcified plaque volume between baseline and end of study, contrasted by study groups. It is obtained by subtracting the total uncalcified plaque volume (expressed in cubic millimetres) at baseline from the same parameter at month 24, measurable by CCTA.

The primary outcome will be modelled using linear regression, with change in uncalcified plaque between baseline and 24 months as the dependent variable, and treatment group as the independent variable, adjusting for baseline values. Preliminary data suggest that this outcome follows a normal distribution and is most likely to respect the model assumptions. A second analysis using a linear mixed model will integrate the stratification variables (sex and statin at recruitment). Considering that Vancouver St Paul's Hospital will only recruit women, we did not include a center effect in the analysis to avoid over-parametrization of the model. We think this strategy is reasonable since the primary outcome will be centrally evaluated by the Corelab, and no center effect is expected.

Sensitivity analyses are planned to address a potential bimodal distribution for the total volume of uncalcified plaque. Indeed, we expect 20-30 % values of 0 both at baseline and 24M follow-up. First, a restriction strategy will be used: the primary analysis will be re-performed on the subset of participants with non-zero volume of uncalcified plaque at baseline. The second strategy considers a zero-inflated Poisson model to estimate the difference in groups for the uncalcified volume of plaque at 24M, adjusting for baseline values. The primary outcome measure, which is change in the volume of non-calcified coronary artery plaque volume between baseline and 24 months, is obtained by subtracting the total uncalcified plaque volume (expressed in cubic millimetres) at baseline from the same parameter at month 24, measurable by cardiac computed tomography angiography. Adjustment for baseline values for this analysis means that the baseline values of total uncalcified plaque volume will be added to the models, which is the recommended approach to avoid confounding bias that could be introduced by imbalances in baseline plaque volumes.

For the primary outcome of change in uncalcified coronary plaque volume, and the secondary outcome of P-FAI (described below), both of which are reliant on the availability of the final CCTA, analyses will be done by complete case analysis (including only participants with available data for the second CCTA) if the criteria outlined by Jakobsen et al. are met for a complete case analysis.[92] If assumptions and criteria are not met, missing data from the second CCTA exam will be imputed using multiple imputations with chained equations.[93]

Analysis plan for secondary outcomes

Effect modification by sex

To study if the effect of the treatment on the change of uncalcified volume of plaque is different between men and women, we will use a linear regression model, with change in uncalcified plaque

between baseline and 24 months as the dependent variable, and treatment group, sex, and an interaction term between sex and treatment group as independent variables. A maximum likelihood test will be used to determine the significance of the interaction term between sex and treatment group. Subgroups analysis in both women and men will also be conducted to study the association of treatment and primary outcome. The same analytic strategy will be applied for the secondary outcomes, using the appropriate model as listed below.

Secondary outcomes

i) Measurements at month 24 of P-FAI, grip strength, and B-CAM scores, are normally distributed continuous variables.[66,72,94] These dependent variables will be modelled as the primary outcome using linear regressions models, with treatment group, sex, baseline values and an interaction term between sex and treatment group as independent variables.

ii) Time to incidence of major adverse cardiovascular events will be analysed using Cox proportional hazards survival analysis, with randomization used as time 0 and treatment group, sex and interaction between sex and treatment group as independent variables.

iii) Incidence of severe adverse events and incidence of treatment discontinuation for side effects will be presented as counts and proportions, with exact 95% confidence intervals. These results will be stratified by treatment group and self-declared gender. No statistical testing is planned.

iv) Biomarker Secondary outcomes:

Biological biomarkers of interest will be modelled using parametric and non-parametric tests, as appropriate, according to their distribution.
A biomarker interim analysis of the data from the biobank results will be performed when 50% of the participants in both groups have completed 1 year of follow-up; a significance threshold of 0.001 will be used for this first exploratory analysis to mitigate the risk of false-positive results induced by the repeated analysis. The final biobank analysis will thus achieve a significance threshold close to 0.05. For the biomarker interim analysis, we will fit a linear regression model (one for each biomarker outcome) to assess the impact of the treatment on the biomarker outcomes at 12 months, adjusting for the baseline biomarker value. For the final analysis, we will use the following strategy: in order to study if the evolution of the biomarker is different throughout the study between the treatment groups, we will be using generalized least squares linear regression models (with log transformation of biomarkers as needed), taking into account repeated measures within individuals. The independent variables will be time points (0, 6,12,18, 24, 27 months), treatment group, and the interaction between treatment group and time, and integrating a random effect for the participant.
If results from this model are compatible with differences between groups for the evolution of biomarkers (i.e. interaction effect), post-hoc comparisons between treatment groups will be assessed at each time point, Bonferroni-adjusted for 6 comparisons. All models will also be with sex and statin use at recruitment, if the convergence of the model allows it. Effect modification by sex will be investigated by stratifying by sex and performing the same models.
Furthermore, for cellular-based outcomes that will be performed on smaller sample sizes, we will use a sampling strategy in order to balance sex, treatment group and statin use at recruitment, in order to have a better representativity in those samples. Both supervised and unsupervised

analytical strategies will then be used to characterize T cell subsets, B cells, monocytes, macrophages, and NK cells.
For all final analyses, the two-sided level of significance will be 0.05. Since the biological biomarkers of interest are secondary outcomes and given the exploratory nature of these analyses, we will not adjust the significance level for multiple testing. However, we will report the number of biomarkers studied and the number of analyses performed. We will recommend interpreting the results aligned with an exploratory analysis.

Statistical methods to account for confounding factors

Intention to treat analysis will be used to ensure that the benefits of the randomization in balancing known and unknown confounders in both groups will be maintained. In case of a significant loss to follow-up (>10%), a comparison of baseline characteristics between treatment groups for participants with complete follow-up will be done, and any imbalances found in potential confounders (age, sex, gender, nadir CD4, prevalence of traditional cardiovascular risk factors, co-medication with statins, type of antiretroviral therapy) will be adjusted for using multivariable models.

Sex and gender analytical considerations: Sex is our most important a priori effect modifier in this study. For all models, effect modification by sex will be tested by adding an interaction term between sex and treatment group, and sex-stratified results will be presented. The significance of the interaction terms will be assessed using likelihood ratio tests and stratified results will be presented when appropriate.

5. Surveillance et sécurité *(Surveillance and safety)*

5.1 Type de données qui seront collectées (*Type of data to be collected*)

At baseline, data will be collected on socio-demographics (self-declared), past medical history (by participant interview and chart review) and medication history, as well as HIV-specific data such as nadir CD4 and duration of infection. Data will be collected on study outcomes at every study visit. Data on compliance (by pill counts at every study visit), side effects and adverse effects will be also collected.

5.2 Mode de collecte des données de sécurité (*Safety data collection method*)

RECORD KEEPING: The Investigator or delegated personnel will maintain detailed records on all study participants. Data for this study will be recorded in the participant's chart and entered into the study-specific eCRFs (Redcap). When applicable, electronic medical records will serve as source documentation. Applicable data from the participant's chart should be recorded in the CRFs completely and promptly, taking time to correct any mistakes. Corrections of data entered on source documents/data collection worksheets must be made in the following manner:

- The incorrect entry will be crossed out with a single line. The correct data should then be entered next to the entry crossed out. Each correction, change or addition of new data must be initiated and dated by the individual making the correction or alteration.
- Data collection must be entered into the CRFs. Data corrections in the eCRFs are automatically tracked.

SOURCE DOCUMENTS: The Investigator or delegated personnel will maintain adequate and accurate source documents upon which CRFs for each participant are based. Records will include detailed notes on:

- Oral and written communication with participants regarding the study treatment (risks/benefits)
- Participation in trial and signed and dated informed consent forms
- Inclusion and exclusion criteria details
- Enrollment number
- Visit dates
- Adverse events
- Results of relevant examinations
- Participant's exposure to any concomitant therapy (start/stop dates, dosing details)
- Reason for premature discontinuation (if applicable)
- Methods of contraception and fertility status (if applicable)
- Compliance/noncompliance protocol deviation information

Patient charts will be the source documents for all lab results and medical history.
The investigator will seek prior ethics approval for any protocol deviations except when the change is intended to eliminate an immediate hazard to participants. In this case, the protocol deviation will be promptly reported.

5.3 Surveillance des données (*Data monitoring*)

Instructions concerning the recording of study data on eCRFs will be provided by the Sponsor and CHUM Database management in the form of a Study Database User Manual and Entry Guidelines. The study site is responsible for submitting the data in a timely fashion. All data will be maintained on secure computer servers at CITADEL.

Monitoring & auditing: Representatives of the Sponsor, following GCP guidelines, will monitor the conduct of the study. Monitoring will be conducted remotely for the sites outside Montreal. In addition, inspections or on-site audits may be carried out by Health Canada or by the Sponsor. The Investigator will allow the Sponsor's representatives and any regulatory agencies to examine all study records, eCRFs, corresponding participant medical records, clinic drug dispensing records, drug storage area, and any other documents considered source documentation. The Investigator also agrees to assist the representative, if required.

