BMJ Open

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2024-094912 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 10-Oct-2024 |
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| Keywords: | HIV & AIDS < INFECTIOUS DISEASES, Randomized Controlled Trial, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT |
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# Booster-free antiretroviral therapy for persons living with HIV and multidrug resistance (B-Free): Protocol of a multicenter, multi-stage, randomized, controlled non-inferiority trial

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**Word count**

Abstract 423; main text 3247.

## Abstract

**Introduction**: Antiretroviral therapy (ART) simplification strategies are needed for treatment-experienced people with HIV (PWH) and multidrug-resistant viruses. These individuals are commonly treated with boosted ART regimens and are thereby at risk for harmful drug-drug interactions (DDI). In this trial, we aim to assess the efficacy of the combination doravirine, dolutegravir, and lamivudine (DOR/DTG/3TC) among people with a history of virological failure who receive boosted ART.

**Methods and analysis**: B-Free is a multi-stage, randomized, multicenter, open-label, non-inferiority trial, embedded within the Swiss HIV Cohort Study (SHCS), and conducted in collaboration with cohorts of PWH in the Netherlands and France. Cohort participants with a history of ART change due to virologic failure, and who maintain HIV virologic suppression with an ART regimen consisting of a pharmacological booster and at least 2 drugs from classes other than nucleoside reverse transcriptase inhibitors are included. Patients with major drug resistance mutations against DTG or DOR, and individuals with chronic hepatitis B virus infection are not eligible for the study. Individuals are randomized 1:1 to either receiving co-formulated DTG/3TC and DOR once daily, or continuing their boosted ART regimen. The primary outcome is the proportion of individuals lacking virologic control (HIV RNA ≥50 cp/mL) at 48 weeks, according to the FDA snapshot algorithm. Changes in DDI burden (assessed using a DDI score), treatment satisfaction (assessed using the HIV Treatment Satisfaction Questionnaire), quality of life, and mental health represent key secondary outcomes. Additional secondary outcomes include the proportion of individuals developing new resistance-associated mutations and changes in quality of life and mental health. In a qualitative sub-study, we will conduct semi-structured interviews with a subset of participants to assess their expectations and experiences towards HIV treatment and clinical research in general. Enrolling 210 individuals will provide 80% power to demonstrate non-inferiority, defined as less than 8% absolute increase in loss of viral suppression in individuals randomized to DOR/DTG/3TC (one-sided type I error rate of 0.025).

**Ethics and dissemination**: The study was approved by the competent ethics committees and the regulatory authority Swissmedic in Switzerland before the enrolment of the first participant. Approval by the European Medicines Agency (EMA) and local ethical committees in the Netherlands and France will be obtained prior to including participants in these countries. The results of all major B-Free study outcomes will be submitted to peer-reviewed journals which enable Open Access publication.

**Trial registration:** clinicaltrials.gov (NCT06037564, registered on 07 September 2023) and Swiss National Clinical Trials Portal (SNCTP000005686, registered on 06 November 2023). Registration in the Clinical Trials Information System (CTIS) from the European Union planned.

**Strengths and limitations of this study:**

- B-Free is one of few studies to evaluate simplified antiretroviral treatment strategies for persons with a history of treatment failure.
- The study aims at improving HIV treatment in an ageing population with a high burden of comorbidities and a high risk for experiencing drug-drug interactions – a pressing clinical concern.
- The study population will be recruited within established cohorts of people with HIV (PWH), facilitating participant identification and recruitment, and guaranteeing long-term outcome assessment after the end of the study.
- The strong collaboration with patient representatives helped us design the study according to priorities and perceptions of people with HIV, and the integration of a strong qualitative part into our work allows us to shape and optimize our multi-stage trial prospectively.
- Due to the heterogeneous antiretroviral treatments used in the control arm, neither participants nor study physicians can be blinded to the treatment allocation. However, all laboratory assessments and statistical analyses of the primary outcome are performed by individuals who are blinded to the treatment allocation.

## Introduction

Multiple antiretroviral therapy (ART) simplification strategies exist for people with HIV (PWH), including dual therapies and long-acting injectable ART. Strong evidence from clinical trials has confirmed the efficacy and safety of these simplified regimens[1–3]. However, these simplification trials were mainly limited to individuals with uncomplicated HIV infection, and only very few clinical trials have assessed ART optimization strategies for PWH and a history of virological failure[4].

Evidence on treatment simplification strategies for individuals with a long-standing HIV infection and acquired resistance is needed. Because of the high barrier to resistance of boosted protease inhibitors, this population commonly receives boosted regimens, increasing their risk of experiencing drug-drug interactions (DDI) with co-medications used to treat comorbidities[5]. New drugs, including late generation non-nucleoside reverse transcriptase inhibitors (NNRTI) and integrase strand transfer inhibitors (INSTI) have a lower potential for DDI while retaining a high barrier to resistance[6,7]. Combining these newer substances may provide simplification strategies for treatment-experienced PWH and multidrug resistance.

"Booster-Free antiretroviral therapy for persons living with HIV and multidrug resistance" (B-Free) is a multistage trial to evaluate ART optimization strategies among individuals with a history of virological failure. B-Free is embedded within the Swiss HIV Cohort Study (SHCS) and is conducted in collaboration with HIV cohorts in the Netherlands and in France. In its first stage, we will assess the efficacy and safety of combining doravirine, dolutegravir, and lamivudine (DOR/DTG/3TC) compared to continuing boosted ART in individuals with multidrug-resistant HIV.

# Methods and analysis

## Design and setting

B-Free is a multi-stage, randomized, multicenter, open-label, non-inferiority trial, which is embedded within the SHCS and cohorts in the Netherlands and France[8–10]. The multi-stage design is adapted from the "Multi-arm multi-stage platform design" framework[11,12]. At each stage, individuals who fulfill the eligibility criteria will be randomly assigned 1:1 to either receive the new booster-free intervention regimen or to remain on their current treatment (**Figure 1**).

This trial protocol describes the first stage of the multi-stage trial. In this stage, we aim to include 210 people with HIV-1 infection who had a history of ART change due to virologic failure, and a have stable HIV suppression on ART including a pharmacological booster (ritonavir or cobicistat) and at least two agents from the NNRTI, PI, or INSTI classes. Eligible study participants will be randomly assigned 1:1 to one of the two following study arms:

- Booster-free intervention arm: Participants are switched to oral DOR 100mg and co-formulated DTG 50mg and 3TC 300mg. This 2-pill regimen is taken once daily, independent of meals.
- Control arm: Participants randomized to this arm continue their current oral booster-containing ART regimen. The dosing schedule remains unchanged. To minimize spill-over effects, changes in ART regimens are discouraged and limited to occurrence of virologic failure, new DDIs, or the onset of ART-related adverse events (AEs) requiring modification.

Treatment-experienced individuals who are not eligible to receive the current intervention regimen ("observational cohort") are identified and followed within the cohort. They will be re-assessed for participation at a later trial stage.

Once the first stage is completed and new drugs or ART combinations become available, a new stage will be planned, and eligibility criteria adapted accordingly. For the next trial stage, all B-Free participants as well as individuals from the observational cohort will be reassessed for eligibility.

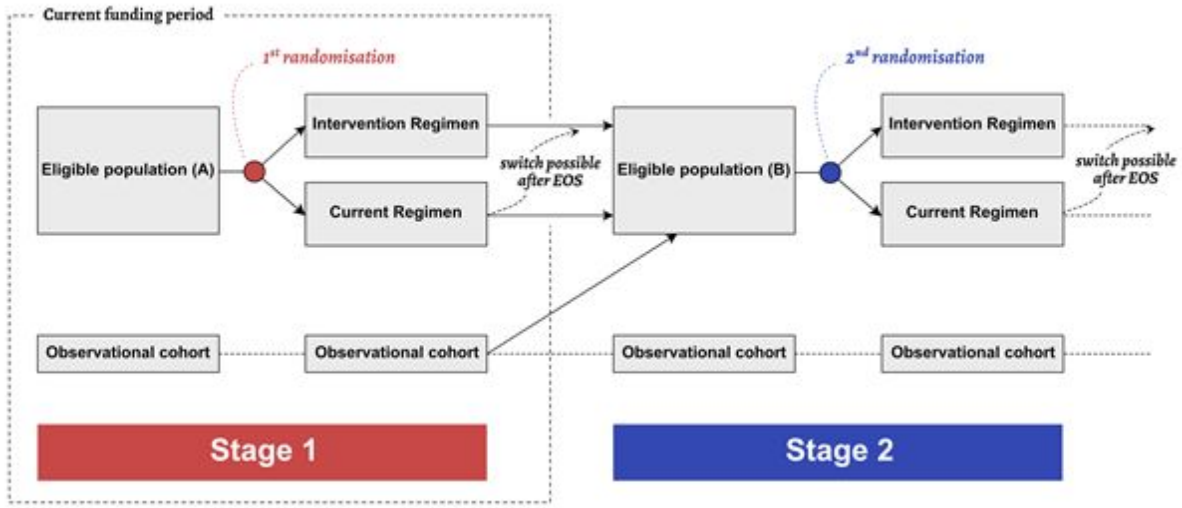


**Figure 1: The multistage trial framework of B-Free**

At each trial stage, eligible participants are randomized into one of two arms. People who are not eligible for stage 1 will continue follow-up in their respective HIV cohort, and will be reassessed for eligibility at a later trial stage. The process can be repeated when new HIV drugs are marketed (here exemplified as Stage 2). This protocol describes the **stage 1 trial**. **EOS** = End of study.

## Objectives and study outcomes

The primary objective is to evaluate whether DOR/DTG/3TC given once daily is non-inferior to a boosted ART regimen in maintaining HIV suppression among PWH and previous virologic failure, with a non-inferiority margin of 8 percentage points. The secondary objective is to determine whether switching to DOR/DTG/3TC leads to a lower burden of DDI and better treatment satisfaction compared to continuing booster-containing ART. The study outcomes are outlined in **Table 1**.

**Table 1: Primary, secondary, and safety outcomes of B-Free**

| |
|---|
| **Primary outcome** |
| - Difference in the proportion of individuals with an **HIV-RNA ≥50 cp/mL** at 48 weeks between the 2 treatment arms (as recommended by the FDA snapshot approach for trials assessing ART switches). |
| **Key secondary outcomes** |
| - Changes in the **burden of drug-drug interactions** (DDI) from week 0 to 48.<br>- Changes in **treatment satisfaction** between weeks 0 and 48. |
| **Further secondary outcomes** |
| - Proportion of patients experiencing confirmed virologic failure, defined as 2 consecutive HIV-RNA measurements ≥200 cp/mL.<br>- Proportion of individuals experiencing impairment or loss of future drug options, defined as new detection of resistance-associated mutations against DOR, DTG, 3TC (intervention-arm) or against the components of the ART regimen that the virus was considered to be sensitive to at randomization (control-arm).<br>- Proportion of individuals with any moderate or severe DDI at any study visit.<br>- Proportion of patients for which the treating physician would have liked to prescribe a drug but abstained from it due to DDI issues with the antiretroviral therapy.<br>- Differences in quality of life between both groups at week 48.<br>- New onset of depression.<br>- Changes in intact proviral HIV-DNA levels in PBMCs.<br>- Proportion of individuals with an "anti-HBc alone" who develop a detectable hepatitis B viral load.<br>- Cumulative cost of all ART drugs used. |
| **Other safety outcomes** |
| - Safety outcomes include changes in CD4 cell count, blood lipid values, body weight, body mass index, renal and liver function, onset of new drug-related central nervous system adverse events, and serious adverse events (SAE). |

**Cp/mL** = copies per milliliter, **FDA** = U.S. Food and Drug Administration, **ART** = antiretroviral therapy, **DDI** = drug-drug interaction, **PBMC** = peripheral blood mononuclear cell, **SAE** = serious adverse event.

## Study population and recruitment

We include treatment-experienced individuals with a history of virological failure, and who currently receive a complex ART regimen which includes a booster. Detailed eligibility criteria are provided in **Table 2**. The established cohort infrastructures greatly facilitate the recruitment of trial participants. Clinical and laboratory data are available to assess trial eligibility. Potential

participants are seen every 3 to 6 months in the participating centers or can be contacted by the treating physicians between study visits. In the trial preparation phase, 328 eligible individuals were identified in the SHCS, and 171 individuals who were followed in two clinics in Amsterdam. In a preliminary survey among 121 potentially eligible SHCS participants, 88 (72%) responded that they were interested in participating in a study aiming at evaluating novel HIV therapy combinations with a reduced risk of DDI. Assuming a more conservative participation rate of 50% of eligible patients, we expect to reach the recruitment targets within two years.

**Table 2: In- and exclusion criteria for B-Free Stage 1**

| **Inclusion criteria** |
|---|
| - Informed consent as documented by signature.<br>- Age ≥18 years.<br>- Documented HIV-1 infection.<br>- On ART including a pharmacological booster (ritonavir or cobicistat) and at least 2 drugs from classes other than NRTI.<br>- A history of ART change due to virologic failure.<br>- HIV-RNA <50 cp/mL at screening and for at least 24 weeks before screening (one blip with less than 200 cp/mL is allowed). |
| **Exclusion criteria** |
| - Creatinine clearance <30mL/min.<br>- Known hypersensitivity, allergy, or intolerance to DOR, DTG, or 3TC.<br>- Presence of major drug resistance mutations against DTG (G118R, G140R, Q148H, Q148K, Q148R, R263K) or DOR (V106A, Y188L, F227C, F227L, M230L, Y318F) according to IAS-USA in individual cumulative resistance analyses*.<br>- Concomitant use of drugs that decrease DTG or DOR blood concentrations.<br>- Chronic hepatitis B infection.<br>- Women who are pregnant or breastfeeding.<br>- Concurrent participation in another ART intervention study. |

*Persons without available resistance testing will not be excluded if no resistance to dolutegravir or doravirine is assumed based on ART history. **ART** = antiretroviral therapy, **NRTI** = nucleos(t)ide reverse transcriptase inhibitor, **cp/mL** = copies per milliliter, **DOR** = doravirine, **DTG** = dolutegravir, **3TC** = lamivudine.

## Qualitative sub-study

We undertake semi-structured interviews to evaluate the acceptability of participating in an interventional ART trial, the needs and expectations concerning booster-free regimens or ART in general, and to evaluate how the needs of persons living with HIV can best be addressed by research. These interviews are conducted among 30 trial participants (15 in the intervention, and 15 in the control arm). Interviews are done at baseline and after one year to identify any changes in perception or expectations resulting from their participation in the trial. In addition, similar interviews are conducted among individuals who were ineligible for the trial (n=15), or who declined participation (n=15). These individuals are only interviewed once, as no major change is expected to occur over time.

## Randomization

Randomization is stratified by participating centers. Participants are randomized 1:1 using randomly permuted blocks of varying sizes to one of the study arms, using a web-based randomization system. Access to the randomization list is restricted to an individual who is not involved in trial-related tasks, and allocation concealment ensured, as the system only releases the treatment allocation at the time of randomization.

