Randomized Comparative Double-Blind Study of Continuing Atripla or Switching to BIC/F/TAF in HIV-1 Infected Adults on Suppressive Atripla Therapy

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Background

Atripla (ATP: FTC/TDF/EFV) was the first antiretroviral (ARV) single tablet regimen (STR), and was the dominant first-line ARV regimen in most western countries from approximately 2008 to 2013, when most of the alternatives were multi-tablet regimens including boosted protease inhibitors. However, ATP has not been recommended as a "preferred" ARV regimen since 2015, due to the availability of potent and well-tolerated integrase strand transfer (ISTI)-based regimens, most of which are available as STRs. Nevertheless, there remain "legacy patients" who take ATP with sustained virological suppression. In some cases, the patients remain on ATP because they take concomitant medication that is not compatible with the CYP 3A4 inhibitors ritonavir or cobicistat used to "boost" protease inhibitors or elvitegravir, or they are taking a proton pump inhibitor and are not candidates for Complera or Odefsey. In the Northern Alberta HIV Program, about 316 of the ~2300 HIV patients were receiving ATP as of December 2017.

While ATP is a good ARV regimen from a virological perspective, it has relatively few drug-drug interactions and it has not been associated with an increased risk of cardiovascular disease (unlike HIV protease inhibitors and abacavir), ATP contains tenofovir disoproxil fumarate (TDF), which is associated with an increased risk of chronic kidney disease and fractures over time, for which a safer alternative, tenofovir alafenamide (TAF) has been developed. Additionally, ATP contains efavirenz (EFV), which is associated with neuropsychiatric toxicity and possibly suicidality. EFV is also not compatible with currently recommended interferon-free anti-HCV therapies for HCV genotypes other than HCV genotype 1.

B/F/TAF (bictegravir/FTC/TAF) is an investigational STR that contains neither TDF nor EFV. B/F/TAF includes TAF and FTC, which are well characterized and approved drugs, and FTC/TAF is arguably the best dual nucleoside backbone currently available (IAS-USA 2016 Guidelines), combined with an investigational ISTI, bictegravir, which does not require a pharmaco-enhancer, has minimal drug interactions (Custidio J. CROI 2017), has a very high genetic barrier to resistance (Tsiang M, et al. AAC 2016) and was potent and well tolerated in a phase 2 clinical trial (Sax P, et al. Lancet HIV 2017;4:e154-60) and 4 phase 3 clinical trials. B/F/TAF is smaller in size than ATP and the 3 currently approved STRs containing ISTIs. Four phase 3 trials of B/F/TAF met criteria for virologic non inferiority at 48 weeks of treatment, all of which have been published. In particular, B/F/TAF has significantly fewer side effects than dolutegravir-containing regimens, and no treatment-emergent resistance has been reported in any patient receiving B/F/TAF to date.

Benefit risk assessment
Adverse events are expected to be low frequency and similar to or lower than other HIV regimens. Potential benefits include ongoing suppression of HIV and fewer side effects. Risk/Benefit ratio is favourable.

Study Design
Randomized, double-blind, placebo-controlled comparison of the efficacy and safety of switching to B/F/TAF or remaining on ATP in HIV+ adults who have been receiving ATP for > 2 years with virologic suppression. After a 52-week period of blinded study therapy, participants will be offered open-label B/F/TAF until it is covered by the provincial drug plan.

Inclusion Criteria
1. HIV-1 seropositive
2. Age > 21 years
3. Receiving ATP > 2 years as their only ART, with HIV-1 RNA < 50 copies/mL at screening and all HIV-1 RNA tests < 100 copies/mL in the past 18 months
4. No documented resistance mutations to the components of ATP
5. Any CD4 count, but no active AIDS-defining opportunistic infections or cancers
6. HBsAg+ permitted if plasma HBV DNA is unquantifiable and the patient does not have decompensated liver disease

Exclusion Criteria
1. Pregnancy, breastfeeding or planned pregnancy in the next 2 years
2. Documented resistance to the components of ATP
3. Active AIDS-defining opportunistic infection or cancer
4. Cancer in past 3 years, except non melanoma skin cancer
5. Active psychotic disease or active depression that may interfere with study participation according investigator discretion
6. Any illness with a life expectancy less than 2 years
7. eGFR < 50 mL/min
8. Urine protein/creatinine > 40 mg/mmoL
9. Patients who the investigator feels are unlikely to commit to the study requirements for any reason
10. Prescription drug therapy for osteoporosis (calcium and/or vitamin D is allowed)

Screening
1. Medical history (including any HIV resistance testing) and physical examination
2. Labs: CBC-D, CD4, creatinine, phosphorus, albumin, ALT, bilirubin, lipids, CD4, HIV RNA, HBsAg (if last result was negative > 6 mo ago), anti-HCV (if last result was negative > 6 mo ago), UPCR, UACR, DEXA hip and spine
3. Add HBV DNA, HBeAg and anti-HBe for all known to be HBsAg+ (if last result was > 3 mo ago)

4. Add HCV RNA for all known to be anti-HCV+, if last test was negative > 12 months ago
5. Add FibroScan for all HCV RNA+ and/or HBsAg+
6. EFV related symptom scores

Any labs performed for standard of care within 30 days of screening visit will be considered baseline results and used to determine inclusion/exclusion criteria.