5.4 Comité de surveillance et de sécurité (Data Safety and Monitoring Board)

The Data Safety Monitoring Board, part of CIHR Canadian HIV Trials Network (CTN) will from the DSMB for this study. The DSMB will meet for the first time three months into the recruitment period, and after 50% of the planned sample size has completed the 6-month visit, to review recruitment rates, safety, and tolerability. Following these meetings, DSMB will meet every 6 months until the end of the study. The DSMB will also review the results of the biomarker interim analysis within 2 months of those results being made available. No early stopping rules have been planned for this trial. While this RCT is an open-label study, assessors of the primary outcome (based on two CCTA scans) and the biobank analyses will remain blinded to treatment allocation.

DSMB mandate:

a. To monitor the conduct and progress of clinical trial to determine if any trial should be modified or stopped, and make recommendations to that effect to the SC;

b. To evaluate accumulating study data for treatment benefit or harm;

c. To recommend protocol changes;

d. To review and approve clinical trial design and methods insofar as these impinge upon the DSMB's functions;

e. To alert clinical trial leaders regarding emerging procedural or ethical issues; and

f. To monitor enrolment to ensure that clinical trials proceed in a timely fashion.

DSMB membership:

DSMB members possess the appropriate range of disciplines needed to assure that the Committee has sufficient expertise to deal with the complexities of the issues it will preside over. The membership should also enjoy sufficient stature among peers to maximize general acceptance of its reasoned judgments.

Members should be:

a. Free from conflicts of interest; and

b. Chosen in such a way as to assure a separation of persons responsible for patient care in the trial from persons responsible for safety and efficacy monitoring.

5.5 Disclosure and publication policy:

The results of the study, regardless of outcome, will be disseminated through peer-reviewed publications, international and national specialist conferences and through the CTN. Dr Durand and/or a post-doctoral research fellow will be responsible for initially drafting these manuscripts and professional writers will not be used. Authorship will be based on criteria defined by the International Committee of Medical Journal Editors. The study protocol will also be submitted for publication in a peer-reviewed journal upon receiving Health Canada and REB approvals. The final paper with study results will be published within 6 months of study completion. All participants involved in the trial will have the option of receiving a summary of the study results.

5.6 Les Événements Indésirables (*Adverse events*)

Adverse Event (AE) will be defined as any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporarily associated with the use of fostemsavir or standard of care, whether or not considered related. The gradation will be guided based on Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 2017, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services. Participants will be asked to report any AEs at the scheduled study visit and include the date of onset, a description of the AE, the severity level, and the event's resolution date. They will also report any concomitant medications taken due to an AE. Targeted Safety Reporting for Adverse Events of Special Interest to ViiV will be reported within 24 hours of awareness (see section 5.1) to REB and ViiV.

Serious adverse event (SAE) will be defined as any medical occurrence or effect that any dose results in any of the following: death, life-threatening AE (participant was at risk of death at the time of the event), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, the abnormal outcome of a pregnancy - criteria including but not limited to spontaneous abortion, fetal death, stillbirth, congenital anomalies and ectopic pregnancy). Important medical events that may not result in death, be life-threatening or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Participants will be monitored during the study period for SAEs. If an SAE is ongoing at the time a participant discontinues/completes the study, the SAE will be followed until the Investigator agrees that the event is satisfactorily resolved, becomes chronic, or that no further follow-up is required.

Adverse Events Descriptions And Recording: AEs will be recorded in the eCRF as soon as they are reported to the study team. AEs will be assigned the following levels of severity and possible relationship to study treatment. Severity and relationship to the treatment will be assessed using GSK two-point scale:

Table 8 - Adverse and Serious Adverse Events Grading and Relationship to Treatment	
SEVERITY	
Grade 1	mild, transient or mild discomfort (<48 hours); no medical intervention/therapy required
Grade 2	moderate, mild to moderate limitation of activity—some assistance may be needed; no or minimal medical intervention/therapy required
Grade 3	severe, marked limitation in activity; some assistance usually required; medical intervention/therapy required, hospitalizations possible
Grade 4	life-threatening, extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
Grade 5	Indicates death.

RELATIONSHIP TO STUDY TREATMENT	
Definitely Related (yes, in the GSK 2-point scale*)	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration/study intervention and cannot be explained by concurrent disease or other drugs or chemicals. The event must be pharmacologically or phenomenological definitive, with the use of a satisfactory re-challenge procedure if necessary
Probably Related (yes, in the GSK 2-point scale*)	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to the administration of the drug/study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response.
Possibly Related (yes, in the GSK 2-point scale*)	There is some evidence to suggest a causal relationship (i.e., the event occurred within a reasonable time after administration of the trial medication/study intervention). However, the influence of other factors may have contributed to the event (i.e., the participant's clinical condition, and other concomitant events).
Unlikely (no, in the GSK 2-point scale*)	A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration/study intervention makes a causal relationship improbable (e.g. The event did not occur within a reasonable time after administration of the trial medication/study medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g. the participant's clinical condition, other concomitant treatments).
Not related (no, in the GSK 2-point scale*)	The AE is completely independent of study drug administration/study intervention, and/or evidence exists that the event is related to another

	etiology. There must be an alternative, definitive etiology documented by the clinician. • By definition, all AEs from the standard of care arm of the study will be labelled as "Not related"

*GSK uses a 2-point (yes = **considered reasonably attributable** and no = possibly, unlikely and not related) scale for investigator/designee causality assessments. Reference: GSK Safety database.

Reporting and evaluation of SAEs, serious unexpected adverse drug reactions and other clinically significant AEs : All SAEs which occur during the study must be reported to the Study doctor and study coordinator within 24 hours of the site becoming aware of the event (through RESTART study contact line [number pending]). Other participating Investigators and ViiV will be notified of all SAEs within 24 hours of awareness via email. The Investigator is responsible for ensuring that the local Research Ethics Board is notified of all SAEs and serious unexpected adverse drug reactions (SUSAR) reports SAEs that meet the criteria for expedited reporting to Health Canada on behalf of the Sponsor. AE and SAE forms provided by ViiV GSK will be used for this reporting.

All additional follow-up evaluations must also be reported as soon as possible. All AEs and SAEs will be followed until resolution or until the Investigator concludes that the AE/SAE has stabilized, and no more follow-up is required. If an SAE is ongoing at the time a participant discontinues/completes the trial, the SAE will be followed up until the Investigator agrees that the event is satisfactorily resolved or that no further follow-up is required.

Follow-up for adverse events: Any AE that occurs between the time that a study participant is randomized and the time that s/he departs the study at the end of the final study visit (or at the time of early discontinuation of the participant from the study for any reason) will be captured and recorded. At each contact with the participant, the investigator (or designate) must seek information on AEs by specific questioning and, as appropriate, by examination. For any study participants who became pregnant, initial notification followed by outcome information, including the status of the perinatal transmission – is to be reported to ViiV within 1 week of awareness.

AEs that had previously been reported by the study participant will also be reassessed for duration, intensity and possible reoccurrence. Any AEs and laboratory abnormalities that occur during the study will be evaluated by the Investigators and will be recorded on CRFs. Any participants who discontinue participation for an unresolved clinically significant AE will be followed until satisfactory clinical resolution is achieved and the AE recorded on the CRF, regardless of severity grade.

5.7 Événements indésirables d'intérêt particulier et autres sujets liés à la sécurité (Adverse Events of Special Interest (AESIs) and other safety topics)

HYPERSENSITIVITY

All clinically suspected reports of hypersensitivity to the study drug, regardless of seriousness/causality. This AE is expected to be recorded on a dedicated CRF, as it is considered an adverse event of special interest (AESI), and reported to the study coordinator and sponsor,

who will report the event to ViiV within 24 hours of finding out about the event. Toxicity management for hypersensitivity is at the discretion of the investigator.

QTC PROLONGATION/ VENTRICULAR TACHYARRYTHMIAS

Participants are to be discontinued in the case of any reported ventricular tachyarrhythmias (regardless of causality). AEs associated with QTcF prolongation and ventricular tachyarrhythmia are to be recorded on a dedicated CRF, as it is considered an adverse event of special interest (AESI), and reported to ViiV within 24 hours. Fostemsavir should be used with caution in patients with a history of QT interval prolongation when co-administered with a medicine with a known risk of Torsade de Pointes (e.g. amiodarone, disopyramide, ibutilide, procainamide, quinidine, or sotalol) or in patients with relevant pre-existing cardiac disease. Additional ECG monitoring should be considered in individuals co-administered with medicines with a known risk of Torsade de Pointes based on the nature and prescribing information of the concomitant medications that are added. Elderly patients may be more susceptible to drug-induced QT interval prolongation.

Participants should be discontinued from the study intervention if there is:

- Confirmed (triplicate averaged) on treatment QTcF value > 500 msec regardless of sex
- On treatment triplicate averaged QTcF value >60msec over baseline, regardless of sex.

If QTcF prolongation is believed secondary to a reversible cause (i.e. a non-essential concomitant medication, electrolyte imbalance), which can be readily acted upon and allows for the timely return of the QTcF interval to below the discontinuation threshold, the participant may remain active in the study. In such circumstances, consultation with the Medical Monitor or designee is required.

In the case of a prolonged QTcF interval on initial recording, ECGs should be repeated in triplicate over a brief time period (≤ 10 mins). Mean QTcF interval of those tracings will be used to help determine the participant's status in the study.