## Intervention and blinding

Participants are randomized to receive DOR 100mg and co-formulated DTG/3TC 50/300mg once daily (intervention) or to continue their current and fully suppressive ART (control, **Figure 2**). The study drugs are dispensed by the study site or local pharmacy at each study visit. Since ART regimens in the intervention and the control arm may differ substantially in the number of pills, blinding of treatment allocation was deemed to be impractical. However, virologic outcome assessment in the laboratory is blinded, and treatment assignments will be masked from the trial statistician for the analyses of the primary and the main secondary outcomes.

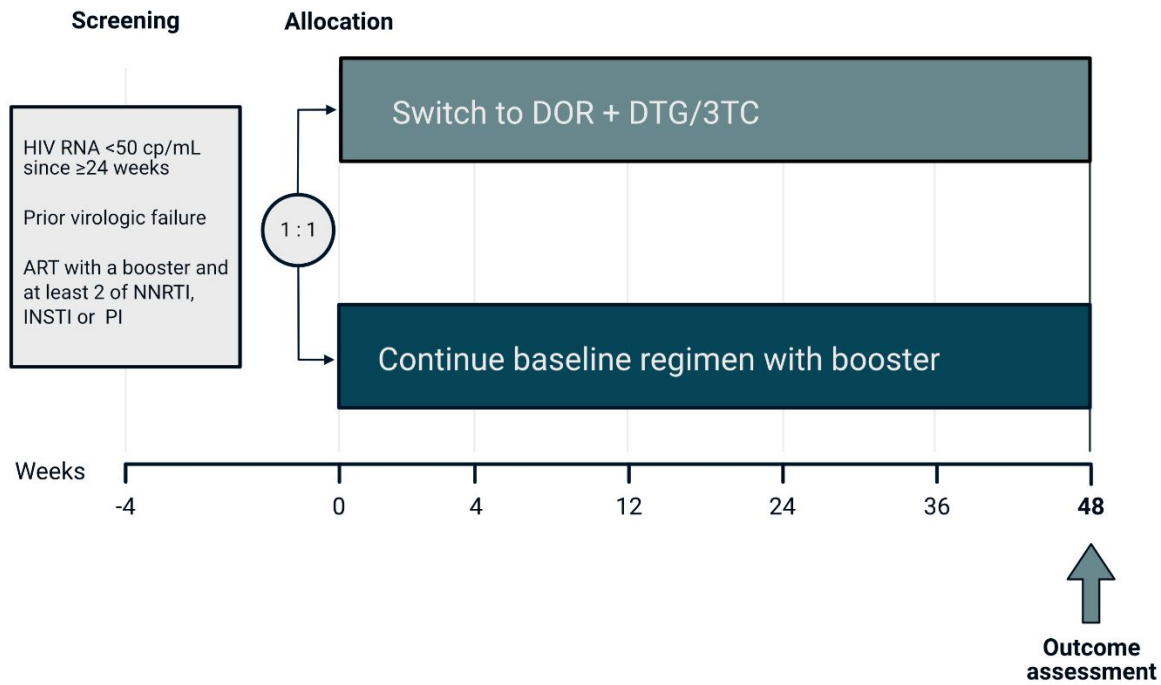


**Figure 2: Flow of study participants included in the first stage of the B-Free trial**
**ART** = antiretroviral therapy, **NNRTI** = non-nucleoside reverse transcriptase inhibitor, **INSTI** = integrase strand transfer inhibitor, **PI** = protease inhibitor, **DOR** = doravirine, **DTG** = dolutegravir, **3TC** = lamivudine.

## Assessment of primary outcome

Study assessments and the study schedule of the B-Free Trial are summarized in **Table S1**. The primary outcome is "lack of HIV viral suppression", defined as an HIV viral load of ≥50 cp/mL at week 48 (time window ±14 days, **Table 2**). HIV-1 RNA levels in plasma will be quantified by polymerase chain reaction (PCR) in local accredited laboratories. In case of technical problems or an HIV viral load ≥50 cp/mL, the study participant is asked to return for a repeat measurement as soon as possible. No more than one HIV viral load re-test is allowed. Individuals who prematurely discontinue the study will be included in the proportion of participants with a lack of viral suppression if their last HIV viral load was ≥50 cp/mL. Individuals without available data at 48 weeks and the last HIV viral load <50 cp/mL will be categorized into one of the following categories: "discontinued due to AE/death", "discontinued for other reasons", or "on study but missing data during analysis window"[13].

## Assessment of key secondary outcomes

Drug-drug interactions: The burden of drug-drug interactions (DDI) is assessed using a DDI score calculated based on the categories of the University of Liverpool Drug Database. Prescribed ART and co-medications are categorized as *red flag* (3 points) when co-administration is contraindicated, *amber flag* (2 points) for DDIs manageable by dose adjustment or monitoring,

*yellow flag* (1 point) for DDIs with no need of a priori dosage adjustment or monitoring, and *green flag* (0 points) for no interaction[14]. The DDI score represents the sum of all points and is assessed at baseline and week 48.

Treatment satisfaction and other patient-reported outcomes: Validated instruments are used to assess treatment satisfaction, quality of life, and mental health at baseline and week 48 (**Table 3**).

**Table 3: Instruments to evaluate patient-reported outcomes**

| Dimension | Description |
|---|---|
| **Treatment satisfaction** | |
| HIV treatment satisfaction questionnaire (status version, HIVTSQ)[1] | HIV-specific measure for treatment satisfaction. |
| HIV treatment satisfaction questionnaire (change version, HIVTSQc)[1] | Based on HIVTSQ, but more sensitive to changes over time. |
| **Quality of life** | |
| WHOQOL-HIV BREF[2] | Instrument to measure quality of life, including HIV-specific questions. |
| **Mental health** | |
| Patient health questionnaire (PHQ-9)[3] | Depression screening instrument. |

[1]**Woodcock** et al. Validation of the revised 10-item HIV Treatment Satisfaction Questionnaire status version and new change version. *Value Health*. Sep-Oct 2006;9(5):320-33.

[2]**WHO**. WHOQOL-HIV BREF 2012 revision. https://apps.who.int/iris/handle/10665/77775 (accessed 04.04.2023)

[3]**Kroenke** et al. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med*. Sep 2001;16(9):606-13.

## Managing detectable HIV viral loads during the study

To ensure equal treatment of individuals in both trial arms and across all study sites, a sequence of steps needs to be followed in participants with detectable HIV viral loads during the study. In addition to repeating the HIV RNA measurement within 2-4 weeks, the steps include assessing treatment adherence, asking for new or inadvertent use of substances that may interfere with the ART regimen, evaluating whether intercurrent illnesses or recent immunizations occurred, measuring plasma drug concentrations, and genotypic resistance testing (**Figure 3**). For patients

with confirmed virologic failure (HIV RNA ≥200 cp/mL in two consecutive measurements), genotypic resistance testing is performed. While waiting for the genotypic resistance testing to return, individuals continue their allocated treatment. Participants will receive an individually optimized antiretroviral treatment based on the results of genotypic resistance testing and will continue to be assessed for follow-up until week 48.

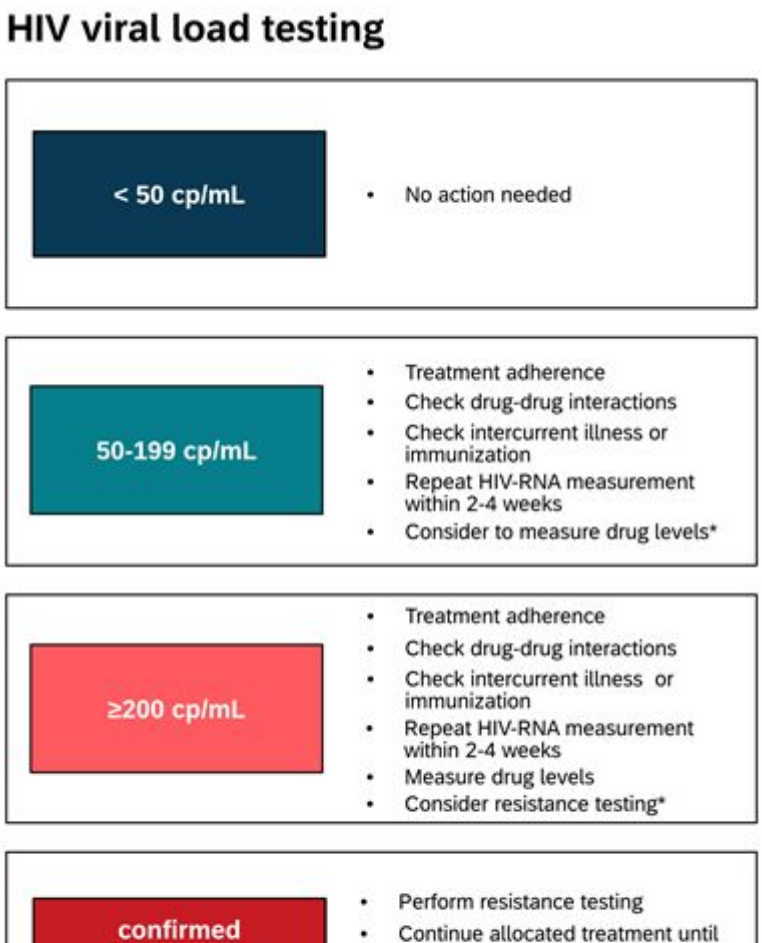


**Figure 3: Guidance for viral load monitoring and further assessment if HIV-RNA is detectable**

cp/mL = copies per milliliter, RNA = ribonucleic acid, ART = antiretroviral therapy.

## Statistical analysis

*Sample size calculation*

For the first trial stage, the sample size was calculated to evaluate the non-inferiority of the primary outcome loss of virologic suppression (proportion of individuals with HIV RNA ≥50cp/mL) at week 48. The sample size was calculated using the following assumptions:

- Proportion with loss of viral suppression at 48 weeks: In a previous switch trial conducted within the SHCS (Simpl'HIV study), 2.2% of individuals had an HIV viral load ≥50 cp/mL after one year[15]. However, individuals considered for the Simpl'HIV study generally did not have viruses with drug-resistance mutations, whereas in the present study, individuals will be required to have had a history of switching treatment due to lack of efficacy. In this second-line setting, we therefore assume the failure rate to be 4%.
- Non-inferiority margin: We set the non-inferiority margin at 8 percentage points. Given that we assume that 4% of individuals will have a detectable HIV viral load at 48 weeks, such a non-inferiority margin would consider 12% of individuals with a detectable HIV viral load to be acceptable with the new treatment. Such a threshold is clinically acceptable for a patient population with long-standing HIV infection and acquired resistance mutations, given the potentially large benefits of the new treatment (lower pill count, improved safety regarding DDIs, and possibly better tolerability).

Given the assumptions above, we need to include 190 individuals (95 in each arm) to have 80% power to show non-inferiority at a one-sided alpha level of 0.025. We accounted for an attrition of 10% of individuals during the study and therefore aim to include 210 individuals. This sample size will provide adequate power for both the intention to treat (ITT) and the per-protocol analysis.

*Analysis populations*

We will test for non-inferiority using two analysis populations: (1) the intention-to-treat (ITT) population including all individuals as randomized, irrespective of whether they received the treatment or not, and (2) the "per protocol" (PP) population. Participants will be excluded from the PP population if they did not meet relevant eligibility criteria, did not start their assigned study treatment, discontinued the study treatment prematurely for other reasons than virologic failure, and if they took less than 80% of ART doses throughout the study period.

*Statistical approach*

For the primary outcome "loss of HIV viral suppression", the intervention regimen will be compared against the current regimen at 48 weeks in the ITT and PP participant set. A risk difference will be calculated for individuals with HIV-RNA ≥50 cp/mL using the Mantel-Haenszel approach stratified for the stratification factor study site, and non-inferiority will be declared if

the corresponding upper one-sided 97.5% confidence limit will be below the margin of 8%. In addition to the risk difference, we will also present a risk ratio and the corresponding 95% confidence interval using the Mantel-Haenszel method. In addition, we will perform a hypothetical estimand analysis using inverse probability weighting (IPW) to account for intercurrent events such as treatment discontinuation for other reasons than virologic failure. One formal interim analysis will be performed after 50% of the patients have completed the week 24 visit. For the interim analysis, will use the same methods as for the primary outcome to evaluate the proportion of trial participants with an HIV-RNA ≥50 cp/mL at 24.

The analysis of secondary outcomes will be based on the ITT participant set. For binary outcomes, we will compare proportions between the intervention and the current regimen also using the Mantel-Haenszel risk difference and risk ratio as described above. The change in DDI score will be summarized using median values and quartiles, and differences between the treatment groups will be compared using the nonparametric van Elteren test stratified for the study site. Changes in treatment satisfaction (HIVTSQ, HIVTSQc), quality of life (WHOQOL-HIV BREF), mental health (PHQ-9), and intact proviral HIV-DNA levels from baseline to week 48 will be assessed in a mixed-effects linear model adjusted for the baseline value as a fixed effect (if applicable) and site as a random effect. Cost data will be evaluated using a generalized mixed-effects linear model.

If we can establish non-inferiority for the primary outcome, we will also test the main secondary outcomes for superiority in a sequential manner: Change in DDI score, followed by treatment satisfaction (HIVTSQc). Both secondary outcomes will be tested at a two-sided alpha level of 0.05. This hierarchical gate-keeping procedure keeps the overall type-I error rate at 0.05.

*Qualitative analyses*

Audio-recorded data from the interviews will be transcribed verbatim and analyzed using Thematic Analysis following Braun and Clarke's approach. Researchers will first familiarize themselves with the data through repeated reading of the transcripts. As interviews are being undertaken (and transcribed) in two languages (French and German), coding will be performed in English on vernacular transcripts to create an overall codebook in close coordination between the teams using MAXQDA software. Codes will be assigned inductively, without a predefined coding framework. The process of identifying themes from codes will involve collaborative sessions among researchers from the two language teams, as initial and final themes will be identified across the complete dataset.

## Data collection and management

All data are collected electronically using a dedicated electronic data capturing system (REDCap®) hosted by the Department of Clinical Research of the University of Bern. Only the system administrators have direct access to the server. Data edit checks were implemented into the EDC system, limiting entries to appropriate, realistic values. Central data monitoring and validation is performed, which includes verifying completeness, plausibility, and consistency of

the entered data on a regular basis, and querying the sites following up on any ambiguity. In addition, on-site monitoring is part of the quality control activities implemented for this study.

## Patient and public involvement (PPI)

Patients and public representatives have been and will remain involved at all stages throughout the planning and conduct of B-Free. Documents including study protocols, data collection instruments, as well as outreach activities have been reviewed by PPI members of the SHCS. Furthermore, patient representatives were involved in the development of a pre-trial survey that was performed among potentially eligible SHCS participants from three centers. The survey aimed to (1) evaluate their willingness to participate in a clinical trial, (2) to adapt the study schedule to a number of visits acceptable for potential study participants, and (3) to align the study outcomes with patients' perception on the importance of ART characteristics.

To engage with patients and the public, we developed a trial website (www.bfree-trial.ch) to provide information about the aim and current status of the study. Potential participants received a flyer containing the main trial information in lay language. Furthermore, we will provide plain and lay summaries of all publications related to B-Free which will be disseminated to patient groups in collaboration with patient representatives. All trial related information are available in English, German, French, Italian, and Dutch. In addition, a patient representative is part of the trial scientific committee.

