

11TH EDITION

DECEMBER 10-13, 2024

HIV PERSISTENCE DURING THERAPY

Reservoirs & Eradication Strategies Workshop



Changes in the composition of HIV-1 reservoir of PWH on ART and dasatinib

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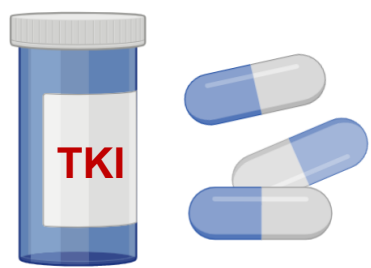
www.hiv-persistence.com

CONFLICTS OF INTEREST

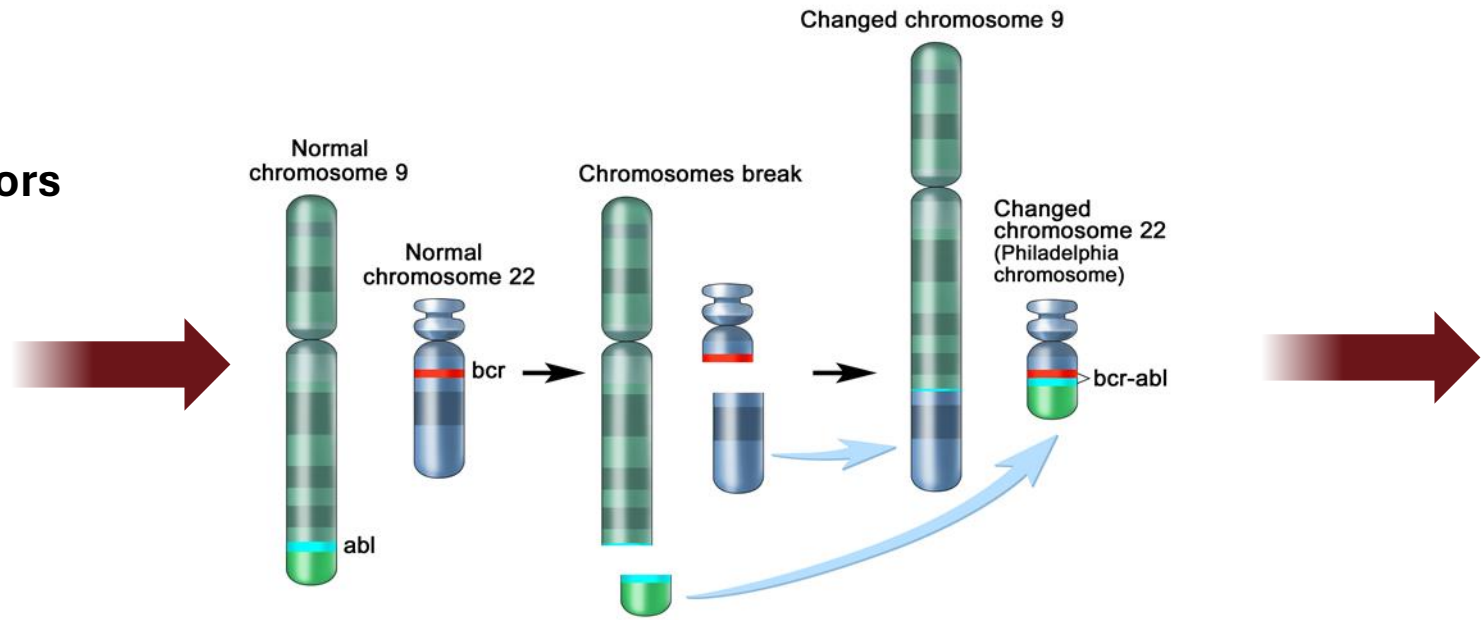
We have no conflicts of interest to disclose

BACKGROUND

Tyrosine Kinase Inhibitors



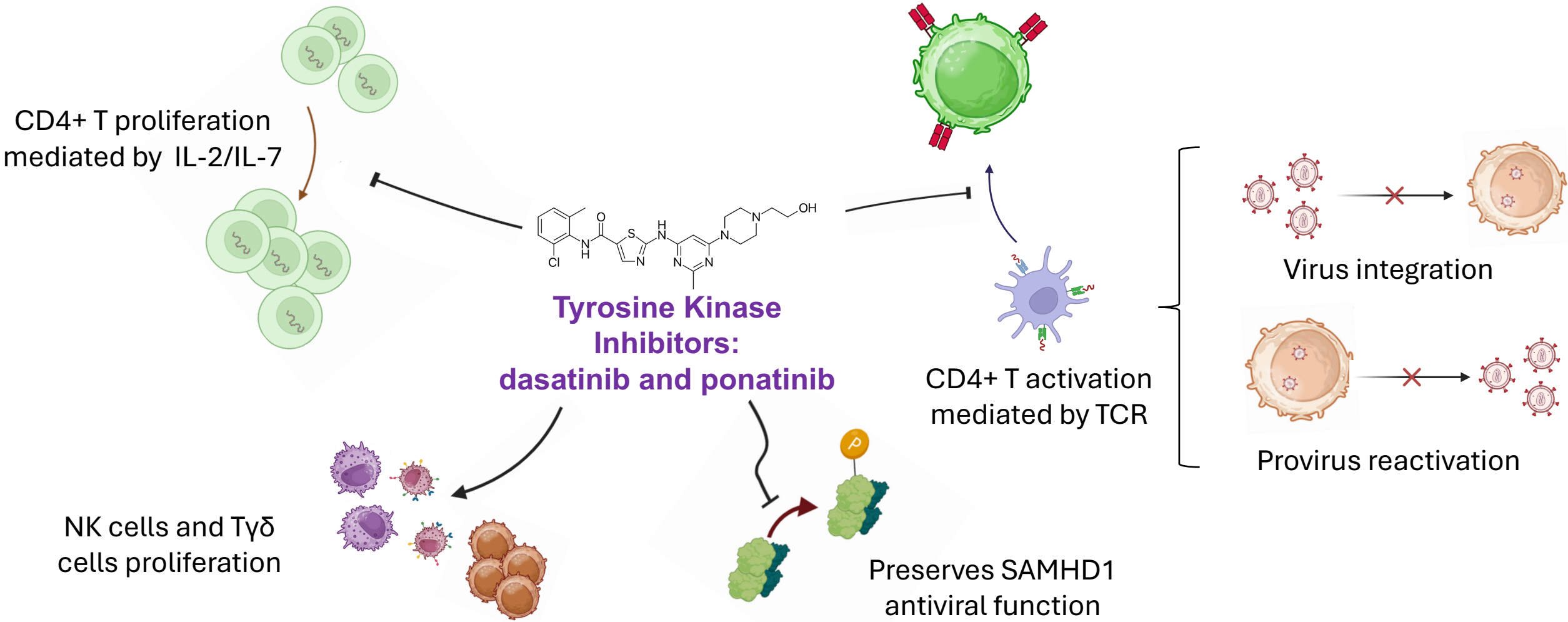
- Imatinib
- Nilotinib
- Bosutinib
- Dasatinib
- Ponatinib