All instances of QTcF prolongation with the potential for discontinuation require direct communication between the PI and the Medical Monitor or designee.

Routine ECG assessments will be performed as per the table of the overview of study procedures, ie at Inclusion, during treatment follow-up visits and at the end of the study visit. ECGs will be read/interpreted by a trained medical doctor within 24-48 hours and will be part of the clinical files of the participant in the electronic medical record system.

DRUG INTERACTIONS

<u>HMG-CoA reductase inhibitors</u>

Dose modifications and/or careful titration of dose is recommended for certain statins that are substrates of OATP1B1/3 or BCRP (rosuvastatin, atorvastatin, pitavastatin, simvastatin and fluvastatin) when co-administered with fostemsavir. Co-administration of fostemsavir increases plasma concentrations of statins caused by OATP1B1/3 and/or BCRP inhibition by temsavir. Use the lowest possible starting dose of other statins that are substrates of OATP1B1/3 and/or BCRP with careful monitoring for HMG-CoA reductase inhibitor-associated adverse events. Clinically relevant increases in plasma concentrations of pravastatin are not expected as it is not a substrate of BCRP. No dose adjustment is anticipated.

For all participants undergoing concurrent treatment with statins, the product labeling of the other components of the ARV regimen should be consulted (especially HIV-1 protease inhibitors) for additional guidance and follow the most restrictive recommendation. Note that simvastatin and lovastatin should not be co-administered with boosted HIV protease inhibitors.

Direct Acting Antivirals

The interaction between temsavir and elbasvir/grazoprevir (ZEPATIER) has not been studied. However, temsavir may increase grazoprevir plasma concentrations to a clinically relevant extent due to organic anion transporting polypeptide (OATP)1B1/3 inhibition by temsavir. Co-administration of fostemsavir with elbasvir/grazoprevir is not recommended, as increased grazoprevir concentrations may increase the risk of ALT elevations.

Ethinyl oestradiol

When fostemsavir was co-administered with oral contraceptives, temsavir increased concentrations of ethinyl estradiol (AUC and Cmax increased by 39% and 40% respectively) and caution is advised particularly in patients with additional risk factors for thromboembolic events. Doses of estrogen-based therapies, including oral contraceptives, should not contain more than 30 µg of ethinyl estradiol per day in patients who are receiving FTR.

5.7 Grossesse (Pregnancy)

Participants of childbearing potential must have a negative blood pregnancy test at Baseline (sensitivity =5–10 mIU/mL) to be eligible for the start of administration of study intervention. Where possible, tests should be performed (and results known) on the same day as and before initiating study intervention or performing CCTA scans. If this is not possible, pregnancy testing should be performed ≤ 7 days prior to first study drug administration or to CCTA scan.

Pregnancy testing (blood, sensitivity =5m-10mIU/mL)) will be conducted at baseline and at every study visit during the study intervention period, as outlined in the table describing study procedures.

A female participant may be eligible to enter and participate in the study if she is not pregnant or breastfeeding and one of the following conditions applies:

Non-childbearing potential is defined as either post-menopausal (12 months of amenorrhea [See Note 1 below for further details] without an alternate medical cause), or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy or bilateral oophorectomy, OR childbearing potential with a negative pregnancy test at Baseline (before the first dose of Investigational Product) and agrees to use one of the following methods of contraception to avoid pregnancy during treatment and until the end of relevant systemic exposure, which is 5 half-lives or 60 hours:

- Complete abstinence from penile-vaginal intercourse from at least 2 weeks before administration of Investigational Product, throughout the study, and for at least 2 weeks after discontinuation of all study medications;
- Male partner sterilization confirmed before the female participant entered into the study and provided this male is the sole partner for that participant

- a highly effective contraceptive method (with an expected failure rate of <1% per year), see [refer to Appendix 2] for a list of acceptable highly effective methods of contraception.

The study-sanctioned contraceptive method must be used consistently (in accordance with the approved contraceptive product label) before dosing (see Note 2 below), during the study intervention period and for at least until the end of relevant systemic exposure, which is 5 half-lives or 60 hours'.

Note 1: A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is recommended.

Participants on HRT and whose menopausal status is in doubt should use one of the highly effective non-estrogen hormonal contraception methods if they wish to continue their HRT during the study. Otherwise, they should discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Note 2: The period the highly effective contraceptive method is used before starting the study medication should be by the contraceptive product label (where applicable) but not shorter than 7 days.

Participants who are found to be pregnant after enrollment do not need to be treated as a protocol violation. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of the Investigational Product.

Note 3: Where other medications to be used in the study (e.g., efavirenz and darunavir) are known, or are likely, to significantly interact with systemic contraceptives, resulting in decreased efficacy of the contraceptive, then alternative methods of non-hormonal contraception are recommended for individuals of childbearing potential receiving these medications (see Appendix 2).

The investigator is responsible for reviewing medical history, menstrual history, and recent sexual activity to decrease the risk of inclusion of a participant with an early undetected pregnancy. Investigators/site staff should remind participants at every visit to inform site personnel if their menstrual cycle has changed or if they have any other reason to suspect they may be pregnant.

In the event of a confirmed pregnancy, the participant will discontinue the study drug.

Notification of a Pregnancy occurring during study participation should be reported to the Sponsor and ViiV Healthcare using the pregnancy initial notification form within 1 week. The pregnancy must be followed up to determine the outcome (including premature termination) and status of mother and child, which must also be reported to the Sponsor and ViiV Healthcare within 1 week.

In addition to reporting the pregnancy outcome as described above, the following should also be reported as an adverse event and/or serious adverse event:

- Pregnancy complications and elective terminations for medical reasons must be reported as an adverse event and/or serious adverse event.

- Abnormal pregnancy outcomes (criteria including but not limited to spontaneous abortion, fetal death, stillbirth, congenital anomalies and ectopic pregnancy) must be reported as a serious adverse event in accordance with SAE reporting timelines.

Any serious adverse event occurring in association with a pregnancy brought to the investigator's attention after the participant has completed the study and considered by the investigator as possibly related to the investigational product must be promptly reported to the Sponsor and ViiV Healthcare.

Investigators are also encouraged to report any pregnancy that occurs during study participation to the Antiretroviral Pregnancy Registry prospectively and before the pregnancy outcome. More information, including copies of applicable case report forms and fax numbers, is available at www.apregistry.com.

5.8 Critères d'arrêt et de suivi des tests de fonction hépatique (Liver Chemistry Stopping And Follow-Up Criteria)

Liver stopping event

Study drug must be stopped if any of the following liver chemistry-stopping criteria are met or if the Investigator believes that it is in the best interest of the participant:

- ALT >= 3xULN **AND** bilirubin >= 2xULN (>35% direct bilirubin) or INR > 1.5 (in the absence of anticoagulation or vitamin K deficiency)

Note: Serum bilirubin fractionation should be performed if testing is available. If unavailable, record the presence of detectable urinary bilirubin on the dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a participant meets the criterion of total bilirubin ≥ 2xULN, then the event meets liver-stopping criteria. INR measurement is not required and the threshold value will not apply to participants on anticoagulants.

- ALT >=5xULN for more than 2 weeks
- ALT >=8xULN
- ALT >=3xULN (or >=3x baseline ALT) with symptoms of worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia

Consideration should also be given to stopping FTR in any participant with aminotransferase elevations > 3x ULN who cannot be monitored every 1-2 weeks

When a liver chemistry-stopping criterion is met, the treating physician must do the following:

- Immediately discontinue FTR.
- If ALT >= 3xULN and bilirubin >=2xULN or INR >1.5, report as a serious adverse event (SAE) to the Sponsor within 24 hours using the SAE case report form.
- For all events meeting liver stopping criteria, perform repeat liver chemistries and liver event follow-up assessments (ideally within 24 hours of knowledge of the liver chemistry

elevations) as described in Appendix 3, and report to the Sponsor using the Liver Event case report form within one week of first becoming aware of the event.
- A specialist or hepatology consultation is recommended.
- Monitor participants 2 times a week until liver chemistries resolve, stabilize or return to within baseline values.

A list of follow-up assessments, which is recommended in any participant meeting liver-stopping criteria, is provided in Appendix 3.

In case of liver stopping event, the participants will be discontinued from the study drug but will stay in the follow-up (intent to treat).

Reporting of liver events

All suspected cases of drug-induced liver injury should be reported as serious adverse events using the following specific serious criterion in addition to the standard definitions for seriousness:

- All events of possible drug-induced liver injury with hyperbilirubinemia defined as: ALT >=3xULN AND bilirubin >=2xULN (>35% direct) or INR>1.5.

NOTE: Bilirubin fractionation is performed if testing is available. If unavailable, detectable urinary bilirubin on a dipstick (indicating direct bilirubin elevations and suggesting liver injury) should be recorded. If testing is unavailable and a subject meets the criterion of total bilirubin >=2xULN, then the event is still reported as a serious adverse event. If an INR is obtained, include values on the serious adverse event form. INR elevations >1.5 suggest severe liver injury.

All events meeting liver-stopping criteria will be reported to the Sponsor using the Liver Event case report form within one week of first becoming aware of the event.