# Ethics and dissemination

## Ethical considerations

The study was approved by the competent ethics committees in Switzerland (reference number BASEC 2023-01060). Approval by the Swiss regulatory authority (Swissmedic; reference number 701655) has been obtained before the enrolment of the first participant. Approval from the European Medicines Agency, as well as local ethical approval in the Netherlands and France will be obtained prior to recruiting participants in these countries. All participants and their data are handled according to the ethical principles of the Declaration of Helsinki, the respective country-specific law on human research as well as data protection law. This study complies with all applicable standards of the International Council on Harmonization E6 Guideline for Good Clinical Practice (ICH-E6 [GCP] 1996) guideline. The ethics committees and regulatory authorities receive annual safety reports and will be informed about the study stop/end in agreement with local requirements.

## Publication and dissemination policy

The results of all major B-Free study outcomes will be submitted to peer-reviewed journals which enable Open Access publication. Statistical codes will be made available through a public repository on www.github.com. Data will be deposited in the Bern Open Repository and Information System (BORIS). All items will be stored with a unique Digital Object Identifier (DOI) that can be referenced in respective publications.

## Discussion

The B-Free multistage trial is a unique platform to study treatment simplification strategies among PWH with prior virologic failure. The study will fill an important research gap, as the concerns of individuals with multidrug-resistant HIV are currently under-studied, and evidence-based treatment recommendations are lacking. Furthermore, given the increasing proportion of PWH who are confronted with comorbidities, our results will offer evidence for ART strategies with a reduced risk of DDI with comedications for this ageing population. The multistage design embedded within well-described cohorts will allow a continuous and resource-effective evaluation of newly available ART combinations, thereby offering simplified treatment options to most individuals in this important population.

Our approach has several strengths: As the study population is recruited within established cohorts of PWH, participant identification and enrolment are greatly facilitated. In addition, long-term outcome assessment after the end of the study is guaranteed since individuals are prospectively followed within their cohort. Furthermore, the inclusion of study participants from multiple countries and across a variety of study center types (university, regional hospitals, and private physicians) will increase the generalizability of the study results. Finally, the strong collaboration with patient representatives allowed us to design the study according to the priorities and perceptions of PWH, and the integration of a strong qualitative part into our work will allow us to shape and optimize our multi-stage trial prospectively.

The main limitation of the study is the inability to blind both participants and trial physicians due to the heterogeneous regimens used in the control arm. Nevertheless, laboratory assessment of the primary outcome (HIV viral load at week 48) and the statistical analyses are performed by individuals who are blinded to the treatment allocation.

## Conclusion

The B-Free trial takes into account contemporary developments in medical conditions of PWH, and addresses some of the most important challenges related to delivering HIV care to an aging population, while ensuring people's treatment satisfaction and quality of life. The trial results will provide evidence-based guidance for choosing the optimal treatment strategy for the understudied population of PWH and a history of virological failure.

## Current status of the B-Free trial

The B-Free trial study setup was initiated in October 2022, and recruitment started in Switzerland on 13.11.2023. The estimated time of recruitment is two years.

## Footnote

**Author's contributions**: Study concept and design: GW, BS, AC, RK, AR, AL, and DLB. Drafting of the manuscript: BS, MB, and GW. Critical revision of the manuscript for important intellectual content: all authors. Planning and analysis of qualitative sub-study: MB, SZ, ME, CA, IPB. Planning of statistical analysis: AL and BS. Obtained funding: GW, AC, RK, AR, and DLB.

**Funding**: This work was supported by the Swiss National Science Foundation (SNSF) grant number 205829.

**Conflicts of interest**: BS reports financial support for travel grants from Gilead Sciences and ViiV healthcare, and for advisory boards from Gilead Sciences and MSD, paid to his institution. GW has received research grants form Gilead Sciences and Roche Diagnostics, as well as fees for advisory boards and lectures form ViiV, MSD, Roche Diagnostics and Gilead Sciences (all paid to his institution). MC's institution received research grants and expert opinion fees from Gilead, MSD and ViiV. DLB received money payed to himself outside of the submitted work for advisory boards and lectures from the companies Gilead, MSD, Pfizer and ViiV and money for a research grant from the company ViiV. The institution of EB received study grants from Merck and Gilead; it also received travel grants and fees for EB participation to advisory boards from Gilead, Merck, ViiV Healthcare, Pfizer AG, Moderna, Astra Zeneca, Abbvie, and Ely Lilly. DH received fees for consultancies from AstraZeneca, Bavarian Nordic, Gilead, UCB, and ViiV Healthcare, a travel grant from Gilead, and institutional funding from AstraZeneca, Gilead, GSK, A. Menarini, MSD, and ViiV Healthcare. MvdV has received research grants and fees for participation in advisory boards from Gilead, MSD and ViiV all paid to his institution. MS reports financial support for travel grants from Gilead Sciences, and for advisory boards from Gilead Sciences, MSD, and ViiV Healthcare, paid to his institution. AR received research grants from Gilead, paid to his institution; travel expenses from Gilead and Pfizer, paid to his institution; and honoraria for advisory board consultations from MSD and Moderna, paid to his institution. PS's institution has received travel grants, congress and advisory fees from ViiV and Gilead unrelated to this work. All other authors report no conflicts of interest.

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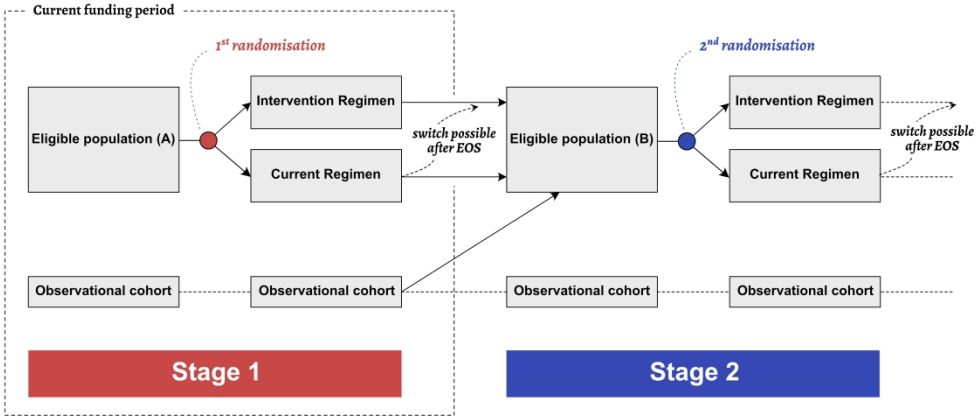


The multistage trial framework of B-Free
At each trial stage, eligible participants are randomized into one of two arms. People who are not eligible for stage 1 will continue follow-up in their respective HIV cohort, and will be reassessed for eligibility at a later trial stage. The process can be repeated when new HIV drugs are marketed (here exemplified as Stage 2). This protocol describes the stage 1 trial. EOS = End of study.

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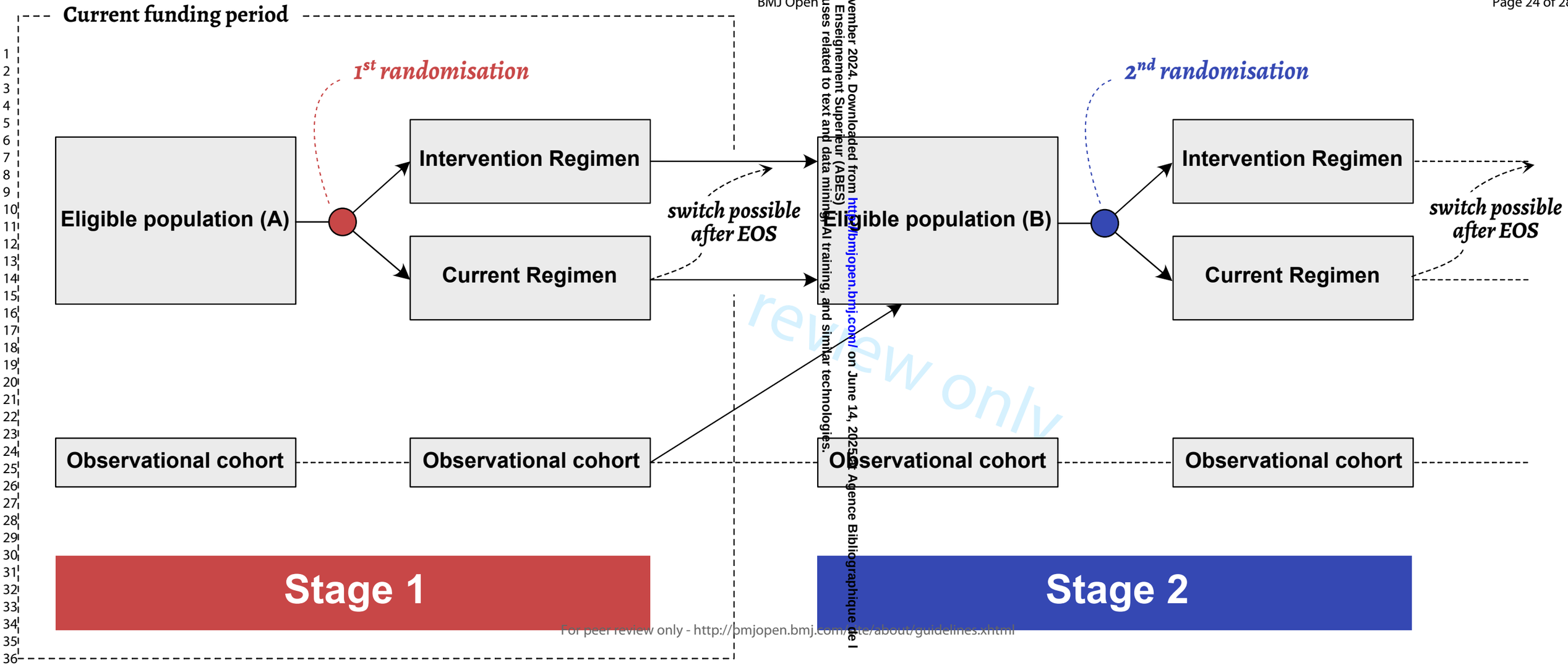

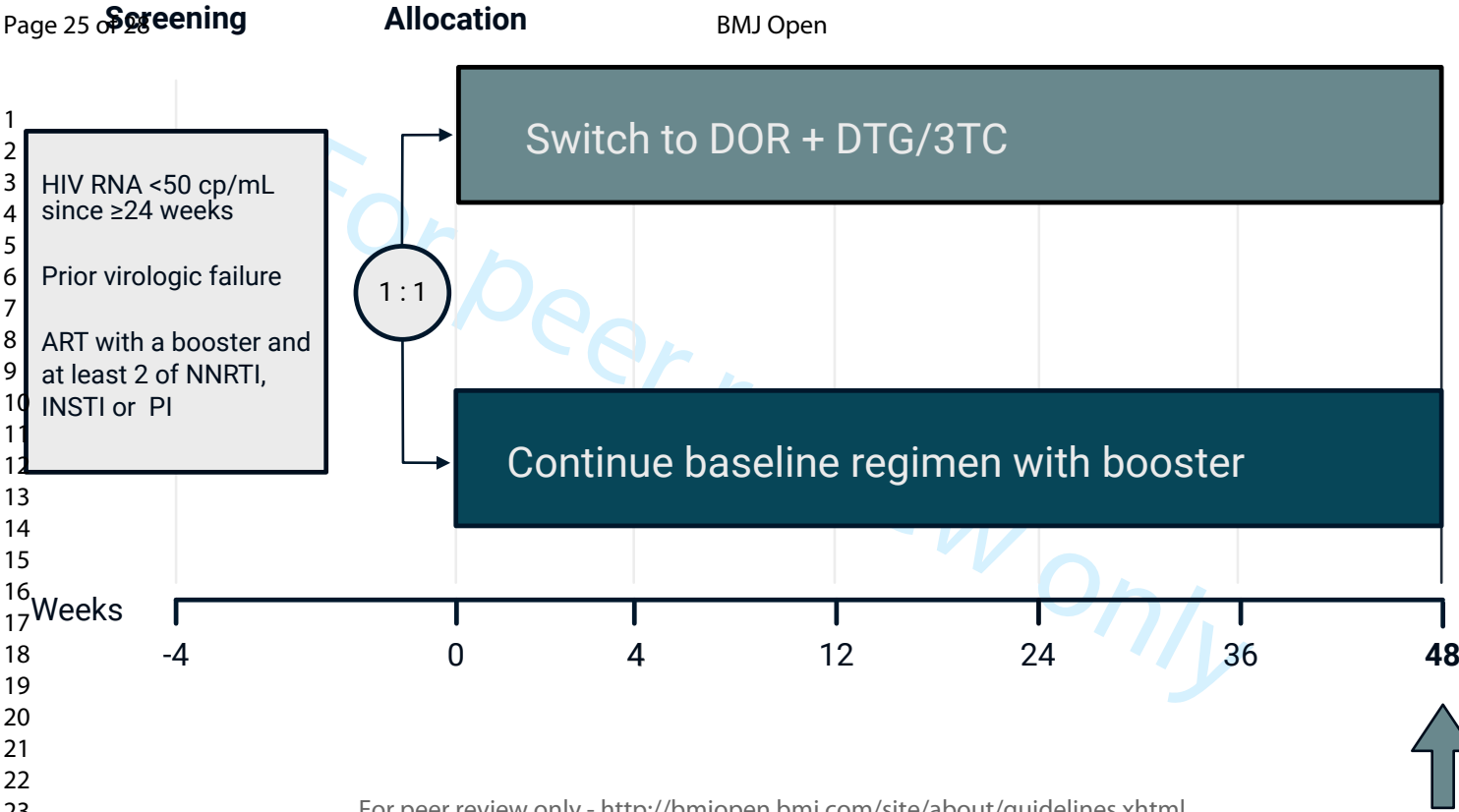

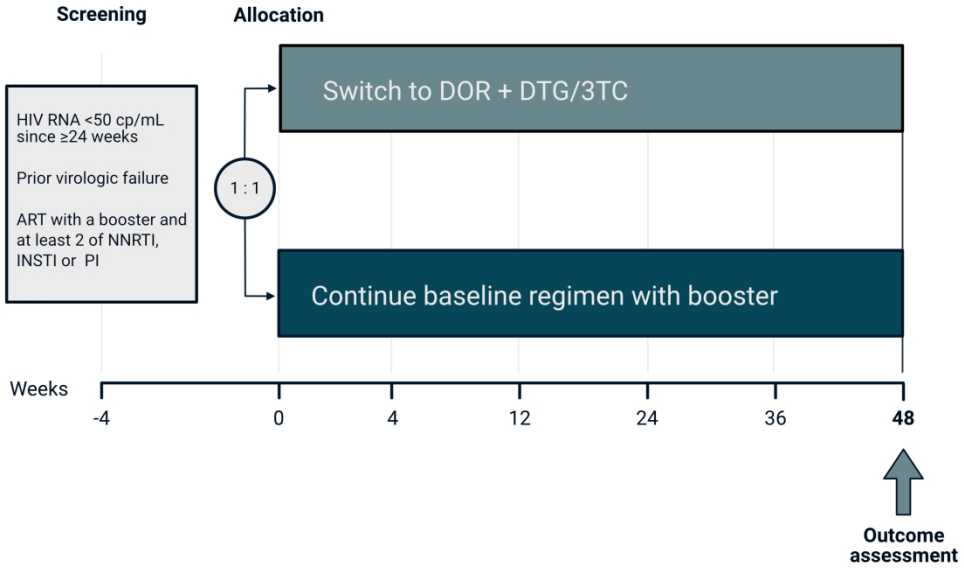


Figure 2: Flow of study participants included in the first stage of the B-Free trialART = antiretroviral therapy, NNRTI = non-nucleoside reverse transcriptase inhibitor, INSTI = integrase strand transfer inhibitor, PI = protease inhibitor, DOR = doravirine, DTG = dolutegravir, 3TC = lamivudine.