Chronic myeloid leukemia (CML)

**Anti-HIV-1
effects?**

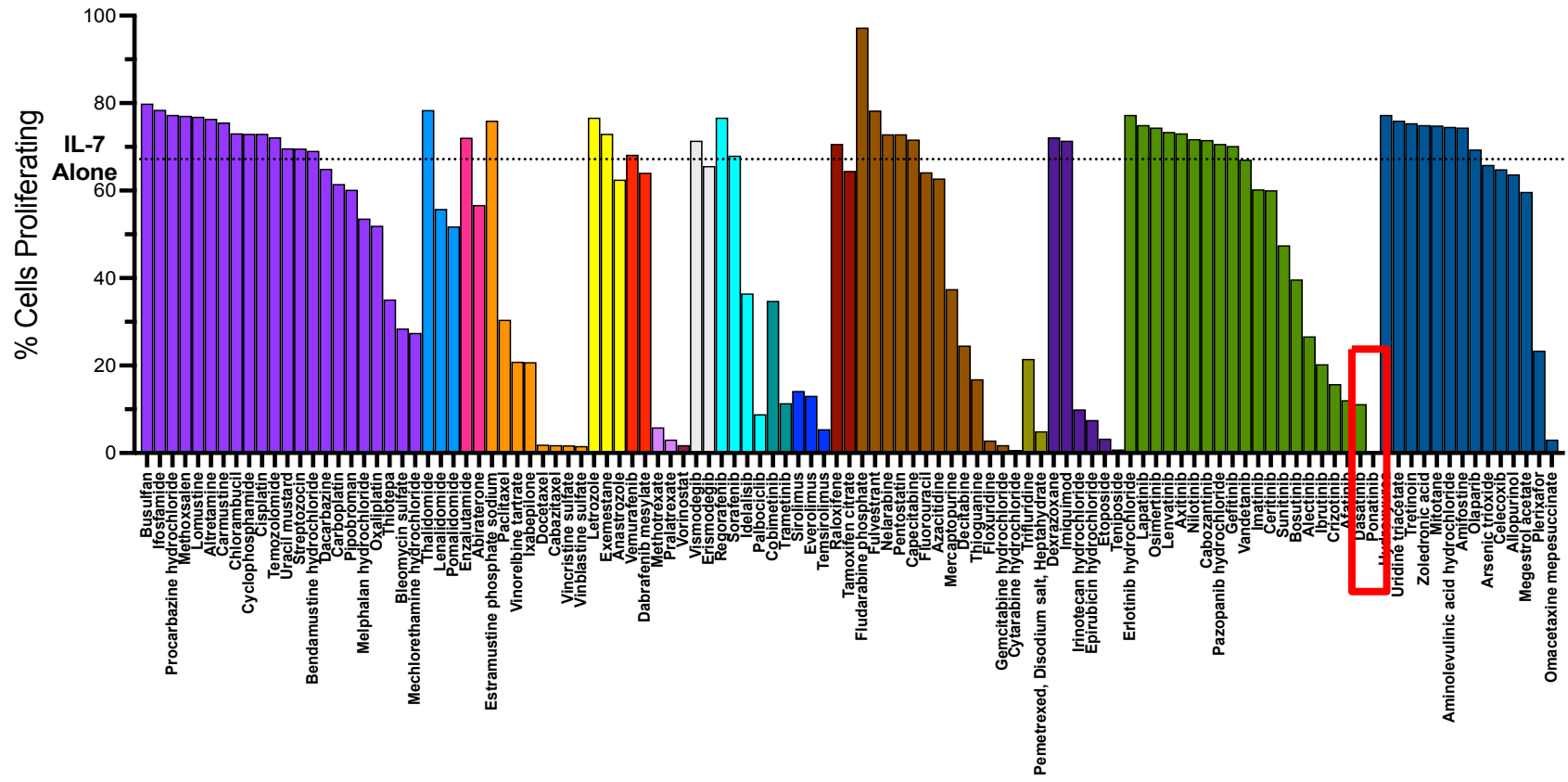
BACKGROUND



Bermejo et al., *Biochem Pharmacol.* 2018 Oct;156:248-264

BACKGROUND

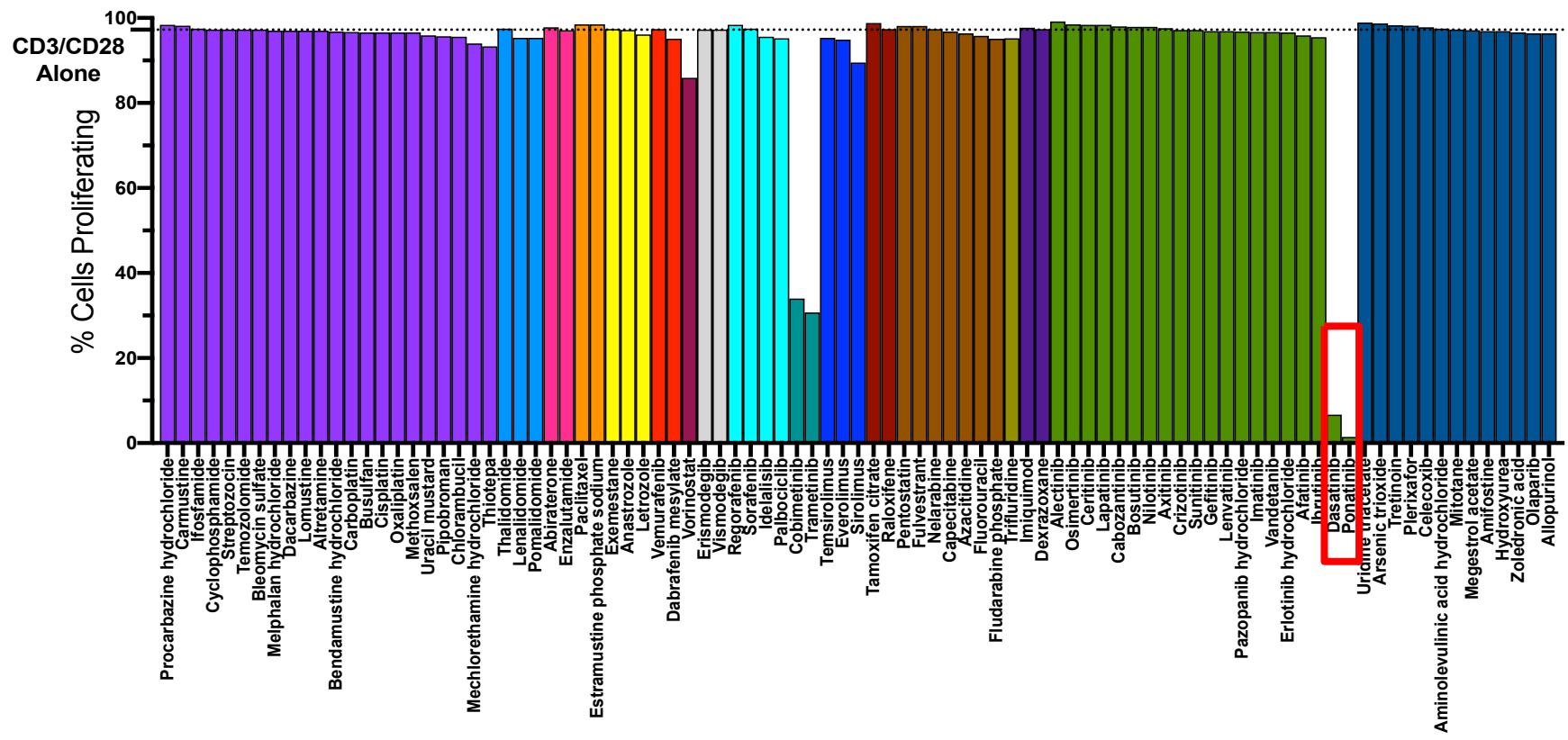
FDA approved anti-cancer drugs screened for their antiproliferative effect against homeostatic (IL-7 stimulated) proliferation



Innis et al., Biochem Pharmacol. 2021 Oct 26:114816

BACKGROUND

FDA approved anti-cancer drugs screened for their antiproliferative effect against antigen-driven (aCD3/aCD28 stimulated) proliferation