HEPATITIS B AND C CO-INFECTION
Investigators should consult current treatment guidelines when considering the choice of therapy for subjects with chronic hepatitis B or C virus infection. Participants with hepatitis C virus infection should have undergone appropriate work-up, the hepatitis C infection should not be advanced, and it is not anticipated to require the introduction of new HCV therapy (e.g. with oral direct activating antivirals) during the study. Monitoring of liver chemistries is recommended in patients with HBV and/or HCV co-infection (see Appendix 1: Fostemsavir risk tables).

5.9 Partage des résultats de l'analyse intérimaire des biomarqueurs (Sharing results from the biomarker interim study analysis)

An executive summary of the key data considered in the biomarker interim analysis and reviewed by the DSMB. A copy of the DSMB meeting minutes and recommendations regarding the biomarker interim analysis will be provided as a CTA notification once completed.

6. Considérations éthiques *(Ethical considerations)*

This study will follow the principles of the Declaration of Helsinki, ICH GCP Guidelines, and applicable province and institution regulations for conducting clinical investigations. The Investigators will be thoroughly familiar with the appropriate use of the study treatment as described in the protocol and Fostemsavir Rukobia (fostemsavir) Product Monograph.Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected and consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. The objective of this ICH GCP guidance document is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The guidance document was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO). This guidance document should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guidance document may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects. As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material or define conditions not specifically described in this guidance in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

6.1 Processus d'identification et de recrutement (*Identification and recruitment process*)

Recruitment of participants will be executed in clinics. The principal investigator and/or the research team will present the RESTART study (objectives, target population, study schedule, etc.) to physicians **at study sites**. Physicians will be able to tell their patients (those corresponding to the target population) about the study themselves or allow us to consult their patient lists and solicit potential participants. Some of their patients are already long-standing participants in the **observational** cohort**s of PWH that** have been followed by the researchers and their research teams for **several** years. There is a special bond with these participants, and an implicit and explicit willingness on their part to participate in any project that advances knowledge in the field of HIV. **During their study visit, they will be offered to learn about RESTART and express their interest in participating**. **Research staff will also consult clinical records of patients visiting the clinics (pre-screening) to be able to inform attending physicians of potential participants actually being present at the clinic.**

6.2 Processus de consentement (*Informed consent process*)

All participants will be given detailed oral and written information about the study. The informed consent form and any subsequent modifications will be reviewed and approved by our local institutional or REB responsible for overseeing the cohort. The subject's consent must be obtained

if they are able to understand the nature, significance, and risks associated with the study. The informed consent will describe the study medication, the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Written informed consent will be obtained from the subject before any procedures are done specifically for the trial. Each participant should have sufficient opportunity to discuss the study, have all of their questions addressed and consider the information in the consent process before agreeing to participate.
Participants may withdraw consent at any time during the study without prejudice. The informed consent form will be signed and dated by the participant and the delegated personnel obtaining consent. The original signed informed consent form will be retained in the participant's study files, and a copy will be provided to the participant. The informed consent process must be conducted, and the form signed before the participant undergoes any screening procedures that are performed solely to determine eligibility for the study.

6.3 Risques et inconvénients (*Risks and inconveniences*)

All predictable risks and disadvantages will be listed in the consent form and discussed with the participant before signing the consent. Throughout the study, participants will be monitored by a team of researchers and medical staff who will record, document and give recommendations for action for any side effects they may develop as a result of the treatment. The following risk categories will be specially monitored: risks associated with study medication, risks associated with procedures (CT scan, blood draw etc) and risks associated with pregnancy.

No deviations from this protocol will be permitted without the prior written approval of the Sponsor, except when the modification is needed to eliminate an immediate hazard or hazards to participants. Any deviations that may affect a participant's treatment or informed consent, especially those increasing potential risks, must receive prior approval from the REB unless performed to remove an immediate safety risk to the participants. In this case, it will be reported to the REB and the Sponsor immediately thereafter. Any departures from the protocol must be documented.

BIOHAZARD CONTAINMENT:

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by le Fonds de la recherche en santé du Québec (FRSQ), Canadian Institutes of Health Research/Health Canada, the Centers for Disease Control and Prevention (CDC- USA), and the National Institutes of Health (NIH-USA). All infectious specimens will be transported in accordance with the requirements mandated by local, regional and International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602 and using packaging mandated in the Federal Code of Regulations.

6.4 Plateforme de collecte de données (*Data collection platform*)

Data from all sites will be entered into the same REDCap system managed by CITADEL (RC CHUM) and on a server hosted by RC CHUM - all investigators on the RESTART study team will have access to anonymous data.

Instructions concerning the recording of study data on eCRFs will be provided by the CHUM Data Management group in the form of a Study Database User Manual and Entry Guidelines. The study site is responsible for submitting the data in a timely fashion. CITADEL is responsible for assuring the quality of computerized data for this study. Detailed aspects of data handling will be described in the Data Management Plan.

RECORD RETENTION: The Investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for 25 years, in accordance with applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Investigator should ensure that no destruction of medical records occurs without the written approval of the Sponsor.

6.5 Compensation des participants

As compensation for the costs incurred as a result of participation in the research project, **participants** will receive $640 **(**calculated **based on** the estimated time required for the visit and any parking and meal expenses**)**: $50 for screening and safety visits, $60 per protocol clinical visit (you will receive no compensation for the telephone visit), for each cardiac scan you will receive $120.00, for a total of eight visits. **In case of withdrawal** from the project (or **termination of** participation) before it is completed, compensation will be proportional to the length of participation.

6.6 Confidentialité et conservations des données, et des échantillons biologiques si applicable

The subjects' anonymity will be strictly maintained, and their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the sponsor, IRB/IEC, or laboratory. Laboratory specimens must be labelled in such a way as to protect the subject identity while allowing the results to be recorded for the proper subject. Refer to specific laboratory instructions.
NOTE: The investigator will keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the study. Subject data will be processed by all applicable regulations
All participant-related information, including Case Report Forms, laboratory specimens, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only accessible to research staff. Participants will be identified only using a coded number specific to each participant (refer to the Randomization section). All computerized databases will identify participants by numeric codes only and will be password-protected.
The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into at least the following 2 categories: (1) investigator's study file, and (2) subject clinical source documents. The investigator's study file will contain the protocol/amendments, case report form (CRF) and query forms, IRB/IEC and governmental approval with

correspondence, ICFs, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence

The required source data should include sequential notes containing at least the following information for each subject:
• Subject identification (name, date of birth, gender)
• Documentation that subject meets eligibility criteria, ie history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
• Documentation of the reason(s) a consented subject is not enrolled
• Participation in the study (including study number)
• Study discussed and date of informed consent
• Dates of all visits
• Documentation that protocol-specific procedures were performed
• Results of efficacy parameters, as required by the protocol
• Start and end date (including dose regimen) of study drug, including dates of dispensing and return
• Record of all AEs and other safety parameters (start and end date, and including causality and severity)
• Concomitant medication (including start and end date, dose if relevant; and dose changes)
• Date of study completion and reason for early discontinuation, if it occurs. All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, or by local regulations.
Upon request, and in the presence of the investigator or his/her representative, participant records will be made available to the study sponsor, monitoring groups representative of the study sponsor, representatives of funding groups, and applicable regulatory agencies for verification.

6.7 Utilisation secondaire des données (et des échantillons biologiques si applicable) et science ouverte (Secondary use of data)

Secondary Human Subject Research is the re-use of de-identifiable data or de-identified bio specimens that were collected from some other ‘‘primary’’ or ‘‘initial’’ activity, such as the data collected in this protocol. Any use of the data for secondary research purposes, however, will be presented in a separate protocol and require separate REB approval. The subject’s decision can be changed at any time by notifying the study doctors or nurses in writing. If the subject subsequently changes his/her decision, the samples will be destroyed if the samples have not been used for research or released for a specific research project.

6.8 Diffusion des résultats généraux de la recherche (Results dissemination)

Our knowledge translation team. will work on developing knowledge translation and exchange materials for the community of PWH, in addition to collaborating with the knowledge transfer hub established through this funding opportunity. People with lived experience will be involved throughout the knowledge mobilization process. The team will design tailored recruitment and knowledge transition materials and gather feedback from their Community Advisory Board and Women Advisory Group to ensure inclusivity, particularly for Indigenous participants. Findings will be shared with institutional, national, and international scientific communities through peer-reviewed articles, conferences, and workshops, The protocol and trial will also be registered at clinicaltrials.gov site.

6.9 Conflit d'intérêt (*Conflict of interst*)

There is no conflict of interest to declare.