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# Booster-free antiretroviral therapy for persons living with HIV and multidrug resistance (B-Free):
## Protocol of a multicenter, multi-stage, randomized, controlled non-inferiority trial

Bernard Surial[1], Marie Ballif[1,2], Dominique L. Braun[3], Alexandra Calmy[4], Enos Bernasconi[5], Matthias Cavassini[6], Frédéric Tissot[6], Marcel Stoeckle[7], Patrick Schmid[8], Christoph A. Fux[9], Marc Van der Valk[10,11], Kees Brinkman[12], Tania Mudrikova[13], Fabrice Bonnet[14,15], Olivier Leleux[14], Manuela Saúde[1], Daniela Hirter[1], Nathalie Schwab[1,4], Andreas Limacher[16], Felix Rintelen[16], Roger Kouyos[3,17], David Haerry[18], Sofia C. Zambrano[2], Martina Egloff[2], Christina Akré[19], Isabelle Peytremann-Bridevaux[19], Andri Rauch[1], Gilles Wandeler[1]

# Supplementary Material

## Table S1: B-Free trial assessment schedule (stage 1)

| Study Periods | Screening | Baseline | Intervention Period | | | | End of Study | Safety Follow-up |
|---|---|---|---|---|---|---|---|---|
| Visit | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Time point | -4 weeks | Day 0 | Week 4 | Week 12 | Week 24 | Week 36 | Week 48 | Week 52[4] |
| STUDY PROCEDURES | | | | | | | | |
| Assess eligibility criteria | x | x | | | | | | |
| Obtain written informed consent | x | | | | | | | |
| Randomization | | x | | | | | | |
| Administration of study drug | | x | x | x | x | x | x | |
| STUDY ASSESSMENTS WITHIN THE COHORT ROUTINE | | | | | | | | |
| Behavioural data | | x | | | x | | x | |
| Adherence assessment questionnaire | | x | x[5] | x[5] | x | x[5] | x | |
| Routine laboratory tests | | x | | | x | | x | x |
| CD4 count | | x | | | x | | x | |
| STUDY SPECIFIC ASSESSMENTS | | | | | | | | |
| Demographics | x | | | | | | | |
| Medical history | | x | | | | | | |
| Documentation of virologic failure and historical ART resistance testing | x | | | | | | | |
| Concomitant medications | x | x | x | x | x | x | x | |
| Pill count | | x | x | x | x | x | x | |
| Physical examination | x | x | x[6] | x[6] | x | x[6] | x | |
| Vital signs | x | x | x | | x | | x | |
| Body weight | | x | | | x | | x | |
| Assessment for central nervous system (CNS) events | | x | x | x | x | x | x | x |
| Assessment for treatment limitations due to DDI | | x | | x | x | x | x | |
| Assessment of treatment satisfaction (HIVTSQ) | | x | | | | | x | |
| Assessment of quality of life (WHOQOL-HIV BREF) | | x | | | | | x | |
| Assessment of mental health (PHQ-9) | | x | | | | | x | |
| In-depth interviews[1] | | x | | | | | x | |

## Table S1 Continued

| Study Periods | Screening | Baseline | Intervention Period | | | | End of Study | Safety Follow-up |
|---|---|---|---|---|---|---|---|---|
| Visit | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Time point | -4 weeks | Day 0 | Week 4 | Week 12 | Week 24 | Week 36 | Week 48 | Week 52[4] |
| LABORATORY ASSESSMENTS | | | | | | | | |
| Blood pregnancy test[2] | x | | | | | | | |
| HBsAg, anti-HBc, anti-HBs | x | | | | | | | |
| HIV viral load | x | x | x | x | x | x | x | x |
| HBV viral load[3] | | x | | | x | | x | |
| Safety laboratory tests | x | | x | x | | x | | |
| Plasma sample storage | | x | x | x | x | x | x | |
| PBMC storage | | x | | | | | x | |
| Drug plasma concentration | | | At any time point if confirmed HIV RNA ≥200 cp/mL | | | | | |
| Genotypic resistance testing | | | At any time point if confirmed HIV RNA ≥200 cp/mL | | | | | |

[1] Only in a subset of 60 individuals. Interviews are conducted at baseline and week 48 in 15 individuals from the intervention arm and 15 from the control arm, once in 15 individuals who were ineligible for the trial, and once in 15 eligible individuals who refused to participate in the trial. Please refer to the section on the **"qualitative sub-study"** for more information.
[2] Only done in women of childbearing potential.
[3] Only individuals with a positive anti-HBc and a negative anti-HBs serology ("anti-HBC alone").
[4] This visit will only be performed in individuals with ongoing CNS/ serious adverse events, in participants with ongoing lab abnormalities, or a detectable HIV viral load at week 48. The visit can be done via telephone if no lab testing is needed.
[5] If a pill count cannot be performed (e.g. the participant forgot to return the used medication bottles), they are asked to complete an adherence assessment questionnaire covering the past 4 weeks.
[6] If clinically indicated, based on the judgment of the investigator.

**DDI** = drug-drug interaction, **HIVTSQ** = HIV Treatment Satisfaction Questionnaire, **WHOQOL-BREF** = Abbreviated World Health Organization Quality of Life questionnaire, **PHQ-9** = Patient Health Questionnaire-9, **HBsAg** = hepatitis B surface antigen, **anti-HBc** = hepatitis B core antibody, **anti-HBs** = hepatitis B surface antibody, **HBV** = hepatitis B virus, **PBMC** = peripheral blood mononuclear cells.

BMJ Open

# Booster-free antiretroviral therapy for persons living with HIV and multidrug resistance (B-Free): protocol for a multicenter, multi-stage, randomized, controlled, non-inferiority trial

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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2024-094912.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 19-Oct-2024 |
| Complete List of Authors: | Surial, Bernard; University of Bern, Department of Infectious Diseases, Inselspital, Bern Univeristy Hospital<br>Ballif, Marie; Department of Infectious Diesease, Inselspital, Bern University Hospital, University of Bern; Institute of Social and Preventive Medicine (ISPM), University of Bern<br>Braun, Dominique; Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich<br>Calmy, Alexandra; Division of Infectious Diseases, Geneva University Hospital, University of Geneva<br>Bernasconi, Enos; Division of Infectious Diseases, Ente Ospedaliero Cantonale Lugano, University of Geneva and University of Southern Switzerland<br>cavassini, matthias; Division of Infectious Diseases, University Hospital of Lausanne, University of Lausanne<br>Tissot, Frédéric; Division of Infectious Diseases, University Hospital of Lausanne, University of Lausanne<br>Stockle, Marcel; Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University of Basel<br>Schmid, Patrick; Division of Infectious Diseases, Infection Prevention and Travel Medicine, Cantonal Hospital of St Gallen<br>Fux, Christoph A.; Division of Infectious Diseases, Cantonal Hospital of Aarau, Aarau, Switzerland<br>Van der Valk, Marc; HIV Monitoring Foundation; Amsterdam UMC, location University of Amsterdam, Department of Infectious Diseases and Amsterdam Institute for Immunology & Infectious diseases<br>Brinkman, Kees; Department of Internal Medicine, OLVG<br>Mudrikova, Tania; Department of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, 3584 CX<br>Bonnet, Fabrice; University of Bordeaux, INSERM, Institut Bergonié, BPH; CHU Bordeaux, Hôpital Saint-André, Service de Médecine Interne et Maladies Infectieuses<br>Leleux, Olivier; University of Bordeaux, INSERM, Institut Bergonié, BPH<br>Saúde, Manuela; Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern<br>Hirter, Daniela; Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern<br>Schwab, Nathalie; Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern |

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| Primary Subject Heading: | HIV/AIDS |
| Secondary Subject Heading: | Infectious diseases, Medical management, Qualitative research |
| Keywords: | HIV & AIDS < INFECTIOUS DISEASES, Randomized Controlled Trial, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT |
| | |

# Booster-free antiretroviral therapy for persons living with HIV and multidrug resistance (B-Free): protocol for a multicenter, multi-stage, randomized, controlled, non-inferiority trial

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**Word count**

Abstract 442; main text 3376.

## Abstract

**Introduction**: Antiretroviral therapy (ART) simplification strategies are needed for treatment-experienced people with HIV (PWH) and multidrug-resistant viruses. These individuals are commonly treated with boosted ART regimens and are thereby at risk for harmful drug-drug interactions (DDI). In this trial, we aim to assess the efficacy of the combination doravirine, dolutegravir, and lamivudine (DOR/DTG/3TC) among people with a history of virological failure who receive boosted ART.

**Methods and analysis**: B-Free is a multi-stage, randomized, multicenter, open-label, non-inferiority trial, embedded within the Swiss HIV Cohort Study (SHCS), and conducted in collaboration with cohorts of PWH in the Netherlands and France. Cohort participants with a history of ART change due to virologic failure, and who maintain HIV virologic suppression with an ART regimen consisting of a pharmacological booster and at least 2 drugs from classes other than nucleoside reverse transcriptase inhibitors are included. Patients with major drug resistance mutations against DTG or DOR, and individuals with chronic hepatitis B virus infection are not eligible for the study. Individuals are randomized 1:1 to either receiving co-formulated DTG/3TC and DOR once daily or continuing their boosted ART regimen. The primary outcome is the proportion of individuals lacking virologic control (HIV RNA ≥50 cp/mL) at 48 weeks, according to the FDA snapshot algorithm. Changes in DDI burden (assessed using a DDI score), treatment satisfaction (assessed using the HIV Treatment Satisfaction Questionnaire), quality of life, and mental health represent key secondary outcomes. Additional secondary outcomes include the proportion of individuals developing new resistance-associated mutations and changes in quality of life and mental health. In a qualitative sub-study, we will conduct semi-structured interviews with a subset of participants to assess their expectations and experiences towards HIV treatment and clinical research in general. Enrolling 210 individuals will provide 80% power to demonstrate non-inferiority, defined as less than 8% absolute increase in loss of viral suppression in individuals randomized to DOR/DTG/3TC (one-sided type I error rate of 0.025).

**Ethics and dissemination**: The study was approved by the competent ethics committees (reference number BASEC 2023-01060) and the regulatory authority Swissmedic (reference number 701655) in Switzerland before the enrolment of the first participant. Approval by the European Medicines Agency (EMA) and local ethical committees in the Netherlands and France will be obtained prior to including participants in these countries. Participant's written informed consent is obtained by the investigators before enrolment. The results of all major B-Free study outcomes will be submitted to peer-reviewed journals that enable Open Access publication.

**Trial registration:** ClinicalTrials.gov (NCT06037564, registered on 07 September 2023) and Swiss National Clinical Trials Portal (SNCTP000005686, registered on 06 November 2023). Registration in the Clinical Trials Information System (CTIS) from the European Union planned.

**Strengths and limitations of this study**

- B-Free will evaluate simplified antiretroviral treatment strategies for persons with a history of treatment failure.
- The study aims at improving HIV treatment in an ageing population with a high burden of comorbidities and a high risk for experiencing drug-drug interactions, which is a pressing clinical concern.
- The study population will be recruited within established cohorts of people with HIV (PWH), facilitating participant identification and recruitment, and guaranteeing long-term outcome assessment after the end of the study.
- The strong collaboration with patient representatives helped us design the study according to priorities and perceptions of people with HIV, and the integration of a strong qualitative part into our work allows us to shape and optimize our multi-stage trial prospectively.
- Due to the heterogeneous antiretroviral treatments used in the control arm, neither participants nor study physicians can be blinded to the treatment allocation, but all laboratory assessments and statistical analyses of the primary outcome are performed by individuals blinded to the treatment allocation.

## INTRODUCTION

Multiple antiretroviral therapy (ART) simplification strategies exist for people with HIV (PWH), including dual therapies and long-acting injectable ART. Strong evidence from clinical trials has confirmed the efficacy and safety of these simplified regimens[1–3]. However, these simplification trials were mainly limited to individuals with uncomplicated HIV infection, and only very few clinical trials have assessed ART optimization strategies for PWH and a history of virological failure[4].

Evidence on treatment simplification strategies for individuals with a long-standing HIV infection and acquired resistance is needed. Because of the high barrier to resistance of boosted protease inhibitors, this population commonly receives boosted regimens, increasing their risk of experiencing drug-drug interactions (DDI) with co-medications used to treat comorbidities[5]. New drugs, including late generation non-nucleoside reverse transcriptase inhibitors (NNRTI) and integrase strand transfer inhibitors (INSTI) have a lower potential for DDI while retaining a high barrier to resistance[6,7]. Combining these newer substances may provide simplification strategies for treatment-experienced PWH and multidrug resistance.

"Booster-Free antiretroviral therapy for persons living with HIV and multidrug resistance" (B-Free) is a multistage trial to evaluate ART optimization strategies among individuals with a history of virological failure. B-Free is embedded within the Swiss HIV Cohort Study (SHCS) and is conducted in collaboration with HIV cohorts in the Netherlands and in France. In its first stage, we will assess the efficacy and safety of combining doravirine, dolutegravir, and lamivudine (DOR/DTG/3TC) compared to continuing boosted ART in individuals with multidrug-resistant HIV.

# METHODS AND ANALYSIS

## Design and setting

B-Free is a multi-stage, randomized, multicenter, open-label, non-inferiority trial, which is embedded within the SHCS and cohorts in the Netherlands and France[8–10]. The multi-stage design is adapted from the "Multi-arm multi-stage platform design" framework[11,12]. At each stage, individuals who fulfill the eligibility criteria will be randomly assigned 1:1 to either receive the new booster-free intervention regimen or to remain on their current treatment (**Figure 1**).

This trial protocol describes the first stage of the multi-stage trial. In this stage, we aim to include 210 people with HIV-1 infection who had a history of ART change due to virologic failure, and a have stable HIV suppression on ART including a pharmacological booster (ritonavir or cobicistat) and at least two agents from the NNRTI, PI, or INSTI classes. Eligible study participants will be randomly assigned 1:1 to one of the two following study arms:

- Booster-free intervention arm: Participants are switched to oral DOR 100mg and co-formulated DTG 50mg and 3TC 300mg. This 2-pill regimen is taken once daily, independent of meals.
- Control arm: Participants randomized to this arm continue their current oral booster-containing ART regimen. The dosing schedule remains unchanged. To minimize spill-over effects, changes in ART regimens are discouraged and limited to occurrence of virologic failure, new DDIs, or the onset of ART-related adverse events (AEs) requiring modification.

Treatment-experienced individuals who are not eligible to receive the current intervention regimen ("observational cohort") are identified and followed within the cohort. They will be re-assessed for participation at a later trial stage.