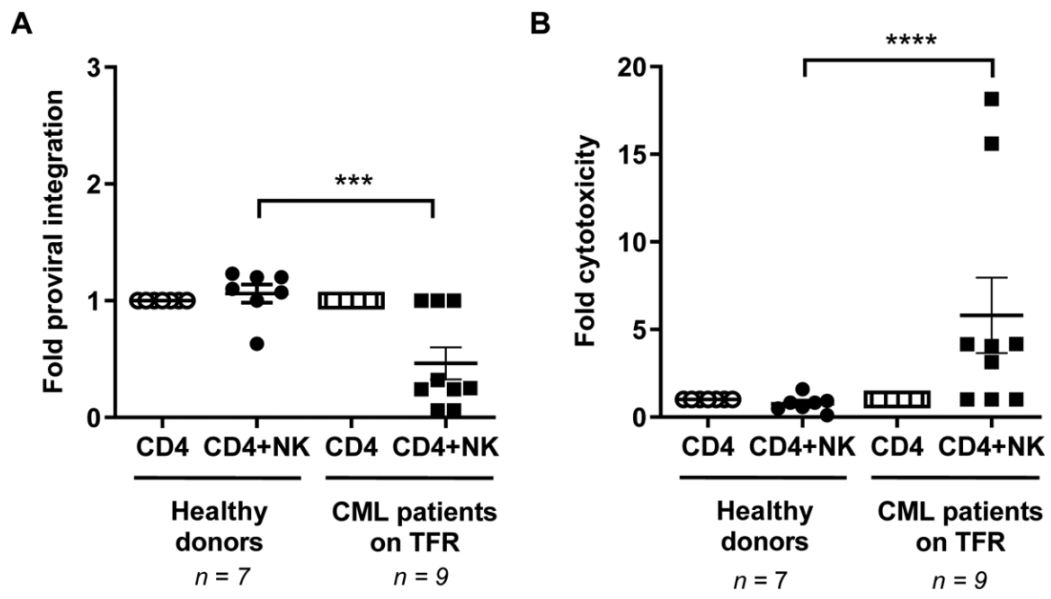


Innis et al., Biochem Pharmacol. 2021 Oct 26:114816

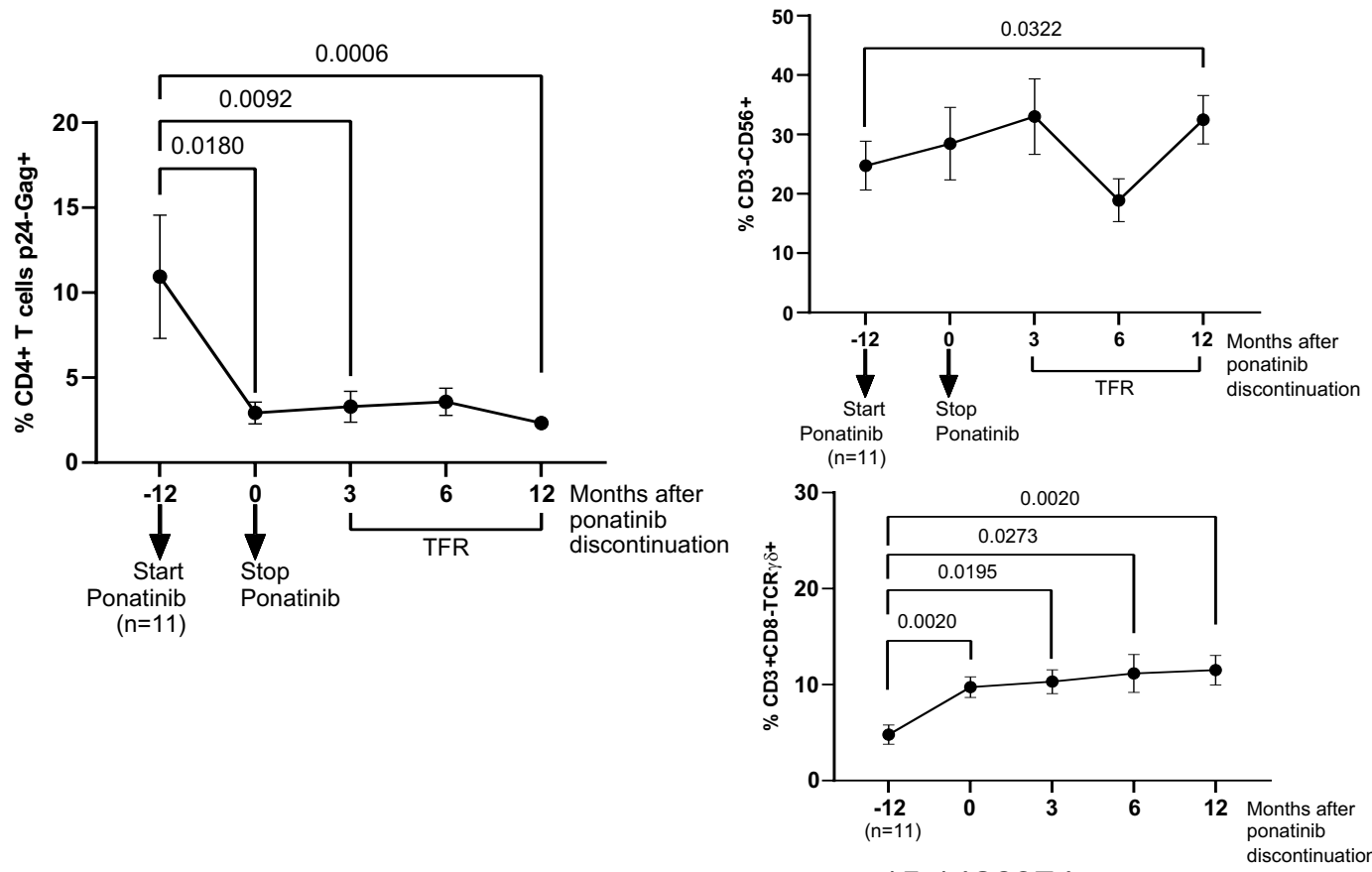
BACKGROUND

CD4+ T cells from individuals with CML that withdrew treatment with TKIs more than 1 year ago are resistant to HIV infection

CD4+ T cells from individuals with CML that withdrew treatment with TKIs more than 1 year ago are resistant to HIV infection