7. Références (References)

1. Collaboration ATC. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. Lancet HIV 2017;4(8):e349-e356. (In eng). DOI: 10.1016/S2352-3018(17)30066-8.
2. Collins LF, Armstrong WS. What It Means to Age With HIV Infection: Years Gained Are Not Comorbidity Free. JAMA Netw Open 2020;3(6):e208023. (In eng). DOI: 10.1001/jamanetworkopen.2020.8023.
3. Marcus JL, Leyden WA, Alexeeff SE, et al. Comparison of Overall and Comorbidity-Free Life Expectancy Between Insured Adults With and Without HIV Infection, 2000-2016. JAMA Netw Open 2020;3(6):e207954. (In eng). DOI: 10.1001/jamanetworkopen.2020.7954.
4. Hsue PY, Waters DD. HIV infection and coronary heart disease: mechanisms and management. Nat Rev Cardiol 2019;16(12):745-759. (In eng). DOI: 10.1038/s41569-019-0219-9.
5. Titanji B, Gavegnano C, Hsue P, Schinazi R, Marconi VC. Targeting Inflammation to Reduce Atherosclerotic Cardiovascular Risk in People With HIV Infection. J Am Heart Assoc 2020;9(3):e014873. (In eng). DOI: 10.1161/jaha.119.014873.
6. Benlarbi M, Richard J, Bourassa C, et al. Plasma Human Immunodeficiency Virus 1 Soluble Glycoprotein 120 Association With Correlates of Immune Dysfunction and Inflammation in Antiretroviral Therapy-Treated Individuals With Undetectable Viremia. J Infect Dis 2024;229(3):763-774. (In eng). DOI: 10.1093/infdis/jiad503.
7. Richard J, Veillette M, Ding S, et al. Small CD4 Mimetics Prevent HIV-1 Uninfected Bystander CD4 + T Cell Killing Mediated by Antibody-dependent Cell-mediated Cytotoxicity. EBioMedicine 2016;3:122-134. (In eng). DOI: 10.1016/j.ebiom.2015.12.004.
8. Richard J, Prévost J, Bourassa C, et al. Temsavir blocks the immunomodulatory activities of HIV-1 soluble gp120. Cell Chem Biol 2023;30(5):540-552.e6. (In eng). DOI: 10.1016/j.chembiol.2023.03.003.
9. Castagna A, Mussini C, Llibre JM, et al. Sustained Improvements in Biomarkers Observed With Fostemsavir in Heavily Treatment-Experienced Adults With Multidrug-Resistant HIV-1 From the Phase 3 BRIGHTE Study Through Week 240. 19th European AIDS Conference. Warsaw, Poland2023.
10. Clark A, Asmuth D, Chabria S, et al. Long-term inflammation biomarker changes with fostemsavir in heavily treatment-experienced adults with HIV-1: exploratory analyses of the phase 3 BRIGHTE study. 18th European AIDS Conference. Virtual and London, United Kingdom2021.
11. Organization WH. HIV and AIDS. (https://www.who.int/news-room/fact-sheets/detail/hiv-aids).
12. Álvarez S, Brañas F, Sánchez-Conde M, Moreno S, López-Bernaldo de Quirós JC, Muñoz-Fernández M. Frailty, markers of immune activation and oxidative stress in HIV infected elderly. PLoS One 2020;15(3):e0230339. (In eng). DOI: 10.1371/journal.pone.0230339.
13. Mazzuti L, Turriziani O, Mezzaroma I. The Many Faces of Immune Activation in HIV-1 Infection: A Multifactorial Interconnection. Biomedicines 2023;11(1) (In eng). DOI: 10.3390/biomedicines11010159.
14. Sieg SF, Shive CL, Panigrahi S, Freeman ML. Probing the Interface of HIV and Inflammaging. Curr HIV/AIDS Rep 2021;18(3):198-210. (In eng). DOI: 10.1007/s11904-021-00547-0.

15. Babu H, Ambikan AT, Gabriel EE, et al. Systemic Inflammation and the Increased Risk of Inflamm-Aging and Age-Associated Diseases in People Living With HIV on Long Term Suppressive Antiretroviral Therapy. Front Immunol 2019;10:1965. (In eng). DOI: 10.3389/fimmu.2019.01965.
16. Frasca D, Pallikkuth S, Pahwa S. Effects of Aging on Metabolic Characteristics of Human B Cells. J Acquir Immune Defic Syndr 2022;89(Suppl 1):S23-s28. (In eng). DOI: 10.1097/qai.0000000000002860.
17. Ghamar Talepoor A, Doroudchi M. Immunosenescence in atherosclerosis: A role for chronic viral infections. Front Immunol 2022;13:945016. (In eng). DOI: 10.3389/fimmu.2022.945016.
18. Wallis ZK, Williams KC. Monocytes in HIV and SIV Infection and Aging: Implications for Inflamm-Aging and Accelerated Aging. Viruses 2022;14(2) (In eng). DOI: 10.3390/v14020409.
19. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol 2018;15(9):505-522. (In eng). DOI: 10.1038/s41569-018-0064-2.
20. Durand M, Sheehy O, Baril JG, Lelorier J, Tremblay CL. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Québec's public health insurance database. J Acquir Immune Defic Syndr 2011;57(3):245-53. (In eng). DOI: 10.1097/QAI.0b013e31821d33a5.
21. Alsheikh MM, Alsheikh AM. Risk of Myocardial Infarction in HIV Patients: A Systematic Review. Cureus 2022;14(11):e31825. (In eng). DOI: 10.7759/cureus.31825.
22. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med 2013;173(8):614-22. (In eng). DOI: 10.1001/jamainternmed.2013.3728.
23. Groenendyk JW, Rivera AS, Sinha A, Lloyd-Jones DM, Feinstein MJ. Changes in proportionate cardiovascular mortality in patients with chronic infectious and inflammatory conditions in the United States, 1999-2018. Sci Rep 2021;11(1):23985. (In eng). DOI: 10.1038/s41598-021-03407-4.
24. Smit M, Brinkman K, Geerlings S, et al. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. Lancet Infect Dis 2015;15(7):810-8. (In eng). DOI: 10.1016/S1473-3099(15)00056-0.
25. Kolakowska A, Maresca AF, Collins IJ, Cailhol J. Update on Adverse Effects of HIV Integrase Inhibitors. Curr Treat Options Infect Dis 2019;11(4):372-387. (In eng). DOI: 10.1007/s40506-019-00203-7.
26. Longenecker CT, Triant VA. Initiation of antiretroviral therapy at high CD4 cell counts: does it reduce the risk of cardiovascular disease? Curr Opin HIV AIDS 2014;9(1):54-62. (In eng). DOI: 10.1097/coh.0000000000000015.
27. O'Halloran JA, Sahrmann J, Butler AM, Olsen MA, Powderly WG. Brief Report: Integrase Strand Transfer Inhibitors Are Associated With Lower Risk of Incident Cardiovascular Disease in People Living With HIV. J Acquir Immune Defic Syndr 2020;84(4):396-399. (In eng). DOI: 10.1097/qai.0000000000002357.
28. Vos AG, Venter WDF. Cardiovascular toxicity of contemporary antiretroviral therapy. Curr Opin HIV AIDS 2021;16(6):286-291. (In eng). DOI: 10.1097/coh.0000000000000702.
29. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352(16):1685-95. (In eng). DOI: 10.1056/NEJMra043430.
30. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999;340(2):115-26. (In eng). DOI: 10.1056/nejm199901143400207.

31. Durand M, Chartrand-Lefebvre C, Baril JG, et al. The Canadian HIV and aging cohort study - determinants of increased risk of cardio-vascular diseases in HIV-infected individuals: rationale and study protocol. BMC Infect Dis 2017;17(1):611. (In eng). DOI: 10.1186/s12879-017-2692-2.
32. Boldeanu I, Sadouni M, Mansour S, et al. Prevalence and Characterization of Subclinical Coronary Atherosclerotic Plaque with CT among Individuals with HIV: Results from the Canadian HIV and Aging Cohort Study. Radiology 2021;299(3):571-580. (In eng). DOI: 10.1148/radiol.2021203297.
33. Grinspoon SK, Fitch KV, Zanni MV, et al. Pitavastatin to Prevent Cardiovascular Disease in HIV Infection. N Engl J Med 2023;389(8):687-699. (In eng). DOI: 10.1056/NEJMoa2304146.
34. Imamichi H, Smith M, Adelsberger JW, et al. Defective HIV-1 proviruses produce viral proteins. Proc Natl Acad Sci U S A 2020;117(7):3704-3710. (In eng). DOI: 10.1073/pnas.1917876117.
35. Yukl SA, Kaiser P, Kim P, et al. HIV latency in isolated patient CD4(+) T cells may be due to blocks in HIV transcriptional elongation, completion, and splicing. Sci Transl Med 2018;10(430) (In eng). DOI: 10.1126/scitranslmed.aap9927.
36. Dubé M, Tastet O, Dufour C, et al. Spontaneous HIV expression during suppressive ART is associated with the magnitude and function of HIV-specific CD4(+) and CD8(+) T cells. Cell Host Microbe 2023;31(9):1507-1522.e5. (In eng). DOI: 10.1016/j.chom.2023.08.006.
37. Scrimieri F, Bastian E, Smith M, et al. Transcriptionally-active "defective" HIV-1 proviruses and their association with immunological non-response to antiretroviral therapy. J Infect Dis 2024 (In eng). DOI: 10.1093/infdis/jiae009.
38. Helseth E, Olshevsky U, Furman C, Sodroski J. Human immunodeficiency virus type 1 gp120 envelope glycoprotein regions important for association with the gp41 transmembrane glycoprotein. J Virol 1991;65(4):2119-23. (In eng). DOI: 10.1128/JVI.65.4.2119-2123.1991.
39. Finzi A, Xiang SH, Pacheco B, et al. Topological layers in the HIV-1 gp120 inner domain regulate gp41 interaction and CD4-triggered conformational transitions. Mol Cell 2010;37(5):656-67. (In eng). DOI: 10.1016/j.molcel.2010.02.012.
40. Yoon V, Fridkis-Hareli M, Munisamy S, Lee J, Anastasiades D, Stevceva L. The GP120 molecule of HIV-1 and its interaction with T cells. Curr Med Chem 2010;17(8):741-9. (In eng). DOI: 10.2174/092986710790514499.
41. Rychert J, Strick D, Bazner S, Robinson J, Rosenberg E. Detection of HIV gp120 in plasma during early HIV infection is associated with increased proinflammatory and immunoregulatory cytokines. AIDS Res Hum Retroviruses 2010;26(10):1139-45. (In eng). DOI: 10.1089/aid.2009.0290.
42. Chirmule N, Pahwa S. Envelope glycoproteins of human immunodeficiency virus type 1: profound influences on immune functions. Microbiol Rev 1996;60(2):386-406. DOI: 10.1128/mr.60.2.386-406.1996.
43. Del Corno M, Donninelli G, Varano B, Da Sacco L, Masotti A, Gessani S. HIV-1 gp120 activates the STAT3/interleukin-6 axis in primary human monocyte-derived dendritic cells. J Virol 2014;88(19):11045-55. DOI: 10.1128/JVI.00307-14.
44. Fantuzzi L, Canini I, Belardelli F, Gessani S. HIV-1 gp120 stimulates the production of beta-chemokines in human peripheral blood monocytes through a CD4-independent mechanism. J Immunol 2001;166(9):5381-7. DOI: 10.4049/jimmunol.166.9.5381.
45. Nazli A, Kafka JK, Ferreira VH, et al. HIV-1 gp120 induces TLR2- and TLR4-mediated innate immune activation in human female genital epithelium. J Immunol 2013;191(8):4246-58. DOI: 10.4049/jimmunol.1301482.