Once the first stage is completed and new drugs or ART combinations become available, a new stage will be planned, and eligibility criteria adapted accordingly. For the next trial stage, all B-Free participants as well as individuals from the observational cohort will be reassessed for eligibility.

## Objectives and study outcomes

The primary objective is to evaluate whether DOR/DTG/3TC given once daily is non-inferior to a boosted ART regimen in maintaining HIV suppression among PWH and previous virologic failure, with a non-inferiority margin of 8 percentage points. The secondary objective is to determine whether switching to DOR/DTG/3TC leads to a lower burden of DDI and better treatment satisfaction compared to continuing booster-containing ART. The study outcomes are outlined in **Table 1**.

**Table 1. Primary, secondary, and safety outcomes of B-Free**

| |
|---|
| **Primary outcome** |
| - Difference in the proportion of individuals with an **HIV-RNA ≥50 cp/mL** at 48 weeks between the 2 treatment arms (as recommended by the FDA snapshot approach for trials assessing ART switches). |
| **Key secondary outcomes** |
| - Changes in the **burden of drug-drug interactions** (DDI) from week 0 to 48.<br>- Changes in **treatment satisfaction** between weeks 0 and 48. |
| **Further secondary outcomes** |
| - Proportion of patients experiencing confirmed virologic failure, defined as 2 consecutive HIV-RNA measurements ≥200 cp/mL.<br>- Proportion of individuals experiencing impairment or loss of future drug options, defined as new detection of resistance-associated mutations against DOR, DTG, 3TC (intervention-arm) or against the components of the ART regimen that the virus was considered to be sensitive to at randomization (control-arm).<br>- Proportion of individuals with any moderate or severe DDI at any study visit.<br>- Proportion of patients for which the treating physician would have liked to prescribe a drug but abstained from it due to DDI issues with the antiretroviral therapy.<br>- Differences in quality of life between both groups at week 48.<br>- New onset of depression.<br>- Changes in intact proviral HIV-DNA levels in PBMCs.<br>- Proportion of individuals with an "anti-HBc alone" who develop a detectable hepatitis B viral load.<br>- Cumulative cost of all ART drugs used. |
| **Other safety outcomes** |
| - Safety outcomes include changes in CD4 cell count, blood lipid values, body weight, body mass index, renal and liver function, onset of new drug-related central nervous system adverse events, and serious adverse events (SAE). |

**Cp/mL** = copies per milliliter, **FDA** = U.S. Food and Drug Administration, **ART** = antiretroviral therapy, **DDI** = drug-drug interaction, **PBMC** = peripheral blood mononuclear cell, **SAE** = serious adverse event.

## Study population and recruitment

We include treatment-experienced individuals with a history of virological failure, and who currently receive a complex ART regimen which includes a booster. Detailed eligibility criteria are provided in **Table 2**. The established cohort infrastructures greatly facilitate the recruitment of trial participants. Clinical and laboratory data are available to assess trial eligibility. Potential

participants are seen every 3 to 6 months in the participating centers or can be contacted by the treating physicians between study visits. In the trial preparation phase, 328 eligible individuals were identified in the SHCS, and 171 individuals who were followed in two clinics in Amsterdam. In a preliminary survey among 121 potentially eligible SHCS participants, 88 (72%) responded that they were interested in participating in a study aiming at evaluating novel HIV therapy combinations with a reduced risk of DDI. Assuming a more conservative participation rate of 50% of eligible patients, we expect to reach the recruitment targets within two years.

**Table 2. In- and exclusion criteria for B-Free Stage 1**

| **Inclusion criteria** |
|---|
| - Informed consent as documented by signature.<br>- Age ≥18 years.<br>- Documented HIV-1 infection.<br>- On ART including a pharmacological booster (ritonavir or cobicistat) and at least 2 drugs from classes other than NRTI.<br>- A history of ART change due to virologic failure.<br>- HIV-RNA <50 cp/mL at screening and for at least 24 weeks before screening (one blip with less than 200 cp/mL is allowed). |
| **Exclusion criteria** |
| - Creatinine clearance <30mL/min.<br>- Known hypersensitivity, allergy, or intolerance to DOR, DTG, or 3TC.<br>- Presence of major drug resistance mutations against DTG (G118R, G140R, Q148H, Q148K, Q148R, R263K) or DOR (V106A, Y188L, F227C, F227L, M230L, Y318F) according to IAS-USA in individual cumulative resistance analyses*.<br>- Concomitant use of drugs that decrease DTG or DOR blood concentrations.<br>- Chronic hepatitis B infection.<br>- Women who are pregnant or breastfeeding.<br>- Concurrent participation in another ART intervention study. |

*Persons without available resistance testing will not be excluded if no resistance to dolutegravir or doravirine is assumed based on ART history. **ART** = antiretroviral therapy, **NRTI** = nucleos(t)ide reverse transcriptase inhibitor, **cp/mL** = copies per milliliter, **DOR** = doravirine, **DTG** = dolutegravir, **3TC** = lamivudine.

**Qualitative sub-study**

We undertake semi-structured interviews to evaluate the acceptability of participating in an interventional ART trial, the needs and expectations concerning booster-free regimens or ART in general, and to evaluate how the needs of persons living with HIV can best be addressed by research. These interviews are conducted among 30 trial participants (15 in the intervention, and 15 in the control arm). Interviews are done at baseline and after one year to identify any changes in perception or expectations resulting from their participation in the trial. In addition, similar interviews are conducted among individuals who were ineligible for the trial (n=15), or who declined participation (n=15). These individuals are only interviewed once, as no major change is expected to occur over time.

**Randomization**

Randomization is stratified by participating centers. Participants are randomized 1:1 using randomly permuted blocks of varying sizes to one of the study arms, using a web-based randomization system. Access to the randomization list is restricted to an individual who is not involved in trial-related tasks, and allocation concealment ensured, as the system only releases the treatment allocation at the time of randomization.

**Intervention and blinding**

Participants are randomized to receive DOR 100mg and co-formulated DTG/3TC 50/300mg once daily (intervention) or to continue their current and fully suppressive ART (control, **Figure 2**). The study drugs are dispensed by the study site or local pharmacy at each study visit. Since ART regimens in the intervention and the control arm may differ substantially in the number of pills, blinding of treatment allocation was deemed to be impractical. However, virologic outcome assessment in the laboratory is blinded, and treatment assignments will be masked from the trial statistician for the analyses of the primary and the main secondary outcomes.

**Assessment of primary outcome**

Study assessments and the study schedule of the B-Free Trial are summarized in **Table S1**. The primary outcome is “lack of HIV viral suppression”, defined as an HIV viral load of ≥50 cp/mL at week 48 (time window ±14 days, **Table 2**). HIV-1 RNA levels in plasma will be quantified by polymerase chain reaction (PCR) in local accredited laboratories. In case of technical problems or an HIV viral load ≥50 cp/mL, the study participant is asked to return for a repeat measurement as soon as possible. No more than one HIV viral load re-test is allowed. Individuals who prematurely discontinue the study will be included in the proportion of participants with a lack of viral suppression if their last HIV viral load was ≥50 cp/mL. Individuals without available data at 48 weeks and the last HIV viral load <50 cp/mL will be categorized into one of the following

categories: “discontinued due to AE/death”, “discontinued for other reasons”, or “on study but missing data during analysis window”[13].

**Assessment of key secondary outcomes**

Drug-drug interactions: The burden of drug-drug interactions (DDI) is assessed using a DDI score calculated based on the categories of the University of Liverpool Drug Database. Prescribed ART and co-medications are categorized as *red flag* (3 points) when co-administration is contraindicated, *amber flag* (2 points) for DDIs manageable by dose adjustment or monitoring, *yellow flag* (1 point) for DDIs with no need of a priori dosage adjustment or monitoring, and *green flag* (0 points) for no interaction[14]. The DDI score represents the sum of all points and is assessed at baseline and week 48.

Treatment satisfaction and other patient-reported outcomes: Validated instruments are used to assess treatment satisfaction, quality of life, and mental health at baseline and week 48 (**Table 3**).

**Table 3. Instruments to evaluate patient-reported outcomes**

| Dimension | Description |
|---|---|
| **Treatment satisfaction** | |
| HIV treatment satisfaction questionnaire (status version, HIVTSQ)[1] | HIV-specific measure for treatment satisfaction. |
| HIV treatment satisfaction questionnaire (change version, HIVTSQc)[1] | Based on HIVTSQ, but more sensitive to changes over time. |
| **Quality of life** | |
| WHOQOL-HIV BREF[2] | Instrument to measure quality of life, including HIV-specific questions. |
| **Mental health** | |
| Patient health questionnaire (PHQ-9)[3] | Depression screening instrument. |

[1]**Woodcock** et al. Validation of the revised 10-item HIV Treatment Satisfaction Questionnaire status version and new change version. *Value Health*. Sep-Oct 2006;9(5):320-33.

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[3]**Kroenke** et al. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med*. Sep 2001;16(9):606-13.

## Managing detectable HIV viral loads during the study

To ensure equal treatment of individuals in both trial arms and across all study sites, a sequence of steps needs to be followed in participants with detectable HIV viral loads during the study. In addition to repeating the HIV RNA measurement within 2-4 weeks, the steps include assessing treatment adherence, asking for new or inadvertent use of substances that may interfere with the ART regimen, evaluating whether intercurrent illnesses or recent immunizations occurred, measuring plasma drug concentrations, and genotypic resistance testing (**Figure 3**). For patients with confirmed virologic failure (HIV RNA ≥200 cp/mL in two consecutive measurements), genotypic resistance testing is performed. While waiting for the genotypic resistance testing to return, individuals continue their allocated treatment. Participants will receive an individually optimized antiretroviral treatment based on the results of genotypic resistance testing and will continue to be assessed for follow-up until week 48.

## Statistical analysis

*Sample size calculation*

For the first trial stage, the sample size was calculated to evaluate the non-inferiority of the primary outcome loss of virologic suppression (proportion of individuals with HIV RNA ≥50cp/mL) at week 48. The sample size was calculated using the following assumptions:

- Proportion with loss of viral suppression at 48 weeks: In a previous switch trial conducted within the SHCS (Simpl'HIV study), 2.2% of individuals had an HIV viral load ≥50 cp/mL after one year[15]. However, individuals considered for the Simpl'HIV study generally did not have viruses with drug-resistance mutations, whereas in the present study, individuals will be required to have had a history of switching treatment due to lack of efficacy. In this second-line setting, we therefore assume the failure rate to be 4%.
- Non-inferiority margin: We set the non-inferiority margin at 8 percentage points. Given that we assume that 4% of individuals will have a detectable HIV viral load at 48 weeks, such a non-inferiority margin would consider 12% of individuals with a detectable HIV viral load to be acceptable with the new treatment. Such a threshold is clinically acceptable for a patient population with long-standing HIV infection and acquired resistance mutations, given the potentially large benefits of the new treatment (lower pill count, improved safety regarding DDIs, and possibly better tolerability).

Given the assumptions above, we need to include 190 individuals (95 in each arm) to have 80% power to show non-inferiority at a one-sided alpha level of 0.025. We accounted for an attrition of 10% of individuals during the study and therefore aim to include 210 individuals. This sample size will provide adequate power for both the intention to treat (ITT) and the per-protocol analysis.

*Analysis populations*

We will test for non-inferiority using two analysis populations: (1) the intention-to-treat (ITT) population including all individuals as randomized, irrespective of whether they received the treatment or not, and (2) the "per protocol" (PP) population. Participants will be excluded from the PP population if they did not meet relevant eligibility criteria, did not start their assigned study treatment, discontinued the study treatment prematurely for other reasons than virologic failure, and if they took less than 80% of ART doses throughout the study period.

*Statistical approach*

For the primary outcome "loss of HIV viral suppression", the intervention regimen will be compared against the current regimen at 48 weeks in the ITT and PP participant set. A risk difference will be calculated for individuals with HIV-RNA ≥50 cp/mL using the Mantel-Haenszel approach stratified for the stratification factor study site, and non-inferiority will be declared if the corresponding upper one-sided 97.5% confidence limit will be below the margin of 8%. In addition to the risk difference, we will also present a risk ratio and the corresponding 95% confidence interval using the Mantel-Haenszel method. In addition, we will perform a hypothetical estimand analysis using inverse probability weighting (IPW) to account for intercurrent events such as treatment discontinuation for other reasons than virologic failure. One formal interim analysis will be performed after 50% of the patients have completed the week 24 visit. For the interim analysis, will use the same methods as for the primary outcome to evaluate the proportion of trial participants with an HIV-RNA ≥50 cp/mL at 24.

The analysis of secondary outcomes will be based on the ITT participant set. For binary outcomes, we will compare proportions between the intervention and the current regimen also using the Mantel-Haenszel risk difference and risk ratio as described above. The change in DDI score will be summarized using median values and quartiles, and differences between the treatment groups will be compared using the nonparametric van Elteren test stratified for the study site. Changes in treatment satisfaction (HIVTSQ, HIVTSQc), quality of life (WHOQOL-HIV BREF), mental health (PHQ-9), and intact proviral HIV-DNA levels from baseline to week 48 will be assessed in a mixed-effects linear model adjusted for the baseline value as a fixed effect (if applicable) and site as a random effect. Cost data will be evaluated using a generalized mixed-effects linear model.

If we can establish non-inferiority for the primary outcome, we will also test the main secondary outcomes for superiority in a sequential manner: Change in DDI score, followed by treatment satisfaction (HIVTSQc). Both secondary outcomes will be tested at a two-sided alpha level of 0.05. This hierarchical gate-keeping procedure keeps the overall type-I error rate at 0.05.

*Qualitative analyses*

Audio-recorded data from the interviews will be transcribed verbatim and analyzed using Thematic Analysis following Braun and Clarke's approach. Researchers will first familiarize

themselves with the data through repeated reading of the transcripts. As interviews are being undertaken (and transcribed) in two languages (French and German), coding will be performed in English on vernacular transcripts to create an overall codebook in close coordination between the teams using MAXQDA software. Codes will be assigned inductively, without a predefined coding framework. The process of identifying themes from codes will involve collaborative sessions among researchers from the two language teams, as initial and final themes will be identified across the complete dataset.

**Independent Data Monitoring Committee**

An Independent Data Monitoring Committee (IDMC) will monitor the trial. The IDMC will meet once before the start of the trial, and once after 50% of the study participants have completed week 24. The IDMC members will be provided with a safety event report every 6 months. Based on the reports, safety IDMC meetings can be called upon request by the sponsor or any of the IDMC member. We will convene an IDMC meeting if >2 individuals experienced virological failure and developed new resistance-associated mutations.

**Data collection and management**

All data are collected electronically using a dedicated electronic data capturing system (REDCap®) hosted by the Department of Clinical Research of the University of Bern. Only the system administrators have direct access to the server. Data edit checks were implemented into the EDC system, limiting entries to appropriate, realistic values. Central data monitoring and validation is performed, which includes verifying completeness, plausibility, and consistency of the entered data on a regular basis, and querying the sites following up on any ambiguity. In addition, on-site monitoring is part of the quality control activities implemented for this study.