Vigón et al., *Biochem Pharmacol.* 2020 Dec;182:114203

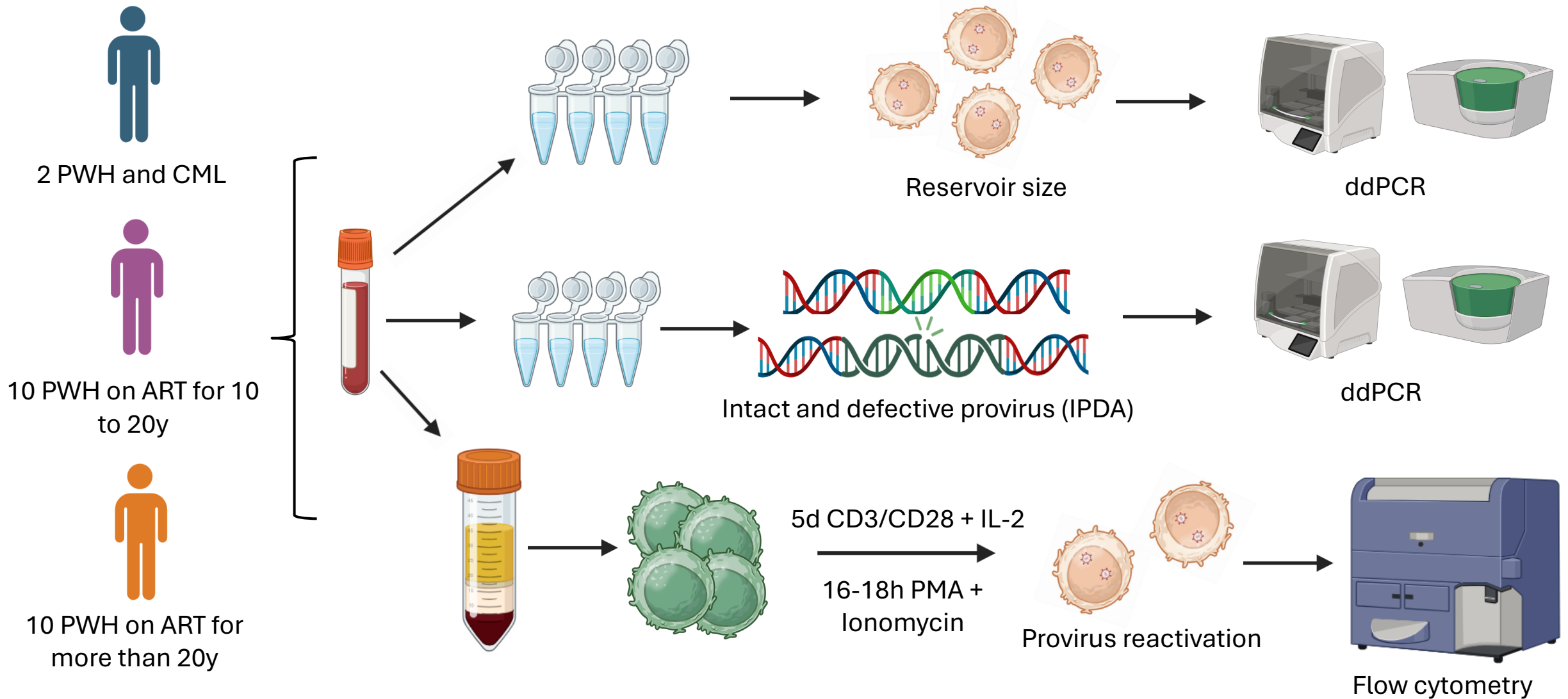


Manzanares et al., *Front Pharmacol.* 2024 Sept; 15:1426974

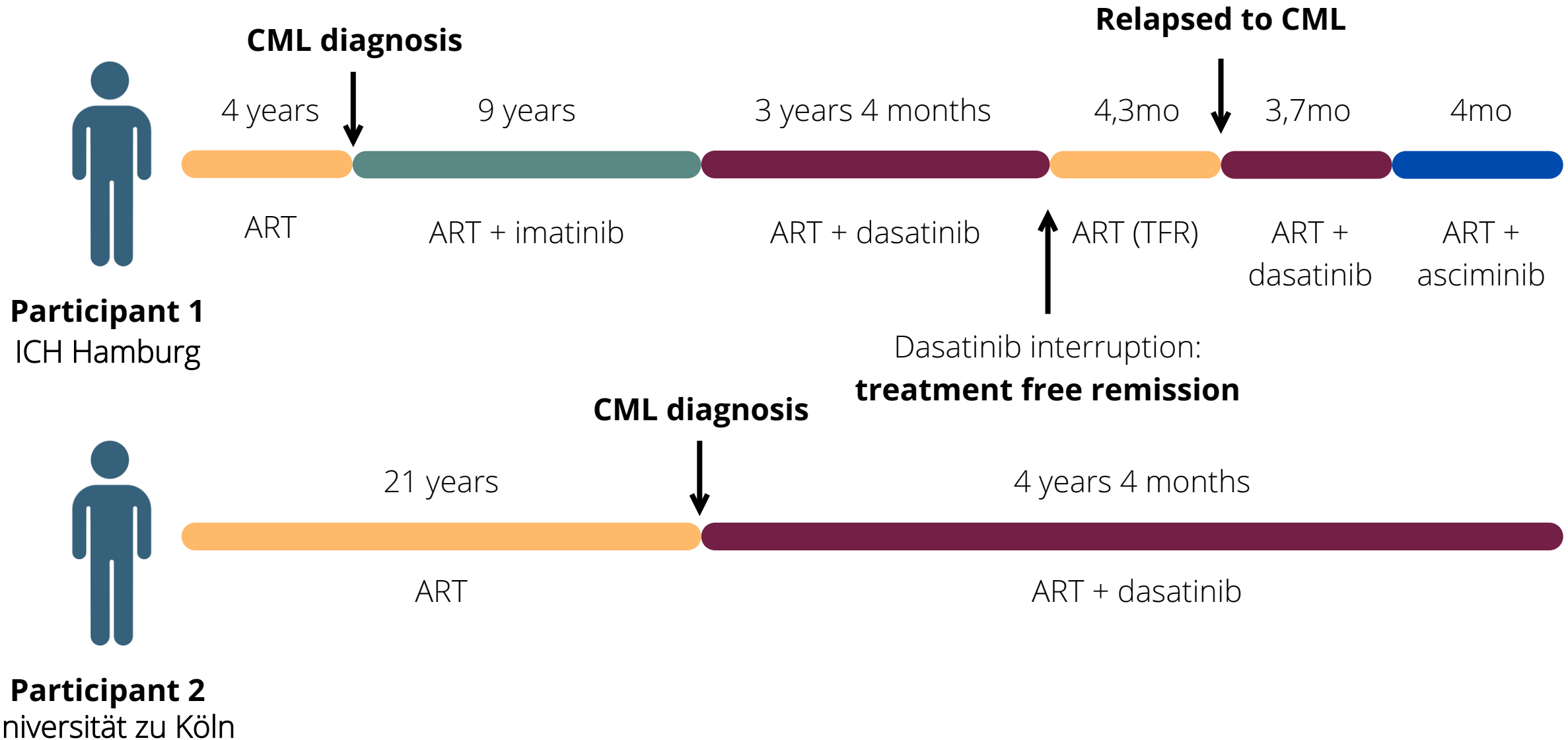
OBJECTIVES

To evaluate the reservoir size, composition