46. Richard J, Prevost J, Baxter AE, et al. Uninfected Bystander Cells Impact the Measurement of HIV-Specific Antibody-Dependent Cellular Cytotoxicity Responses. mBio 2018;9(2). DOI: 10.1128/mBio.00358-18.
47. Levast B, Barblu L, Coutu M, et al. HIV-1 gp120 envelope glycoprotein determinants for cytokine burst in human monocytes. PLoS One 2017;12(3):e0174550. DOI: 10.1371/journal.pone.0174550.
48. Acharya P, Lusvarghi S, Bewley CA, Kwong PD. HIV-1 gp120 as a therapeutic target: navigating a moving labyrinth. Expert Opin Ther Targets 2015;19(6):765-83. (In eng). DOI: 10.1517/14728222.2015.1010513.
49. Lataillade M, Lalezari JP, Kozal M, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study. Lancet HIV 2020;7(11):e740-e751. (In eng). DOI: 10.1016/s2352-3018(20)30240-x.
50. Kozal M, Aberg J, Pialoux G, et al. Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection. N Engl J Med 2020;382(13):1232-1243. (In eng). DOI: 10.1056/NEJMoa1902493.
51. Wonderlich ER, Prakash M, Clark A, et al. Early and Durable Reductions in Soluble CD14 Concentrations Among Treatment-Experienced Persons With HIV-1 Through 96 Weeks of Fostemsavir Treatment in a Phase 2b Clinical Trial. 19th European AIDS Conference. Warsaw, Poland2023.
52. Heidary M, Shariati S, Nourigheimasi S, et al. Mechanism of action, resistance, interaction, pharmacokinetics, pharmacodynamics, and safety of fostemsavir. BMC Infect Dis 2024;24(1):250. (In eng). DOI: 10.1186/s12879-024-09122-5.
53. Xu F, Acosta EP, Liang L, et al. Current Status of the Pharmacokinetics and Pharmacodynamics of HIV-1 Entry Inhibitors and HIV Therapy. Curr Drug Metab 2017;18(8):769-781. (In eng). DOI: 10.2174/1389200218666170724112412.
54. Magee M, Slater J, Mannino F, Ackerman P, Llamoso C, Moore K. Effect of Renal and Hepatic Impairment on the Pharmacokinetics of Temsavir, the Active Moiety of Fostemsavir. J Clin Pharmacol 2021;61(7):939-953. (In eng). DOI: 10.1002/jcph.1810.
55. ULC VH. RUKOBIA fostemsavir extended-release tablets 600 mg - Product Monograph Including Patient Medication Information. Laval, Quebec: 2021.
56. Huang W, Liu X, Cheng P, et al. Prognostic value of plaque volume combined with CT fractional flow reserve in patients with suspected coronary artery disease. Clin Radiol 2023;78(12):e1048-e1056. (In eng). DOI: 10.1016/j.crad.2023.08.024.
57. van Rosendael AR, Lin FY, van den Hoogen IJ, et al. Progression of whole-heart Atherosclerosis by coronary CT and major adverse cardiovascular events. J Cardiovasc Comput Tomogr 2021;15(4):322-330. (In eng). DOI: 10.1016/j.jcct.2020.12.007.
58. Foldyna B, Lo J, Mayrhofer T, Grinspoon SK, Hoffmann U, Lu MT. Individual coronary plaque changes on serial CT angiography: Within-patient heterogeneity, natural history, and statin effects in HIV. J Cardiovasc Comput Tomogr 2020;14(2):144-148. (In eng). DOI: 10.1016/j.jcct.2019.08.011.
59. Lo J, Lu MT, Ihenachor EJ, et al. Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. Lancet HIV 2015;2(2):e52-63. (In eng). DOI: 10.1016/s2352-3018(14)00032-0.

60. Shaikh K, Bhondoekhan F, Haberlen S, et al. Coronary artery plaque progression and cardiovascular risk scores in men with and without HIV-infection. Aids 2022;36(2):215-224. (In eng). DOI: 10.1097/qad.0000000000003093.
61. CATIE. The Epidemiology of HIV in Canada. (https://www.catie.ca/the-epidemiology-of-hiv-in-canada).
62. Chen Z, Boldeanu I, Nepveu S, et al. In vivo coronary artery plaque assessment with computed tomography angiography: is there an impact of iterative reconstruction on plaque volume and attenuation metrics? Acta Radiol 2017;58(6):660-669. (In eng). DOI: 10.1177/0284185116664229.
63. Leber AW, Knez A, Becker A, et al. Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of coronary atherosclerotic plaques: a comparative study with intracoronary ultrasound. J Am Coll Cardiol 2004;43(7):1241-7. (In eng). DOI: 10.1016/j.jacc.2003.10.059.
64. Feuchtner G, Langer C, Barbieri F, et al. Relationship of exercise to coronary artery disease extent, severity and plaque type: A coronary computed tomography angiography study. J Cardiovasc Comput Tomogr 2019;13(3):34-40. (In eng). DOI: 10.1016/j.jcct.2019.02.001.
65. Park JK, Kim JY, Kwon HM, et al. Multidetector computed tomography for the evaluation of coronary artery disease; the diagnostic accuracy in calcified coronary arteries, comparing with IVUS imaging. Yonsei Med J 2014;55(3):599-605. (In eng). DOI: 10.3349/ymj.2014.55.3.599.
66. Oikonomou EK, Antonopoulos AS, Schottlander D, et al. Standardized measurement of coronary inflammation using cardiovascular computed tomography: integration in clinical care as a prognostic medical device. Cardiovasc Res 2021;117(13):2677-2690. (In eng). DOI: 10.1093/cvr/cvab286.
67. Oikonomou EK, Marwan M, Desai MY, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. Lancet 2018;392(10151):929-939. (In eng). DOI: 10.1016/s0140-6736(18)31114-0.
68. Foldyna B, Mayrhofer T, Zanni MV, et al. Pericoronary Adipose Tissue Density, Inflammation, and Subclinical Coronary Artery Disease Among People With HIV in the REPRIEVE Cohort. Clin Infect Dis 2023;77(12):1676-1686. (In eng). DOI: 10.1093/cid/ciad419.
69. Freeman ML, Hossain MB, Burrowes SAB, et al. Association of Soluble Markers of Inflammation With Peri-coronary Artery Inflammation in People With and Without HIV Infection and Without Cardiovascular Disease. Open Forum Infect Dis 2023;10(8):ofad328. (In eng). DOI: 10.1093/ofid/ofad328.
70. Antonopoulos AS, Sanna F, Sabharwal N, et al. Detecting human coronary inflammation by imaging perivascular fat. Sci Transl Med 2017;9(398) (In eng). DOI: 10.1126/scitranslmed.aal2658.
71. Giguère K, Chartrand-Lefebvre C, Baril JG, et al. Baseline characteristics of a prospective cohort study of aging and cardiovascular diseases among people living with HIV. HIV Med 2023;24(12):1210-1221. (In eng). DOI: 10.1111/hiv.13550.
72. Brouillette MJ, Fellows LK, Finch L, Thomas R, Mayo NE. Properties of a brief assessment tool for longitudinal measurement of cognition in people living with HIV. PLoS One 2019;14(3):e0213908. (In eng). DOI: 10.1371/journal.pone.0213908.