**Patient and public involvement**

Patients and public representatives have been and will remain involved at all stages throughout the planning and conduct of B-Free. Documents including study protocols, data collection instruments, as well as outreach activities have been reviewed by Patient and Public Involvement members of the SHCS. Furthermore, patient representatives were involved in the development of a pre-trial survey that was performed among potentially eligible SHCS participants from three centers. The survey aimed to (1) evaluate their willingness to participate in a clinical trial, (2) to adapt the study schedule to a number of visits acceptable for potential study participants, and (3) to align the study outcomes with patients' perception on the importance of ART characteristics.

To engage with patients and the public, we developed a trial website (www.bfree-trial.ch) to provide information about the aim and current status of the study. Potential participants received a flyer containing the main trial information in lay language. Furthermore, we will provide plain and lay summaries of all publications related to B-Free which will be disseminated to patient groups in collaboration with patient representatives. All trial related information are

available in English, German, French, Italian, and Dutch. In addition, a patient representative is part of the trial scientific committee.

# ETHICS AND DISSEMINATION

## Ethical considerations

The study was approved by the competent ethics committees in Switzerland (reference number BASEC 2023-01060). Approval by the Swiss regulatory authority (Swissmedic; reference number 701655) has been obtained before the enrolment of the first participant. Approval from the European Medicines Agency, as well as local ethical approval in the Netherlands and France will be obtained prior to recruiting participants in these countries. Participant's written informed consent is obtained by the investigators before enrolment (see consent form in **Supplementary Material**). All participants and their data are handled according to the ethical principles of the Declaration of Helsinki, the respective country-specific law on human research as well as data protection law. This study complies with all applicable standards of the International Council on Harmonization E6 Guideline for Good Clinical Practice (ICH-E6 [GCP] 1996) guideline. The ethics committees and regulatory authorities receive annual safety reports and will be informed about the study stop/end in agreement with local requirements. The trial is registered on clinicaltrials.gov (NCT06037564, registered on 07 September 2023) and in the Swiss National Clinical Trials Portal (SNCTP000005686, registered on 06 November 2023, see **Table S2**).

## Publication and dissemination policy

The results of all major B-Free study outcomes will be submitted to peer-reviewed journals that enable Open Access publication. Statistical codes will be made available through a public repository on www.github.com. Data will be deposited in the Bern Open Repository and Information System (BORIS). All items will be stored with a unique Digital Object Identifier (DOI) that can be referenced in respective publications.

# DISCUSSION

The B-Free multistage trial is a unique platform to study treatment simplification strategies among PWH with prior virologic failure. The study will fill an important research gap, as the concerns of individuals with multidrug-resistant HIV are currently under-studied, and evidence-based treatment recommendations are lacking. Furthermore, given the increasing proportion of PWH who are confronted with comorbidities, our results will offer evidence for ART strategies with a reduced risk of DDI with comedications for this ageing population. The multistage design embedded within well-described cohorts will allow a continuous and resource-effective evaluation of newly available ART combinations, thereby offering simplified treatment options to most individuals in this important population.

Our approach has several strengths: As the study population is recruited within established cohorts of PWH, participant identification and enrolment are greatly facilitated. In addition, long-term outcome assessment after the end of the study is guaranteed since individuals are prospectively followed within their cohort. Furthermore, the inclusion of study participants from multiple countries and across a variety of study center types (university, regional hospitals, and private physicians) will increase the generalizability of the study results. Finally, the strong collaboration with patient representatives allowed us to design the study according to the priorities and perceptions of PWH, and the integration of a strong qualitative part into our work will allow us to shape and optimize our multi-stage trial prospectively.

The main limitation of the study is the inability to blind both participants and trial physicians due to the heterogeneous regimens used in the control arm. Nevertheless, laboratory assessment of the primary outcome (HIV viral load at week 48) and the statistical analyses are performed by individuals who are blinded to the treatment allocation.

The B-Free trial takes into account contemporary developments in medical conditions of PWH, and addresses some of the most important challenges related to delivering HIV care to an aging population, while ensuring people's treatment satisfaction and quality of life. The trial results will provide evidence-based guidance for choosing the optimal treatment strategy for the understudied population of PWH and a history of virological failure.

## Current status of the B-Free trial

The B-Free trial study setup was initiated in October 2022, and recruitment started in Switzerland on 13.11.2023. The estimated time of recruitment is two years.

## Footnotes

**Contributors**: Study concept and design: GW, BS, AC, RK, AR, AL, and DLB. Drafting of the manuscript: BS, MB, and GW. Critical revision of the manuscript for important intellectual content: all authors. Planning and analysis of qualitative sub-study: MB, SZ, ME, CA, IPB. Planning of statistical analysis: AL and BS. Obtained funding: GW, AC, RK, AR, and DLB.

**Funding**: This work was supported by the Swiss National Science Foundation (SNSF) grant number 205829. The funder of the study had no role in study design, writing of the protocol, or the decision to submit the manuscript for publication.

**Competing interests**: BS reports financial support for travel grants from Gilead Sciences and ViiV healthcare, and for advisory boards from Gilead Sciences and MSD, paid to his institution. GW has received research grants from Gilead Sciences and Roche Diagnostics, as well as fees for advisory boards and lectures form ViiV, MSD, Roche Diagnostics and Gilead Sciences (all paid to his institution). MC's institution received research grants and expert opinion fees from Gilead, MSD and ViiV. DLB received money payed to himself outside of the submitted work for advisory boards and lectures from the companies Gilead, MSD, Pfizer and ViiV and money for a research grant from the company ViiV. The institution of EB received study grants from Merck and Gilead; it also received travel grants and fees for EB participation to advisory boards from Gilead, Merck, ViiV Healthcare, Pfizer AG, Moderna, Astra Zeneca, Abbvie, and Ely Lilly. DH received fees for consultancies from AstraZeneca, Bavarian Nordic, Gilead, UCB, and ViiV Healthcare, a travel grant from Gilead, and institutional funding from AstraZeneca, Gilead, GSK, A. Menarini, MSD, and ViiV Healthcare. MvdV has received research grants and fees for participation in advisory boards from Gilead, MSD and ViiV all paid to his institution. MS reports financial support for travel grants from Gilead Sciences, and for advisory boards from Gilead Sciences, MSD, and ViiV Healthcare, paid to his institution. AR received research grants from Gilead, paid to his institution; travel expenses from Gilead and Pfizer, paid to his institution; and honoraria for advisory board consultations from MSD and Moderna, paid to his institution. PS's institution has received travel grants, congress and advisory fees from ViiV and Gilead unrelated to this work. All other authors report no conflicts of interest.

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# Figure legends

**Figure 1. The multistage trial framework of B-Free**
At each trial stage, eligible participants are randomized into one of two arms. People who are not eligible for stage 1 will continue follow-up in their respective HIV cohort, and will be reassessed for eligibility at a later trial stage. The process can be repeated when new HIV drugs are marketed (here exemplified as Stage 2). This protocol describes the **stage 1 trial**. **EOS** = End of study.

**Figure 2. Flow of study participants included in the first stage of the B-Free trial**
**ART** = antiretroviral therapy, **NNRTI** = non-nucleoside reverse transcriptase inhibitor, **INSTI** = integrase strand transfer inhibitor, **PI** = protease inhibitor, **DOR** = doravirine, **DTG** = dolutegravir, **3TC** = lamivudine.

**Figure 3. Guidance for viral load monitoring and further assessment if HIV-RNA is detectable**
cp/mL = copies per milliliter, RNA = ribonucleic acid, ART = antiretroviral therapy.

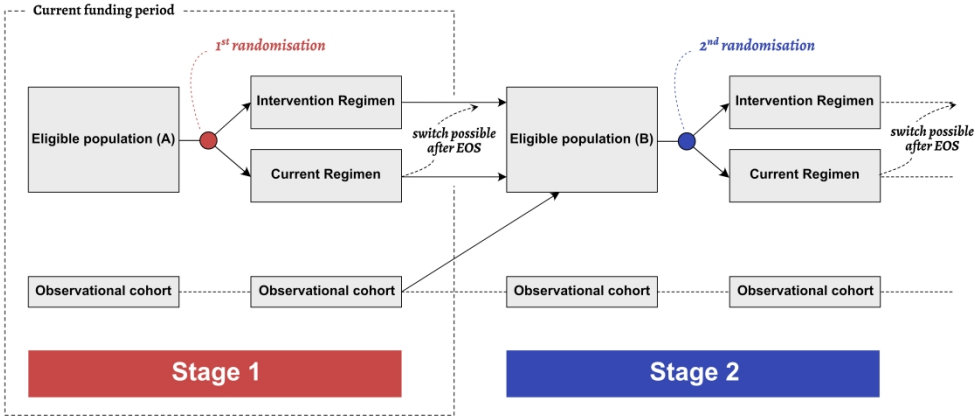


Figure 1: The multistage trial framework of B-Free. At each trial stage, eligible participants are randomized into one of two arms. People who are not eligible for stage 1 will continue follow-up in their respective HIV cohort, and will be reassessed for eligibility at a later trial stage. The process can be repeated when new HIV drugs are marketed (here exemplified as Stage 2). This protocol describes the stage 1 trial. EOS = End of study.

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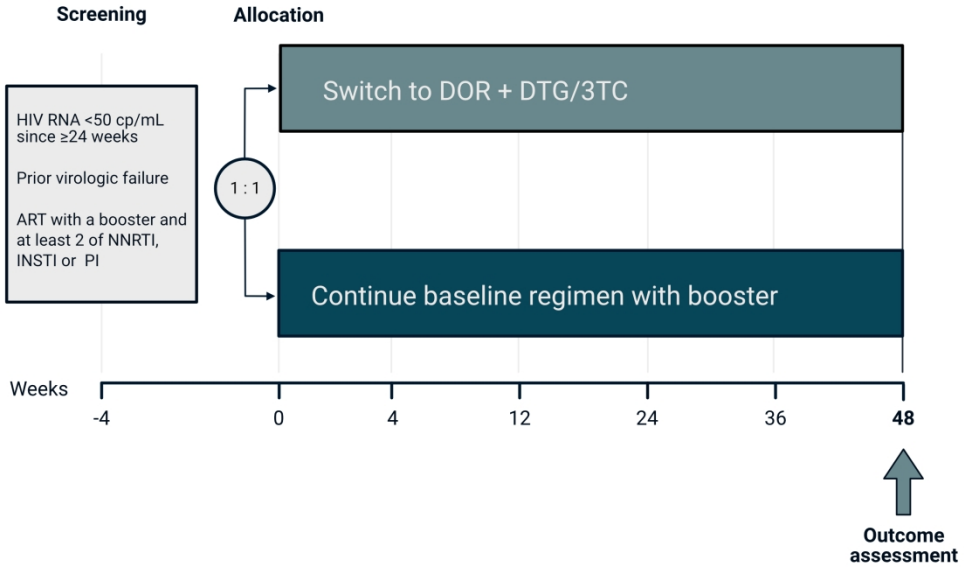


Figure 2: Flow of study participants included in the first stage of the B-Free trial. ART = antiretroviral therapy, NNRTI = non-nucleoside reverse transcriptase inhibitor, INSTI = integrase strand transfer inhibitor, PI = protease inhibitor, DOR = doravirine, DTG = dolutegravir, 3TC = lamivudine.

212x123mm (300 x 300 DPI)

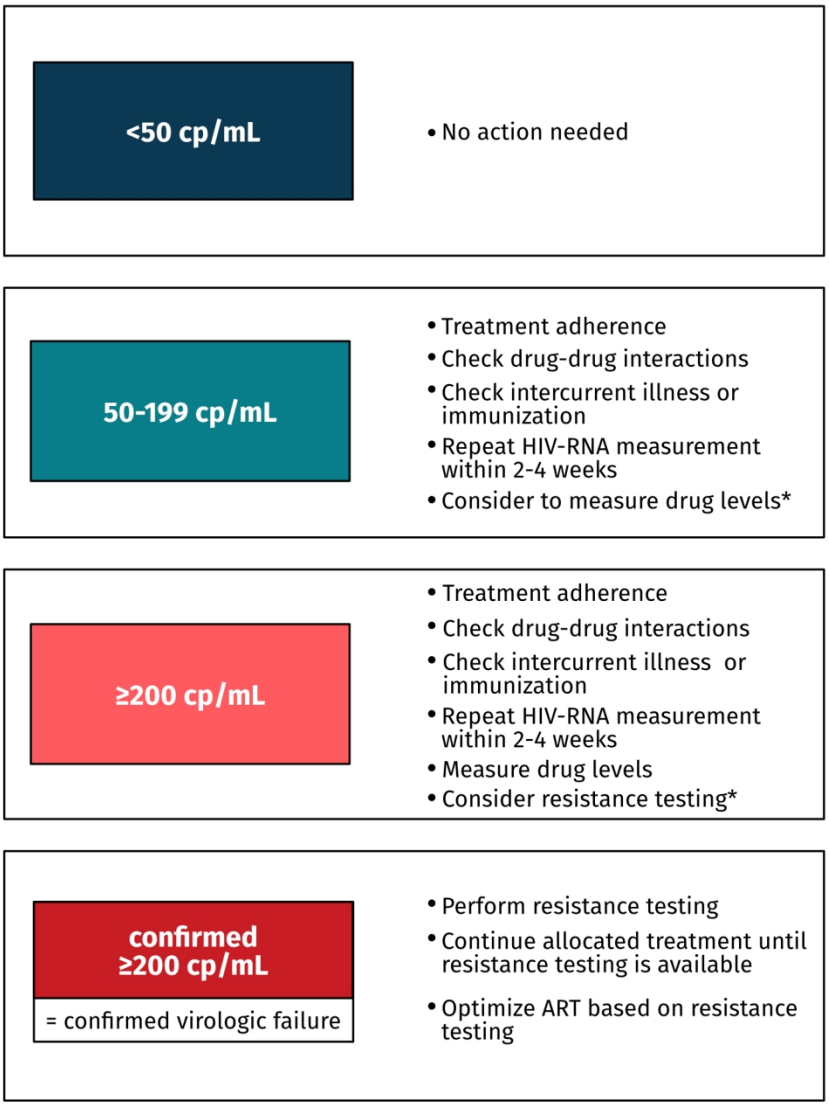


Figure 3: Guidance for viral load monitoring and further assessment if HIV-RNA is detectable. cp/mL = copies per milliliter, RNA = ribonucleic acid, ART = antiretroviral therapy.