and reactivation in two PWH on ART who afterwards developed CML and started long-term treatment with the tyrosine kinase inhibitor dasatinib.

STUDY DESIGN



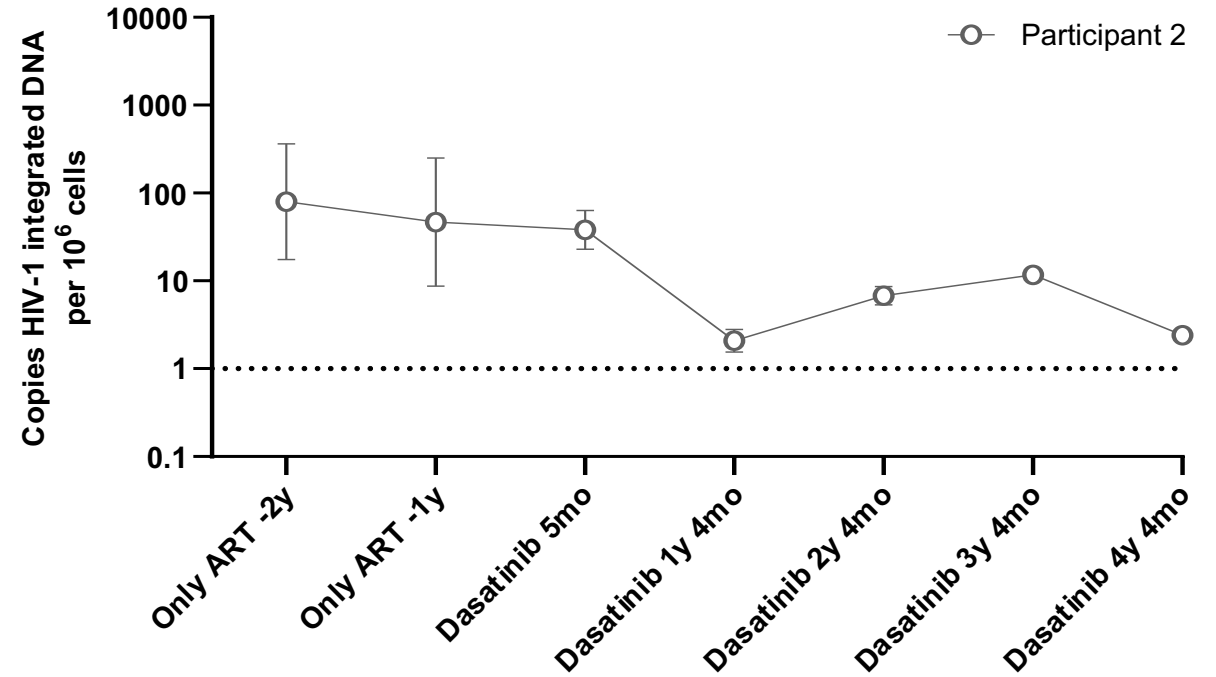
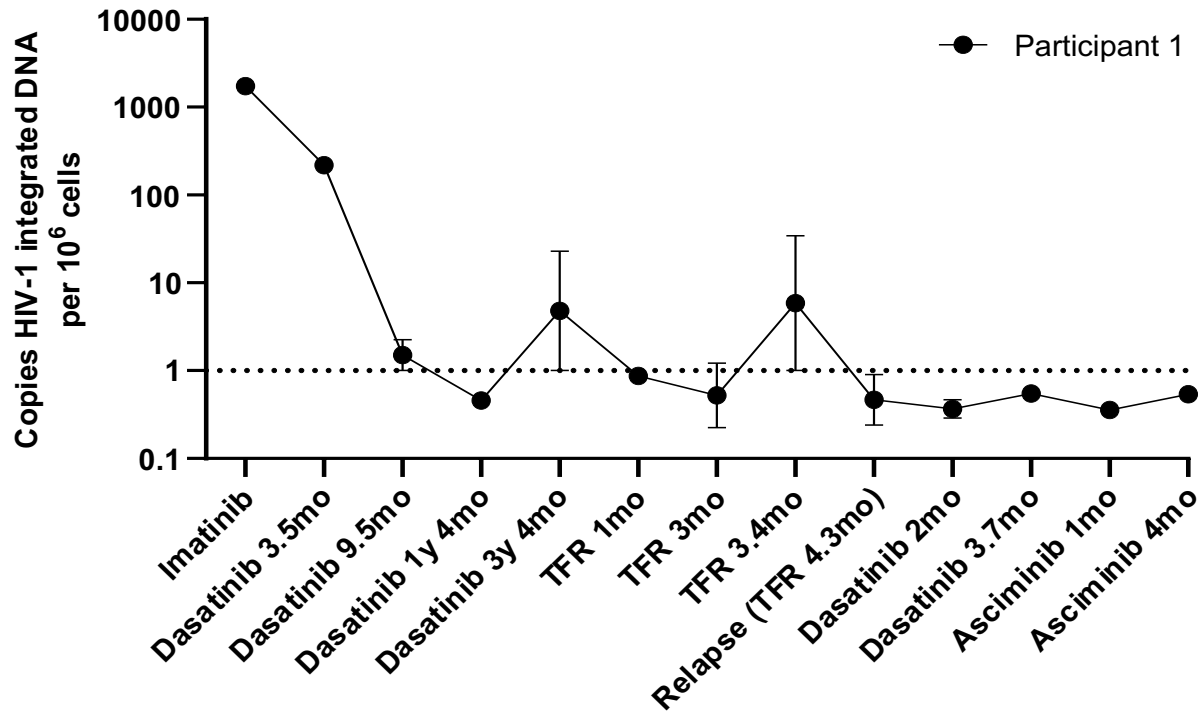
STUDY DESIGN