Study Intervention

Randomized 1:1, double-blind treatment with ATP and placebo for B/F/TAF (control arm) **or** B/F/TAF and placebo for ATP (experimental arm). Study medication (two tabs, one active, one placebo) will be taken once daily at the same time of day and with the same amount of food (or not) that the patient was doing when taking ATP prior to study entry. Patients will take double-blinded study medications for 52 weeks, but the primary efficacy analysis will be based on treatment week (TW) 48 data.

At TW52, patients will be told whether they were taking ATP or B/F/TAF, and offered the option of continuing on B/F/TAF, if they were assigned to that arm, or switching to B/F/TAF if they were in the control group receiving ATP. Gilead will supply B/F/TAF to patients after TW52 until B/F/TAF is covered by the provincial formulary.

Study Flow and Monitoring after Screening

Patients whose screening lab tests are satisfactory will return within 30 days to initiate double-blinded study therapy. Repeat lab testing will not be done on the day that blinded study therapy is initiated.

Blood will be collected at TW4 (± 7 days), TW12 (± 30 days), TW24 (± 30 days), TW36 (± 30 days), and TW48 (± 7 days) for HIV RNA.. CD4 and phosphorus will be measured at TW24 and TW48. Lipids will be done at TW48. Creatinine, ALT, and albumin will be measured at TW12, TW24, TW36 and TW48. Urine tests will be done at TW24 and TW48. Samples will be discarded once analyzed and will not be stored for future use. DEXA will be done at TW48. EFV-related symptom scores will be done at TW4.

Physical exams will be completed if needed based on symptoms. Adverse events will be assessed and treatment adherence discussed. Serious adverse events will be collected and reported to Gilead Sciences, Inc and Health Canada. In women of childbearing potential, highly effective birth control is required and pregnancy testing will be performed. Visits will be performed in clinic, via telehealth, or via telephone.

Concomitant medications will be recorded. Prescription drug therapy for osteoporosis is not allowed at enrollment. Antacids (e.g., Tums or Rolaids), the ulcer medication sucralfate, and vitamin or mineral supplements that contain calcium, iron, or zinc are to be taken at least 2 hours before or 2 hours after study drug.

Stopping criteria

- Investigator determines it is not safe for individual to continue study treatment (including but not limited to intercurrent illness or participant noncompliance)
- Lack of study drug efficacy
    - >100 copies/mL for two consecutive tests
- Pregnancy
- Participant request for any reason
- Discontinuation of study by Health Canada or Research Ethics Board

SAE definition (from Health Canada)

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.* Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse

Breaking the Blind

In the event of a medical emergency, the investigator will be able to obtain treatment assignment of each participant.

Sample Size

200 patients, 100 per arm

Analysis

The primary analysis will be the difference between baseline and week 48 in urine albumin/creatinine ratio (UACR) between ATP and B/F/TAF treated participants. Safety and tolerability will also be assessed.

Eight secondary statistical analyses will be performed comparing the ATP and B/F/TAF arms of the study:

(1) HIV-1 RNA < 50 copies/mL at TW48

(2) Differences from baseline to TW4 in EFV symptom scores (as per GS-US-292-0109)
(3) Differences from baseline to TW48 in urine protein/creatinine ratio (UPCR)
(4) Differences from baseline to TW48 in estimated glomerular filtration rate (eGFR)
(5) Differences from baseline to TW48 in bone mineral density (BMD) at the hip
(6) Differences from baseline to TW48 in BMD at the spine
(7) Differences from baseline to TW48 in CD4 lymphocyte counts
(8) Differences from baseline to TW48 in serum lipids

Safety Analysis
Investigator will review data and safety information annually including adverse events, efficacy lab results, and safety lab results.

Ethical Considerations
This study will be conducted according to Canadian and international standards of Good Clinical Practice for all studies. Applicable government regulations and University of Alberta research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the University of Alberta HREB for formal approval to conduct the study. The decision of the HREB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the HREB. The formal consent of a subject, using the HREB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.