73. Brunet-Ratnasingham E, Anand SP, Gantner P, et al. Integrated immunovirological profiling validates plasma SARS-CoV-2 RNA as an early predictor of COVID-19 mortality. Sci Adv 2021;7(48):eabj5629. (In eng). DOI: 10.1126/sciadv.abj5629.
74. Zaidan SM, Leyre L, Bunet R, et al. Upregulation of IL-32 Isoforms in Virologically Suppressed HIV-Infected Individuals: Potential Role in Persistent Inflammation and Transcription From Stable HIV-1 Reservoirs. J Acquir Immune Defic Syndr 2019;82(5):503-513. DOI: 10.1097/QAI.0000000000002185.
75. El-Far M, Durand M, Turcotte I, et al. Upregulated IL-32 Expression And Reduced Gut Short Chain Fatty Acid Caproic Acid in People Living With HIV With Subclinical Atherosclerosis. Front Immunol 2021;12:664371. (In eng). DOI: 10.3389/fimmu.2021.664371.
76. Massanella M, Bender Ignacio RA, Lama JR, et al. Long-term effects of early antiretroviral initiation on HIV reservoir markers: a longitudinal analysis of the MERLIN clinical study. Lancet Microbe 2021;2(5):e198-e209. (In eng). DOI: 10.1016/S2666-5247(21)00010-0.
77. Okoye AA, Fromentin R, Takata H, et al. The ingenol-based protein kinase C agonist GSK445A is a potent inducer of HIV and SIV RNA transcription. PLoS Pathog 2022;18(1):e1010245. (In eng). DOI: 10.1371/journal.ppat.1010245.
78. Turcotte I, El-Far M, Sadouni M, et al. Association Between the Development of Subclinical Cardiovascular Disease and Human Immunodeficiency Virus (HIV) Reservoir Markers in People With HIV on Suppressive Antiretroviral Therapy. Clin Infect Dis 2023;76(7):1318-1321. (In eng). DOI: 10.1093/cid/ciac874.
79. Vandergeeten C, Fromentin R, Merlini E, et al. Cross-clade ultrasensitive PCR-based assays to measure HIV persistence in large-cohort studies. J Virol 2014;88(21):12385-96. (In eng). DOI: 10.1128/jvi.00609-14.
80. Benlarbi M, Richard J, Bourassa C, et al. Plasmatic HIV-1 soluble gp120 is associated with correlates of immune dysfunction and inflammation in ART-treated individuals with undetectable viremia. J Infect Dis 2023 (In eng). DOI: 10.1093/infdis/jiad503.
81. Tauzin A, Marchitto L, Bélanger É, et al. Three families of CD4-induced antibodies are associated with the capacity of plasma from people living with HIV to mediate ADCC in the presence of CD4-mimetics. J Virol 2024;98(10):e0096024. (In eng). DOI: 10.1128/jvi.00960-24.
82. Morou A, Brunet-Ratnasingham E, Dubé M, et al. Altered differentiation is central to HIV-specific CD4(+) T cell dysfunction in progressive disease. Nat Immunol 2019;20(8):1059-1070. (In eng). DOI: 10.1038/s41590-019-0418-x.
83. Marchitto L, Benlarbi M, Prevost J, et al. Impact of HIV-1 Vpu-mediated downregulation of CD48 on NK-cell-mediated antibody-dependent cellular cytotoxicity. mBio 2023;14(4):e0078923. DOI: 10.1128/mbio.00789-23.
84. Bryceson YT, March ME, Barber DF, Ljunggren HG, Long EO. Cytolytic granule polarization and degranulation controlled by different receptors in resting NK cells. The Journal of experimental medicine 2005;202(7):1001-12. DOI: 10.1084/jem.20051143.
85. McKay HS, Margolick JB, Martínez-Maza O, et al. Multiplex assay reliability and long-term intra-individual variation of serologic inflammatory biomarkers. Cytokine 2017;90:185-192. (In eng). DOI: 10.1016/j.cyto.2016.09.018.
86. Osuji FN, Onyenekwe CC, Ahaneku JE, Ukibe NR. The effects of highly active antiretroviral therapy on the serum levels of pro-inflammatory and anti-inflammatory cytokines in HIV infected subjects. J Biomed Sci 2018;25(1):88. (In eng). DOI: 10.1186/s12929-018-0490-9.

87. Williams JC, Zhang X, Karki M, et al. Soluble CD14, CD163, and CD27 biomarkers distinguish ART-suppressed youth living with HIV from healthy controls. J Leukoc Biol 2018;103(4):671-680. (In eng). DOI: 10.1002/JLB.3A0717-294RR.
88. Serrano-Villar S, López-Huertas MR, Jiménez D, et al. Long-Term Changes of Inflammatory Biomarkers in Individuals on Suppressive Three-Drug or Two-Drug Antiretroviral Regimens. Front Immunol 2022;13:848630. (In eng). DOI: 10.3389/fimmu.2022.848630.
89. Olejnik S, Algina J. Generalized eta and omega squared statistics: measures of effect size for some common research designs. Psychol Methods 2003;8(4):434-47. (In eng). DOI: 10.1037/1082-989x.8.4.434.
90. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.
91. Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front Psychol 2013;4:863. (In eng). DOI: 10.3389/fpsyg.2013.00863.
92. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. BMC Med Res Methodol 2017;17(1):162. (In eng). DOI: 10.1186/s12874-017-0442-1.
93. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software 2011;45(3):1-67.
94. Senn S. Testing for baseline balance in clinical trials. Stat Med 1994;13(17):1715-26. (In eng). DOI: 10.1002/sim.4780131703.

8. Annexe (Appendix)

Appendix 1: Fostemsavir risk tables

Ventricular tachyarrhythmias due to QTc prolongation	Increases in QT were detected in vivo in the telemetered dog study at temsavir (TMR) concentrations ≥ 3.6 µg/mL (≥7.6 µM). In the in vitro hERG assay, the nominal IC50 of TMR was 27 µM (12.8 µg/mL) which is approximately 63x higher than the TMR free Cmax at the recommended human dose (RHD). In the rabbit Purkinje fibre assay, TMR prolonged action potential duration (by 11-12%) at a nominal concentration of 30 µM, with no effect at lower concentrations. There was no significant effect of FTR in either assay (note: plasma concentrations of FTR are generally not detectable). In a Phase 1 tQT study (206275) in healthy adults, the upper bounds of the two-sided 90% confidence intervals (CIs) for ΔΔQTcF exceeded 10 msec with a maximum upper bound of 13.299 ms at 5 hours following a supra-therapeutic dose of 2400 mg twice daily. Administration of a dose of 1,200 mg once daily, did not have a clinically meaningful effect on QTc interval since the upper bounds of the two-sided 90% CIs for ΔΔQTcF did not exceed 10 msec	<u>Exclusion criteria:</u> Confirmed QT value>500ms, QTcF value >470ms for women and >450ms for men at the inclusion visit, Acquired/ congenital long QT syndrome, known congestive heart failure with NYHA class 3 or 4, current or anticipated treatment with any of the following medications: amiodarone disopyramide, dofetilide, ibutilide, procainamide, sotalol, and quinidine. <u>Discontinuation criteria</u>: Confirmed (triplicate averaged) QTcF interval > 500 msec, regardless of sex. On treatment triplicate averaged QTcF value > 60 msec over baseline, regardless of sex.

	(maximum upper bound = 6.343 ms at 6 hours) [206275 (AI438016) CSR]. A positive relationship was demonstrated between TMR plasma concentrations (Cp) and change in the QTc interval. The relationship between Cp and the change in baseline corrected QTcF interval between active and placebo (ddQTcF) (msec) was best described by a linear slope-intercept model. Based on simulations from the modelling of the tQT clinical data, the threshold for clinically significant QTc prolongation (≥10 ms) is 7,500 ng/mL temsavir, which is 4.2x higher than the maximum concentration associated with indicated FTR 600 mg BID regimen in HTE HIV-1 infected patients [Clinical Pharmacology Modelling Report, Document number: 2018N392689_00]. In the ongoing Phase 3 study, through Week 240 (cut-off date 24-Jun-2021), the mean change in QTcF was +4.2 msec (SD 18.6, n=189). 11/371 participants were withdrawn from the Phase 3 study after meeting QTc prolongation discontinuation criteria, and the majority of these participants continued to receive FTR via the Named Patient Program or commercial	Clinical monitoring: Routine ECG assessments will be performed as per the table of overview of study procedures, ie at Inclusion, during treatment follow-up visits and at the end of study visit. Additional ECG monitoring should be considered in individuals co-administered medicines with a known risk of Torsade de Pointes based on the nature and prescribing information of the concomitant medications that are added. Warnings and precautions: Fostemsavir should be used with caution in patients with a history of QT interval prolongation, when co-administered with a medicine with a known risk of Torsade de Pointes (e.g. amiodarone, disopyramide, ibutilide, procainamide, quinidine, or sotalol) or in patients with relevant pre-existing cardiac disease

	supply. . No subjects were withdrawn from the Phase 2b study (205889) for QTc prolongation. In the Phase 2a study (206267), no QTcF or QTcB values of more than 450 msec were observed, and in most subjects, the changes from Baseline were <30 msec.	Elderly patients may be more susceptible to drug-induced QT interval prolongation.
Reproductive Risk	The use of FTR in pregnant women has not been studied. In studies in pregnant rats and rabbits during the period of organogenesis, FTR was not a selective developmental toxicant at temsavir AUC levels of 3,840 µg●h/mL and 626 µg●h/mL, respectively (AUC multiples of 170× and 28×, respectively, at the anticipated clinical dose). In repeat-dose toxicity studies in rats, FTR produced testicular toxicity in the rat at 100 mg/kg/day; the NOAEL was 30 mg/kg/day (AUC 751 µg●h/mL; AUC multiple 33×). In a fertility study, FTR had no effect on overall fertility in males or females at doses ≤ 300 mg/kg/day and ≤ 600 mg/kg/day, respectively. Testicular toxicity was present in male rats at doses ≥ 100	Exclusion criteria: Participants who are pregnant, breastfeeding, plan to be come pregnant or breastfeed during the study. Contraception and pregnancy testing for people of childbearing potential (POCBP) will be maintained during treatment and until the end of relevant systemic exposure, which is 5 half-lives or 60 hours. Mandatory pregnancy avoidance procedures are described in the protocol.