CLINICAL DATA

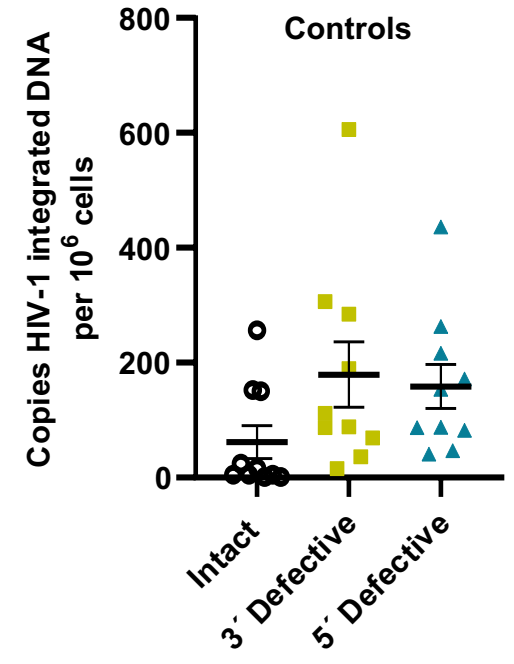
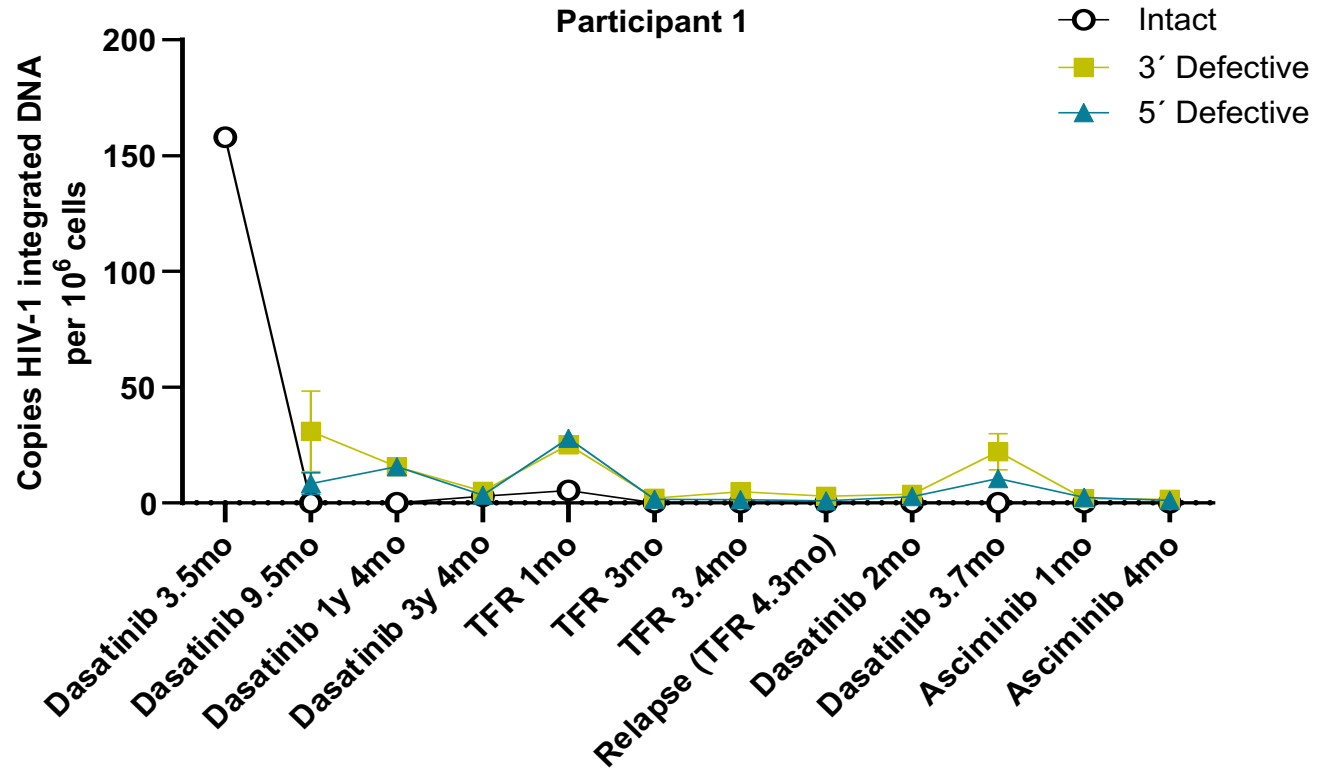
	Participant 1	Controls for participant 1 (n=10)	Participant 2	Controls for participant 2 (n=10)
Age, median (IQR)	46	47.5 (41-52.5)	58	58 (54-64)
Male gender, n (%)	1 (100)	8 (80)	1 (100)	7 (70)
Age at HIV-1 diagnosis, median (IQR); years	29	32 (24.75-40.5)	33	30.5 (24.5-37.8)
Time of HIV-1 infection, median (IQR); years	17	15 (12.75-19)	25	29.5 (23.8-32.3)
Time on ART, median (IQR); years	17	14.5 (12-17.5)	25	28 (22-31.5)
Time on current ART regime, median (IQR); years	2.1	3.24 (1.91-4.43)	5.5	3.79 (1.17-5.37)
Ratio CD4/CD8, median (IQR)	1.6	1.08 (0.8-1.43)	0.36	0.77 (0.54-0.95)
Time from CML diagnosis, years	13	-	4.3	-
Time on dasatinib, years	4.1	-	4.3	-
Previous treatment with TKI (Yes/No, which)	Yes, Imatinib	-	-	-
Time on previous TKI, years	9	-	-	-
Sokal Risk score	UD	-	High	-