133x181mm (300 x 300 DPI)

# Supplementary Material

## Table S1: B-Free trial assessment schedule (stage 1)

| Study Periods | Screening | Baseline | Intervention Period | | | | End of Study | Safety Follow-up |
|---|---|---|---|---|---|---|---|---|
| Visit | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Time point | -4 weeks | Day 0 | Week 4 | Week 12 | Week 24 | Week 36 | Week 48 | Week 52[4] |
| STUDY PROCEDURES | | | | | | | | |
| Assess eligibility criteria | x | x | | | | | | |
| Obtain written informed consent | x | | | | | | | |
| Randomization | | x | | | | | | |
| Administration of study drug | | x | x | x | x | x | x | |
| STUDY ASSESSMENTS WITHIN THE COHORT ROUTINE | | | | | | | | |
| Behavioural data | | x | | | x | | x | |
| Adherence assessment questionnaire | | x | x[5] | x[5] | x | x[5] | x | |
| Routine laboratory tests | | x | | | x | | x | x |
| CD4 count | | x | | | x | | x | |
| STUDY SPECIFIC ASSESSMENTS | | | | | | | | |
| Demographics | x | | | | | | | |
| Medical history | | x | | | | | | |
| Documentation of virologic failure and historical ART resistance testing | x | | | | | | | |
| Concomitant medications | x | x | x | x | x | x | x | |
| Pill count | | x | x | x | x | x | x | |
| Physical examination | x | x | x[6] | x[6] | x | x[6] | x | |
| Vital signs | x | x | x | | x | | x | |
| Body weight | | x | | | x | | x | |
| Assessment for central nervous system (CNS) events | | x | x | x | x | x | x | x |
| Assessment for treatment limitations due to DDI | | x | | x | x | x | x | |
| Assessment of treatment satisfaction (HIVTSQ) | | x | | | | | x | |
| Assessment of quality of life (WHOQOL-HIV BREF) | | x | | | | | x | |
| Assessment of mental health (PHQ-9) | | x | | | | | x | |
| In-depth interviews[1] | | x | | | | | x | |

## Table S1 Continued

| Study Periods | Screening | Baseline | Intervention Period | | | | End of Study | Safety Follow-up |
|---|---|---|---|---|---|---|---|---|
| Visit | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Time point | -4 weeks | Day 0 | Week 4 | Week 12 | Week 24 | Week 36 | Week 48 | Week 52[4] |
| LABORATORY ASSESSMENTS | | | | | | | | |
| Blood pregnancy test[2] | x | | | | | | | |
| HBsAg, anti-HBc, anti-HBs | x | | | | | | | |
| HIV viral load | x | x | x | x | x | x | x | x |
| HBV viral load[3] | | x | | | x | | x | |
| Safety laboratory tests | x | | x | x | | x | | |
| Plasma sample storage | | x | x | x | x | x | x | |
| PBMC storage | | x | | | | | x | |
| Drug plasma concentration | | | At any time point if confirmed HIV RNA ≥200 cp/mL | | | | | |
| Genotypic resistance testing | | | At any time point if confirmed HIV RNA ≥200 cp/mL | | | | | |

[1] Only in a subset of 60 individuals. Interviews are conducted at baseline and week 48 in 15 individuals from the intervention arm and 15 from the control arm, once in 15 individuals who were ineligible for the trial, and once in 15 eligible individuals who refused to participate in the trial. Please refer to the section on the **"qualitative sub-study"** for more information.
[2] Only done in women of childbearing potential.
[3] Only individuals with a positive anti-HBc and a negative anti-HBs serology ("anti-HBC alone").
[4] This visit will only be performed in individuals with ongoing CNS/ serious adverse events, in participants with ongoing lab abnormalities, or a detectable HIV viral load at week 48. The visit can be done via telephone if no lab testing is needed.
[5] If a pill count cannot be performed (e.g. the participant forgot to return the used medication bottles), they are asked to complete an adherence assessment questionnaire covering the past 4 weeks.
[6] If clinically indicated, based on the judgment of the investigator.

**DDI** = drug-drug interaction, **HIVTSQ** = HIV Treatment Satisfaction Questionnaire, **WHOQOL-BREF** = Abbreviated World Health Organization Quality of Life questionnaire, **PHQ-9** = Patient Health Questionnaire-9, **HBsAg** = hepatitis B surface antigen, **anti-HBc** = hepatitis B core antibody, **anti-HBs** = hepatitis B surface antibody, **HBV** = hepatitis B virus, **PBMC** = peripheral blood mononuclear cells.

## Table S2: Trial registration data

| DATA CATEGORY | INFORMATION |
|---|---|
| Primary registries, trial identifying numbers, and date of registration | clinicaltrials.gov (NCT06037564, 07.11.2023) and Swiss National Clinical Trials Portal (SNCTP000005686, 06.11.2023) |
| Source of monetary support | Swiss National Science Foundation, ) grant number 205829 |
| Sponsor | Insel Gruppe AG, Bern University Hospital, Bern, Switzerland |
| Sponsor representative | Prof. Dr. med. Gilles Wandeler |
| Contact for public queries | Prof. Dr. med. Gilles Wandeler, gilles.wandeler@insel.ch |
| Contact for scientific queries | Prof. Dr. med. Gilles Wandeler, gilles.wandeler@insel.ch |
| Public title | B-Free Multistage Trial |
| Official title | Booster-free antiretroviral therapy for persons living with HIV and multidrug resistance (B-Free): A Multicenter, multi-stage, randomized, controlled non-inferiority trial |
| Countries of recruitment | Switzerland, the Netherlands, France |
| Health conditions studied | HIV; Drug resistance; Drug-drug interaction |
| Interventions | Intervention: Doravirine 100 mg administered once daily in combination with co-formulated dolutegravir/lamivudine 50/300 |
| | Control: Continuation of participant's fully suppressive booster-containing antiretroviral therapy at baseline. |
| Key inclusion criteria | Informed consent as documented by signature. |
| | Age ≥18 years. |
| | Documented HIV-1 infection. |
| | On ART including a pharmacological booster (ritonavir or cobicistat) and at least 2 drugs from classes other than NRTI. |
| | A history of ART change due to virologic failure. |
| | HIV-RNA <50 cp/mL at screening and for at least 24 weeks before screening (one blip with less than 200 cp/mL is allowed). |
| Key exclusion criteria | Creatinine clearance <30mL/min. |
| | Known hypersensitivity, allergy, or intolerance to DOR, DTG, or 3TC. |
| | Presence of major drug resistance mutations against DTG (G118R, G140R, Q148H, Q148K, Q148R, R263K) or DOR (V106A, Y188L, F227C, F227L, M230L, Y318F) according to IAS-USA in individual cumulative resistance analyses*. |
| | Concomitant use of drugs that decrease DTG or DOR blood concentrations. |
| | Chronic hepatitis B infection. |
| | Women who are pregnant or breastfeeding. |
| | Concurrent participation in another ART intervention study. |
| Study type | Interventional |
| | Phase 4 |
| | Allocation: Randomized |
| | Interventional Model: Parrallel Assignment |
| | Masking: Single (Outcomes Assessor) |
| | Primary Purpose: Treatment |
| Date of first enrollment | 13 November 2023 |
| Target sample size | 210 |
| Recruitment status | Recruiting |
| Primary outcome | Loss of viral suppression at week 48 |
| Key secondary outcomes | Changes in the burden of drug-drug interactions (DDI) from week 0 to 48. |
| | Changes in treatment satisfaction between weeks 0 and 48. |

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# Supplementary Material – Patient informed consent

## Request for participation in medical research, "B-Free"

Study title: **Booster-free antiretroviral therapy for persons living with HIV and multidrug resistance: A multicentre multi-stage randomized trial ("B-Free")**

Layperson title: **Booster-free HIV therapy for persons with pre-existing HIV resistance**

Dear Madam or Sir

We would like to inform you about the study mentioned above and ask you whether you would like to participate. Before the study treatment consisting of the new combination of Dovato® and Pifeltro® may be used, its efficacy must be determined.

In this study, we want to evaluate if the booster-free study medication Dovato® and Pifeltro® is as effective as your previous HIV treatment that includes a booster. A booster does not act directly against the viruses, but rather supports and prolongs the efficacy of the other active substances in the HIV treatment. However, boosters can cause interactions with other medicines not used for the HIV infection. This is why we want to investigate whether the new treatment results in fewer interactions between the HIV treatment and other drugs, and whether your quality of life improves with the study treatment.

Your participation is voluntary. The following **patient information** should help you decide. You can **discuss** any questions about study participation **with the study doctor**. The study doctors are the ones who are responsible for the study and who look after you during this time. If you want to take part, please sign the **informed consent form** at the end. With your signature, you confirm that you have read and understood the patient information. If there is something you do not understand, please ask the study doctor.

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The patient information and informed consent form consist of four parts:

**Part 1** **The most important points at a glance**
**Part 2** **More details: Information on the study**
**Part 3** **Data protection and insurance coverage**
**Part 4** **Informed consent form**

In **Part 1** you will get an overview of the study. In **Part 2** we explain the study procedures and the background of the study in more detail. **Part 3** contains the information on data protection and insurance coverage. With your signature at the end of the document, **Part 4**, you confirm that you have understood everything and that you consent to take part.

This study will be conducted by Inselgruppe. The responsible person is Prof. Dr. med. Gilles Wandeler, Senior Physician at the Department of Infectious Diseases at the Inselspital in Bern, Switzerland. The study is financed by the Swiss National Science Foundation (SNSF).

As part of this study, the following person is responsible for you:

| | |
|---|---|
| Name | Dr. med. Bernard Surial |
| Address | Inselspital, Department of Infectious Diseases |
| Telephone | +41 (0)31 632 88 44 → Weekdays 8:00am-5:00pm<br>+41 (0)31 632 21 11 → Ask for Infectious Diseases doctor on call (24-hour availability) |
| E-mail | b-free@insel.ch |

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# Part 1:
# The most important points at a glance

## 1. Why are we doing this study?

In this study, we are investigating whether the study medication Dovato® and Pifeltro® is as effective as previous tried-and-tested HIV treatments. The combination of Dovato® and Pifeltro® is well suited for patients with resistance to available HIV medication and previous treatment failure.

The study medication is considered to be effective if the HIV viral load can be suppressed with this treatment. Furthermore, we would like to assess whether the study medication results in fewer interactions with other drugs, and if your quality of life improves with this medication. In **Chapter 4** you will find out more about the scientific background of the study.

## 2. What do you have to do if you take part?

Your participation in this study will last 52 weeks. We will invite you for 8 study visits. At least 3 of these visits are part of your general treatment, and will take place regardless of your participation in the study. The other visits are additional study visits. A visit will last between 30 minutes and 1 hour and 30 minutes. The number of visits is stated in the **table in Chapter 5**.

If you decide to participate, you will be allocated randomly to one of two groups: the trial or the control group. In the trial group, you will receive the study medication Dovato® and Pifeltro®, 2 tablets to be taken at the same time once daily. In the control group, you will continue with your current HIV treatment.

In addition, we would like to conduct a 60 to 90-minute interview with 30 study participants from the different study sites at two different time points. These interviews will be conducted according to a guideline and will be recorded for the scientific analysis of the statements. The interviews will be conducted by specialists from the Universities of Bern and Lausanne. With these interviews, we aim to better understand patient needs in terms of clinical studies and research in general, and to analyse the expectations for optimal HIV treatments. The analyses of these interviews will be included in the final results of this study.

In **Chapter 5** you will find out more about the course and procedure of the study.

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## 3. What are the benefits and risks associated with participation?

### Benefits

You might have no direct benefit by participating in the study. However, you may help future patients by taking part. A benefit arises from the fact that we will gain further insights into the impact of booster-free therapeutic approaches, which may have the potential of having fewer side effects compared to current HIV treatments.

### Risks

The drugs Dovato® and Pifeltro® are approved in Switzerland, and are prescribed on a regular basis for the treatment of HIV. However, there are insufficient studies on the administration of this combination of Dovato® and Pifeltro® to patients with a history of HIV resistance and virological failure, and therefore Dovato® and Pifeltro® are not licenced for this group of patients. Their efficacy for your situation remains unknown.

In **Chapter 6** you will find further information on the risks and burdens.

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# Part 2:
# More details: Information on the study

## 4. The scientific background of the study

### 4.1 Background: Why are we doing this study?

Effective antiretroviral therapy has increased the life expectancy of people with HIV so that it almost corresponds to that of people without HIV. As we get older, concomitant diseases such as cardiovascular diseases become more frequent, which may require additional medication. Therefore, interactions between HIV drugs and concomitant medications represent an increasing problem. In the Swiss HIV Cohort Study (SHCS), for example, two thirds of the people aged 50 years or older have one or more other diseases, for which almost 50% have to take one or more additional medication.

People who previously had HIV treatment failure usually receive what is known as a "boosted" HIV treatment, which contains the ingredients ritonavir or cobicistat. These substances are called "boosters". Boosted HIV treatments are particularly prone to lead to drug interactions. In the SHCS, three quarters of the drug interactions occurred in patients who received boosted HIV treatments. These drug interactions may result in serious complications, and sometimes affect the treatment of concomitant diseases, e.g. with chemotherapy or blood-thinning medication.

In this study we want to investigate the efficacy and acceptance of booster-free HIV treatment in treatment-experienced individuals. The high efficacy and good tolerability of Dovato® and Pifeltro® make this combination a suitable therapy, with the objective of simultaneously reducing the risk of drug interactions. The drugs Dovato® and Pifeltro® are approved in Switzerland, and are prescribed on a regular basis for the treatment of HIV. However, there are insufficient studies on the administration of this combination to patients with HIV resistance and a history of virological failure and therefore Dovato® and Pifeltro® are not licenced for this group of patients.

Furthermore, we would like understand the needs of people with HIV in terms of HIV research, to know how the current study is evaluated, and what the expectations of future HIV treatments are. For this, in-depth interviews will be conducted with a selection of 30 patients from the different study sites, and these will then be analysed by experts from the universities of Bern and Lausanne. You can take part in the study even if you do not want to do these interviews.

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### 4.2 Design of the study: How will we proceed?

Participants will be allocated randomly to groups in our study. This is important to have reliable study results. In our study, there are two groups at a 1:1 ratio:

- **Group 1** (trial group) receives the study medication (Dovato® and Pifeltro®), one tablet of each daily. The tablets can be taken independently of meals.
- **Group** 2 (control group) continues the current HIV treatment with booster.

Both you and the study doctor as well as the study staff will be aware of what treatment you will receive.

### 4.3 Regulations for scientific research in humans

We are conducting this study in accordance with Swiss laws and all internationally recognised guidelines. The competent Ethics Committee and Swissmedic have reviewed and approved the study.

This is an international study conducted in Switzerland and additionally in European countries. In total, we will include 210 study participants, of whom 120 will be recruited in Switzerland.

You can also find a description of this study on the website of the Swiss Federal Office of Public Health: www.kofam.ch using the SNCTP registry number 000005686 or the BASEC number 2023-01060.

## 5. Course of the study

### 5.1 What do you have to do if you participate in the study?

Participation in the study is voluntary and lasts 52 weeks. You must follow the schedule (→ Chapter 5.2) and all requirements set by your study doctor.

You will need to tell your study doctor

- if your health condition changes, e.g. if you feel worse or if you have new symptoms; this also applies if you end the study early (→ Chapter 5.3 and 5.4)

You should also be aware of the following:

- During participation, women of childbearing age must use contraception to avoid pregnancy (→ Chapter 5.5).

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### 5.2 What happens at the visits?

Over the course of your participation, you will come in for 8 study visits. At least 3 of these visits are part of your general treatment and also take place regardless of your participation in the study. The other visits are additional visits and are only part of the research study. A visit lasts about 30 minutes to 1 hour and 30 minutes. The sequence of the visits is outlined in the table below.

We will do the following at all of the visits:

- We will answer your questions.
- We will check the regularity of your medicine intake. This is why you must always bring all HIV medication with you.
- We will give you the study medication/HIV medication.
- We will do a physical examination.
- We will assess any new physical symptoms.
- We will record any new medicines you are taking.
- We will take blood samples, namely at least 14.5 mL (approximately 3 teaspoons) and max. 31 mL (approximately 6 teaspoons).