	mg/kg/day (AUC 1,560 µg●h/mL; AUC multiple 69×). The NOAEL for testicular toxicity in this study was 10 mg/kg/day (AUC 189 µg●h/mL; AUC multiple of 8.4x). Based on nonclinical data, FTR is not considered to be teratogenic, genotoxic or fetotoxic.	In the event of confirmed pregnancy, the pregnant participant will discontinue the study drug.
Liver enzyme elevations in patients coinfected with Hepatitis B and/or Hepatitis C	A total of 29 subjects with Hepatitis B and/or Hepatitis C co-infection were enrolled in the Phase 3 trial 205888 (randomized and nonrandomized cohorts combined). Grade 3 and 4 elevations in ALT and AST were more common in these subjects compared to those without viral hepatitis co-infection (24% vs 4% respectively for both ALT and AST). Some of these elevations occurred in subjects who were not receiving treatment for HBV.	Monitoring of liver chemistries is recommended in patients with HBV and/or HCV co-infection. Particular diligence should be applied in initiating or maintaining effective HBV therapy (referring to treatment guidelines) when starting fostemsavir therapy in HIV-HBV co-infected patients.
Drug interactions with strong CYP3A4 inducers	Biotransformation of TMR to two circulating metabolites, BMS-646915 and BMS-930644, is mediated by unidentified esterases (36.1%) and by CYP3A4 enzyme (21.2%), respectively. Therefore, TMR exposures may be influenced by modulators of CYP3A4. However, because esterase is the primary metabolism	Exclusion criteria: Subjects taking strong CYP3A4 inducers and those unable to refrain from the use of prescription or non-prescription drugs including vitamins, herbal and dietary supplements (including St John's Wort) within 7

	pathway, effects are expected to be less than that of substrates primarily metabolized by CYP3A4. In a Phase 1 drug-drug interaction study, when FTR was co-administered with rifampin (a strong CYP3A4 inducer) there was a significant (approximately 80%) reduction in exposure of TMR (206277 CSR). Significant decreases in temsavir plasma concentrations may also occur when fostemsavir is coadministered with other strong CYP3A inducers. Fostemsavir is contraindicated in combination with strong CYP3A inducers including, but not limited to: carbamazepine, phenytoin (anticonvulsants), mitotane (antineoplastic), enzalutamide (androgen receptor inhibitor), rifampicin (antimycobacterial) and St John's wort (Hypericum perforatum, herbal supplement) (see Interactions).	days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer), prior to the first dose of study medication. Concomitant treatment with strong CYP3A inducers prohibited throughout duration of study.
Drug interactions with OATP1B1/1B3 substrates	In vitro, TMR was an inhibitor of OAT1B1 and OAT1B3 (IC50= 32 and 16 µM respectively), and TMR and TMR's two metabolites (BMS-646915 and BMS-930644) inhibited BCRP (IC50=12.4, 35.2, 3.5 µM respectively).	An alternative HCV regimen that does not contain GZR or VOX is recommended with FTR. Dose modifications and/or titration of dose is recommended for

	When FTR was co-administered with rosuvastatin (OAT1B1/1B3 and BCRP substrate) the exposure of rosuvastatin increased (AUC increased by 69%) [206276 (AI438048) CSR]. The effect of FTR co-administration with grazoprevir (GZR) or volixaprevir (VOX) have not been studied. OATP1B1/3 inhibition is the primary mechanism for increased GZR exposures in other drug interaction studies, although inhibition of other transporters and drug metabolizing enzymes contribute. Co-administration of FTR with GZR is predicted to increase GZR concentrations. Increased GZR concentrations are associated with clinically relevant ALT increases. Exposure to VOX, also a substrate of OATP1/3 may also be increased by FTR co-administration.	statins that are substrates of OATP1B1/3 or BCRP (rosuvastatin, atorvastatin, pitavastatin, simvastatin and fluvastatin). Use the lowest possible starting with careful monitoring for HMG-CoA reductase inhibitor-associated adverse events.
Drug interactions with ethinyl estradiol	When FTR was co-administered with oral contraceptives, TMR increased concentrations of ethinyl estradiol and caution is advised particularly in patients with additional risk factors for thromboembolic events.	Doses of estrogen-based therapies, including oral contraceptives, should not contain more than 30µg of ethinyl estradiol per day in patients who are receiving fostemsavir. Use to be decided by the study doctor if benefit outwaits the risk

Appendix 2: Highly Effective Methods for Avoiding Pregnancy in Individuals of childbearing Potential

The following is the all-inclusive list of the highly effective methods that meet the ICH, M3(R2) and Clinical Trial Facilitation Group (CTFG) definition of highly effective (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label.

The list does not apply to individuals of childbearing potential with same sex partners or for participants who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis during the entire period of risk with the study intervention, when this is their preferred and usual lifestyle.

Note: Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal, spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
• ***Highly Effective Methods[b] That Have Low User Dependency***
• *Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]*
• *Intrauterine device (IUD)*
• *Intrauterine hormone-releasing system (IUS)[c*]*
• *Bilateral tubal occlusion*
• *Azoospermic partner (vasectomized or due to a medical cause)* *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the individual of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* *Note: documentation of azoospermia for a cis-male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*
• ***Highly Effective Methods[b] That Are User Dependent***
• *Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation. Combined estrogen (ethinyl estradiol) daily dose should not exceed 30mcg per day.* • *oral* • *intravaginal* • *transdermal* • *injectable*
• *Progestogen-only hormone contraception associated with inhibition of ovulation* • *oral* • *injectable*

• *Sexual abstinence* *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. *Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.* b. *Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.* *Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction)*

**Use of hormonal contraception methods must be supplemented by male condoms as hormonal contraception efficacy may be reduced*

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

Appendix 3: Follow Up Assessments for Any Liver Stopping Event

Follow up Assessment following ANY Liver Stopping Event

Make every attempt to carry out liver event follow-up assessments as described below

- Viral hepatitis serology, including:
- Hepatitis A immunoglobulin M (IgM) antibody;
- HBsAg and hepatitis B core antibody;
- Hepatitis C RNA;
- Hepatitis E IgM antibody.
- Cytomegalovirus IgM antibody.
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
- Syphilis screening.
- Drugs of abuse screen, including alcohol. Record alcohol use on the liver event case report form if using.
- Serum acetaminophen/paracetamol levels
- Serum creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin >=1.5xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (or gamma globulins).
- Gamma glutamyl transferase (GGT), glutamate dehydrogenase (GLDH), and serum albumin
- International normalised ratio (INR)
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease.
- Obtain history and record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, rash as relevant on the AE/SAE report form.
- Obtain history and record use of concomitant medications including acetaminophen, herbal remedies, other over-the-counter medications or putative hepatotoxins.

Appendix 4: List of Abbreviations

A-FABP	Adipocyte Fatty Acid-Binding Protein (also known as FABP4)
ADCC	Antibody dependant cellular cytotoxicity
AE	Adverse Event
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
ASCVD	Atherosclerotic Cardiovascular Disease
B-CAM	Brief-Cognitive Ability Measure
BDNF	Brain-Derived Neurotrophic Factor
CCTA	Coronary Computed Tomography Angiography
CHACS	Canadian HIV and Aging Cohort Study
CHUM	Centre Hospitalier de l'Université de Montréal
CRF	Case Report Form
CTN	Canadian HIV Trials Network
CVD	Cardiovascular Disease
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
hs-CRP	High-Sensitivity C-Reactive Protein
IFN	Interferon
IL	Interleukin
INR	International Normalized Ratio
MACE	Major Adverse Cardiovascular Events
MDRD	Modification of Diet in Renal Diseases
MoCA	Montréal Cognitive Assessment score
NYHA	New York Heart Association (Functional Classification)
P-FAI	Pericoronary Fat attenuation
PWH	Persons With HIV
SAE	Serious Adverse Event
sgp 120	Soluble glycoprotein 120
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF-α	Tumor Necrosis Factor Alpha
TRAIL	TNF-related apoptosis-inducing ligand
TSLP	Thymic Stromal Lymphopoietin
ULN	Upper Limint Normal
VCAM-1	Vascular Cell Adhesion Molecule-1