RESULTS: Reservoir size



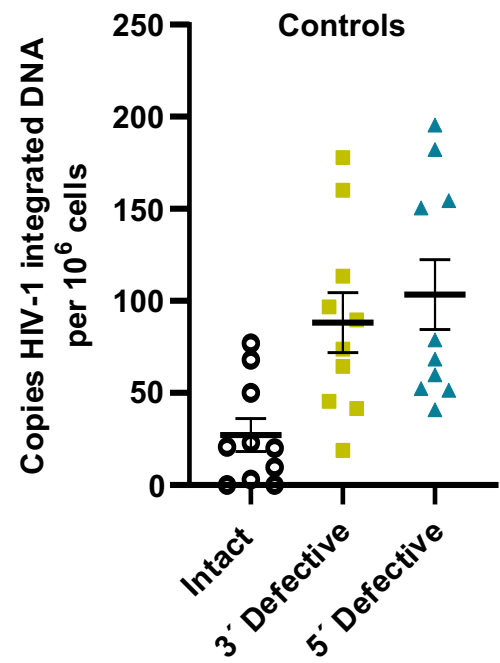
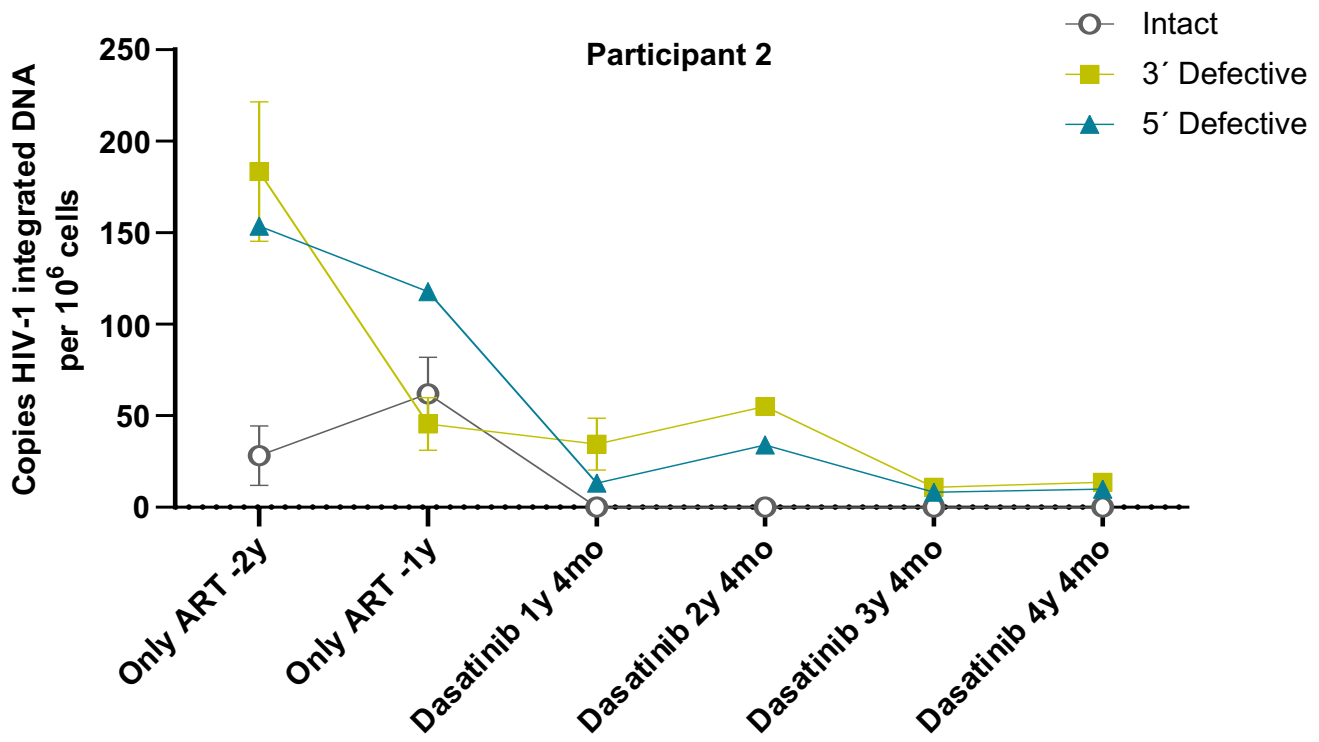
**Dasatinib treatment reduces integrated provirus
in both participants**