At individual visits, we will also do the following:

- At the first visit, we will record your medical history and, if you are a woman of childbearing potential, a pregnancy test will be performed.
- We measure your weight, blood pressure and pulse.
- You will receive questionnaires about your quality of life and mental health.
- We will ask you questions regarding employment, physical activity, mental well-being, alcohol and drug consumption, as well as relationships and sexual behaviour.
- We will perform urine tests, and these will require a urine sample from you (maximum 7.5 mL, or approximately 1.5 teaspoons)

These examinations enable us to see whether the study treatment works and whether it is safe, whether you have fewer interactions with other medicines and whether your quality of life has changed.

We will arrange the visits together with you.

The schedule on the next page shows all of the visits in detail. The visits and activities highlighted in grey are specific for the B-Free study.

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## Schedule: General and additional examinations (activities in grey are study specific)

| Study visit/ visit | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| | Screening | Day 0 | Week 4 | Week 12 | Week 24 | Week 36 | Week 48 | Week 52 |
| Duration | 1 hr 30 min | 1 hr 30 min | 30 min | 30 min | 1 hr 30 min | 30 min | 1 hr 30 min | 15 min |
| Checking in- and exclusion criteria for the study | ✓ | ✓ | | | | | | |
| Signing patient information and informed consent form | ✓ | | | | | | | |
| Random allocation to trial or control group | | ✓ | | | | | | |
| Recording medical history, general and HIV-specific | | ✓ | | | | | | |
| Recording demographic data | ✓ | | | | | | | |
| Pregnancy test for women of childbearing potential | ✓ | | | | | | | |
| Various questionnaires | | ✓ | | | ✓ | | ✓ | |
| Blood + urine sampling | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Measurement of blood pressure and pulse | ✓ | ✓ | ✓ | | ✓ | | ✓ | |
| Body weight measurement | | ✓ | | | ✓ | | ✓ | |
| Physical examination | ✓ | ✓ | (✓) | (✓) | ✓ | (✓) | ✓ | |
| Recording of all current medication | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| We will ask your doctor whether there were any problems with other drugs due to the study medication | | ✓ | | ✓ | ✓ | ✓ | ✓ | |
| Evaluate for symptoms | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Assess study medication adherence | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Handing out study medication | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| In-depth interview, if agreed (approx. 60-90 min) | | ✓ | | | | | ✓ | |

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### 5.3 When does the study participation end?

Your participation will last 52 weeks and ends after the eighth visit. You can also end your participation earlier at any time (→ Chapter 5.4). You do not need to explain why you no longer want to participate. If you decide discontinue the study early, please talk to your study doctor.

Even if you discontinue prior to the end of the study, we will continue to treat you and look after you as good as medically possible according to the current standards (→ Chapter 5.4 for alternative treatment options). For your safety, we will examine you at the time of study discontinuation.

If you end the study early, we ask that you continue to inform your study doctor if your health condition changes, e.g. if you feel worse or have new symptoms. In case you stop the study early, we will analyse the data and samples collected until that point (e.g. blood values) for the study.

We might also have to ask you to end the study early. This could happen, for example, if you experience serious side effects occur due to the study medication, or if you develop new HIV resistances during the study.

### 5.4 What happens if you do not wish to take part?

Even if you do not take part in this study, we will treat you and look after you with the best possible medical care according to the current standards. If you do not wish to take part in the study, your study doctor will advise you of alternative treatment choices.

### 5.5 Pregnancy

There may be pregnancy risks. It is not known whether the study medication may harm an unborn or breastfed child. If you are pregnant, want to become pregnant, or are breastfeeding, you cannot take part in the study.

For women of childbearing age, a pregnancy test will be performed before the start of the study. There are still not enough data as to whether the study medication has an effect on the unborn child. This is why study participants must use a method of contraception during the study (condoms, hormonal methods such the pill, or intrauterine device). Your study doctor will discuss the suitable methods with you.

If you become pregnant despite contraception during the study, you have to inform your study doctor immediately. In this case, there will be regular follow-up of your pregnancy, and your study doctor will collect health data about your child. Your study doctor will talk to you about your HIV treatment options, which may also include further intake of the study medication. To continue the study medication Dovato® and Pifeltro®, you must sign a separate informed consent form (see *information and informed consent form for pregnancy follow-up in pregnant study participants*). Your study doctor will discuss with you what happens next.

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## 6. Risks, burdens and side effects

### 6.1 What risks and burdens may occur?

As with any medical treatment, there are risks and burdens involved in participation in this study. Both Dovato® and Pifeltro® are approved in Switzerland and are prescribed on a regular basis. We already know many of the associated risks, while others may remain unknown. This uncertainty is common in the study setting. You can find a list of the most common and most serious risks in **Chapter 6.2**. Many side effects can be treated. We will inform you of any new finding regarding risks and side effects during the study.

In addition, there are risks involved in the medical examinations that we perform in this study. You will already know some examinations. You can find a list of these risks of the examinations in **Chapter 6.3**.

### 6.2 The most common and most serious risks caused by the study medication

You can find information here about the most common side effects that we already know about.

**Dovato®** film-coated tablets 50 mg/300 mg (active ingredients: dolutegravir and lamivudine)

Very common side effects (occurs in more than 10%): Headache, diarrhoea, nausea

More information can be found in the medical product information.

**Pifeltro®** film-coated tablets 100 mg (active ingredient: doravirine)

Very common side effects (occurs in more than 10%): none.

More information can be found in the medical product information.

### 6.3 Risks and burdens caused by examinations in the study

We will carry out various medical examinations for this study (→ Chapter 5.2). These examinations are tried-and-tested procedures. Nevertheless, they may involve risks and burdens, which means that they may be unpleasant or have unwanted side effects. In this study, blood sampling may cause bruising, bleeding or swelling at the puncture site. It may rarely cause an infection at the puncture site.

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## 7. Financing and compensation

This study is organised by the sponsor and wholly financed by the Swiss National Science Foundation. The study medication and HIV medication of the control group as well as the routine medical checks are covered by your health insurance company. Study visits 2, 3, 5 and 7 (in accordance with the schedule) will be conducted as part of the study and will not be charged to the health insurance company.

The researchers involved do not have a financial benefit from the conduct of this study.

There will be no additional costs for you or for your health insurance company from your participation in the study. For study visits 2, 3 and 5 (in accordance with the schedule) you will receive a compensation of 50 Swiss Francs for each visit as well as reimbursement of the travel costs. Participation in the in-depth interviews will be compensated with an additional 50 Swiss Francs per interview.

## 8. Results from the study

Your study doctor will inform you of results that are important to you. There are also incidental findings. Incidental findings are "side results" that are not anticipated. This can be, for example, results from liver values. We will inform you if these incidental results are important for your health.

We will inform you, for example, if we discover a disease by chance that you know nothing about and that we can treat.

There are also the overall results of the study that come from the data of all participants. This includes, e.g. the fact that we know more about the efficacy and drug interactions (→ Chapter 4.1). Your study doctor will be happy to give you a summary of the overall study results at the end of the study if you wish.

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# Part 3:
# Data protection and insurance coverage

## 9. Protection of data and samples

We protect your data (e.g. information such as blood pressure and pulse from your medical history), and your samples (e.g. your blood samples). Switzerland has strict legal regulations in place for the protection of data and samples.

### 9.1 Coding of data and samples

As with all studies, information arises from the examinations (e.g. blood values, blood pressure, pulse). These data will be entered in an electronic database. The data will be documented in coded form. "Coded" means that your data will not be connected with personal information such as name, date of birth or place of residence, but rather only via a code. We manage a list at the institution that we use to determine which code belongs to you. This means that your name, your date of birth or your place of residence, etc. are *not* directly written in the database. This list will remain with us at the institution for 10 years. Nobody else will receive this list.

At the end of the study (at the earliest time point after the legally stipulated storage duration) your data will be completely anonymised. This means that it will no longer be possible to identify you without unreasonable effort. Various measures are used for anonymisation, e.g. destruction of the code and the list.

All samples that are analysed in external laboratories (e.g. blood and urine samples) are always coded in the way described above. Your personal data are therefore protected if we send samples.

### 9.2 Secure processing of data and samples during the study

The sponsor is responsible for the secure processing of your data and samples from this study. The sponsor is responsible for the compliance with the applicable laws, such as data protection laws

In this study, your data will be recorded in an electronic database of the sponsor. The data are stored on a server in Switzerland, and the access rights are restricted to a group of people who need access for work on the study. Nevertheless, there is always a residual risk that third parties can access your personal data (e.g. risk of hacking).

It is often important for your GP to share data from your medical history with the study doctor. This also applies to other doctors treating you. By giving your consent at the end of the document, you give your permission for this.

During the screening visit, we will test you for hepatitis B virus. In the event of a new positive hepatitis B virus result, certain information (including name, sex, date of birth and place of residence) will be reported in uncoded form to the cantonal physician and the federal office of public health (FOPH) to comply with national health regulations.

### 9.3 Secure processing of data and samples after the study

The sponsor remains responsible for the secure processing of your data and samples even after the end of the study. The law mandates that all study documents, including the data in the database, are stored for at least 10 years.

If, after the end of the study, there are still residual samples left, we will collect them and store them coded in a safe place after the end of the study. In this way, they can be used later for further analyses (→ Chapter 9.4). This type of collection of coded samples is called a "biobank". There are strict rules for biobanks to make sure the information from your samples is well protected.

After completion of a study, the results are usually published in scientific journals. For this, the results are assessed by other specialists. Your coded data must therefore be forwarded to these specialists. However, the data must not be used for new research purposes. This would require your separate informed consent (see 9.4).

### 9.4 Further use of your data and samples in other future studies

Your data and samples from this study are very important for future research. Data and samples that were not completely used for this study may possibly be used for other studies. We need your separate informed consent for the further use of your data and your samples. This is voluntary. Please read the additional informed consent form at the end of the document carefully. Please sign the informed consent form if you would like to support further research in the future with your data and samples. Even if you do not consent to this, you can still participate in the study.

### 9.5 Rights of inspection during controls

The conduct of this study may be reviewed. The review is carried out by authorities such as the competent Ethics Committee or the regulatory authority Swissmedic or also by foreign regulatory authorities. The sponsor also has to carry out such reviews to ensure the quality of this study and the results.

For this, a few specially trained individuals will take a look at your personal data and medical history. The data are therefore *not* coded for this review. The individuals who see your uncoded data are bound by medical confidentiality.

## 10. Insurance coverage

You are insured if you sustain an injury due to the study. The procedure is regulated by law. The sponsor has obtained an insurance policy for this from Zürich Versicherungs-Gesellschaft AG in Zurich, Switzerland. If you think you have sustained an injury due to the study, please contact your study doctor or the insurance company directly.

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# Part 4:
# Informed consent forms

This informed consent has two informed consent forms:

- Informed consent form for participation in this study B-Free
- Informed consent form for the further use of data and samples from this study in coded form (only if you agree to take part in B-Free)

Please read the forms carefully. Please ask us if there is something you do not understand or if there is something you would like to know. Your written consent is required for participation.

**Informed consent form for participation in the study B-free**

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| **BASEC number** | 2023-01060 |
| **Study title** | Booster-free antiretroviral therapy for persons living with HIV and multidrug resistance: A multi-centre multi-stage randomized trial (“B-Free”) |
| **Layperson title** | Booster-free HIV therapy for persons with pre-existing HIV resistance |
| **Responsible institution**<br>(Sponsor with address) | Inselgruppe AG, Freiburgstrasse 8, 3010 Bern<br>Represented by Prof. Dr. med. Gilles Wandeler<br>Inselspital, Department of Infectious Diseases |
| **Site where the study is to be conducted** | Inselspital, Department of Infectious Diseases |
| **Head of the study at the study site** | Dr. med. Bernard Surial |
| **Participant**<br>Last name and first name (please print):<br>Date of birth: | |

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- I have received verbal and written information about the study from the study doctor whose signature appears below.
- The study doctor has explained the purpose, the course and the risks of the study.
- I am taking part in the study of my own free will.
- The study doctor explained to me what possible standard treatments are available outside of the study.
- I have had enough time to make my decision. I can keep the written information, and I will receive a copy of my written informed consent form.
- I am free at any time to stop taking part. I do not have to explain why. Even if I stop taking part, I will still receive my medical treatment. The data and samples collected until then will continue to be stored and evaluated as part of the study.
- If it is better for my health, the study doctor may exclude me from the study at any time.
- I have understood that my data and samples will only be passed on in coded form. The sponsor guarantees that data protection in accordance with Swiss standards will be observed.
- In the event of results and/or incidental findings that affect my health directly, I will be informed.
- My GP may share data from my medical history that are important for the study with the study doctor. This also applies to other doctors treating me.
- The competent specialists employed by the sponsor, the Ethics Committee and the medicinal product authority Swissmedic may view my uncoded data for inspection purposes. All of these individuals are bound by medical confidentiality.
- I know that the sponsor has taken out an insurance policy. This insurance policy pays if I sustain an injury – but only if the injury is directly associated with the study.

- **Consent for two in-depth interviews (each 60 to 90 minutes long):**
  ☐ YES ☐ NO

| Place, date | Signature of the participant |
|---|---|
| | |

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**Confirmation of the study doctor:** I hereby confirm that I have informed this participant of the nature, significance and scope of the study. I affirm that I shall fulfil all of my obligations in connection with this study in accordance with Swiss law. If at any point during the conduct of the study I learn of aspects that could influence the willingness of the participant to take part in the study, I will inform him/her of this immediately.

| Place, date | Last name and first name of the study doctor (please print)<br><br>Signature of the study doctor |
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**Informed consent form for the further use of data and samples in coded form**

This informed consent does not affect your personal participation in a study. "Further use" means that data and samples can be stored beyond the time of your study participation and used in coded form for further research. This may mean, for example, that a blood sample and corresponding laboratory values from you are statistically analysed together with a large number of other values or new examinations are carried out on them.

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| **BASEC number:** | 2023-01060 |
| **Study title:** | Booster-free antiretroviral therapy for persons living with HIV and multidrug resistance: A multi-centre multi-stage randomized trial (“B-Free”) |
| **Layperson title:** | Booster-free HIV therapy for persons with pre-existing HIV resistance |
| **Participant:**<br>Last name and first name (please print):<br>Date of birth: | |

- I consent to my coded data and samples from this study being used for further medical research. The samples will be stored in a biobank. They will then be available for an in-definite period of time for other future research projects.
- I have understood that the samples are coded and the key will be stored securely.
- The data may be analysed here and abroad and stored in a database here or abroad. The samples may be examined here or abroad and stored in a biobank. Research insti-tutions abroad must observe the same data protection standards as applicable in Switzerland.
- I am making this decision of my own free will, and I can withdraw this decision at any time. If I withdraw, all of my data will be anonymised and my samples will be destroyed. I only have to inform my study doctor and do not need to justify this decision.
- Normally, all data and samples will be assessed as a whole. If a result randomly appears that is very important for my health, I will be contacted.

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| | |
|---|---|
| Place, date | Signature of the participant |

**Confirmation of the study doctor:** I confirm that I have informed the participant of the nature, significance and scope of the further use of samples and data.

| | |
|---|---|
| Place, date | Last name and first name of the study doctor (please print)<br><br>Signature of the study doctor |