RESULTS: IPDA



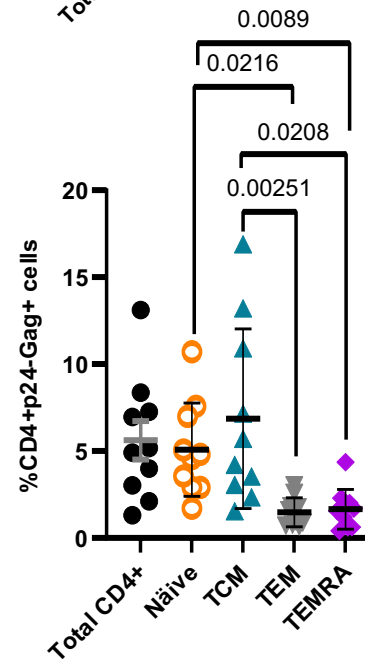
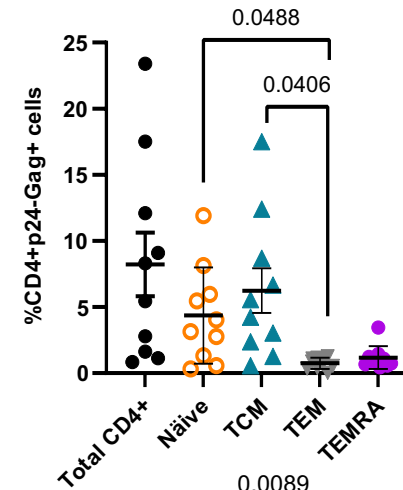
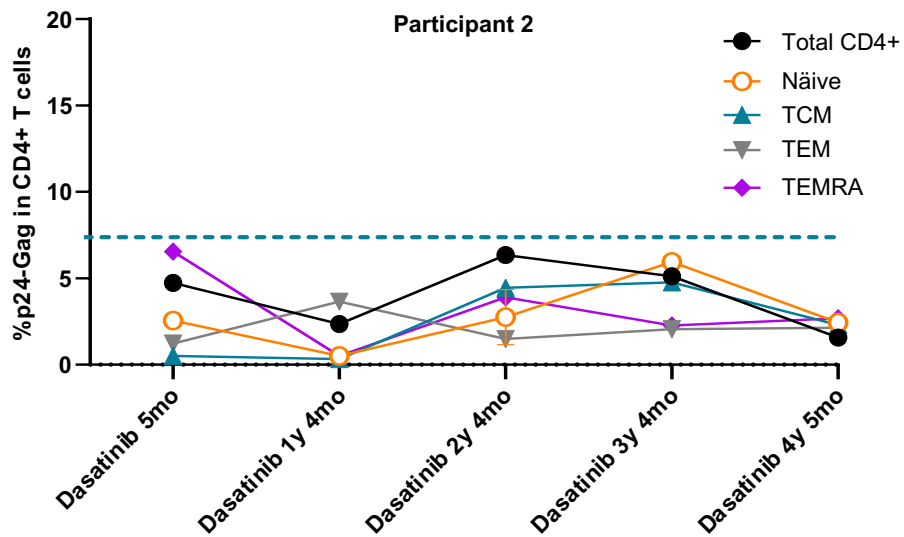
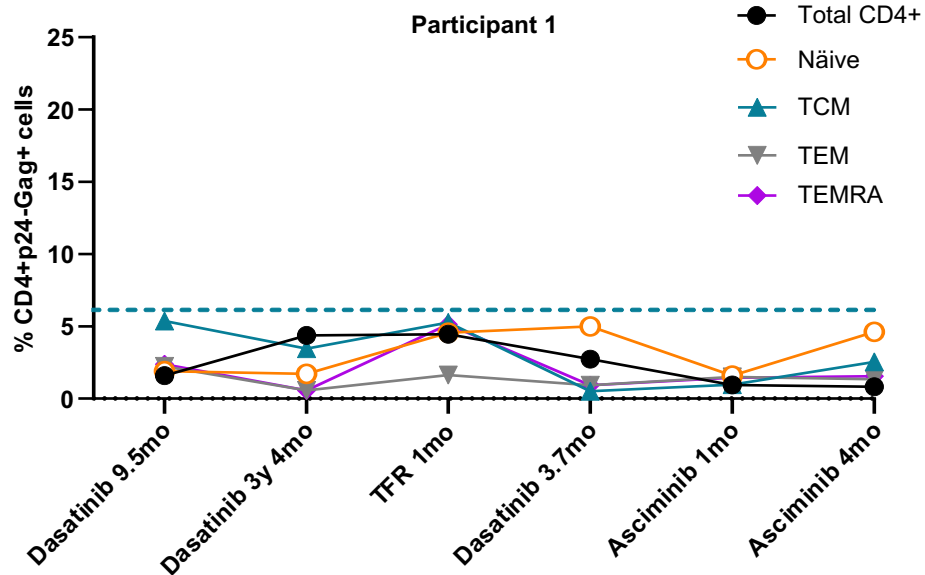
Intact proviruses were undetectable during most of dasatinib treatment, TFR and asciminib

RESULTS: IPDA



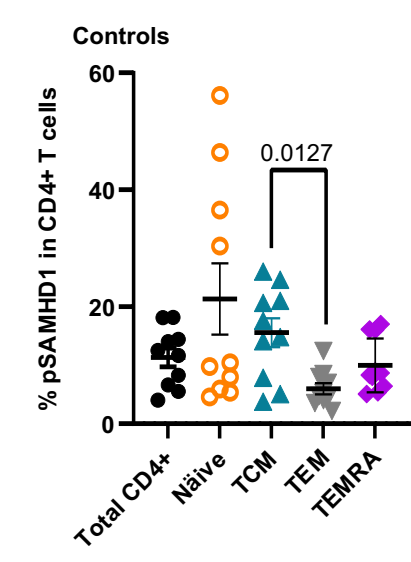
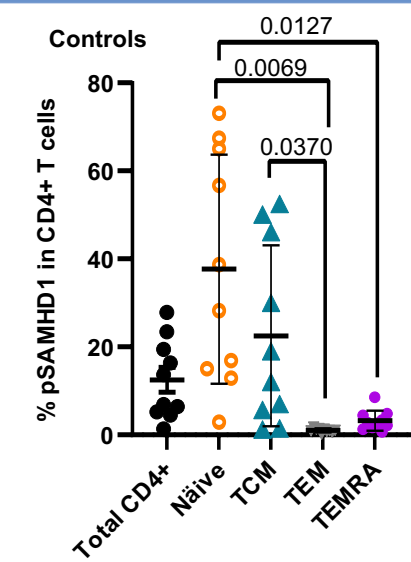
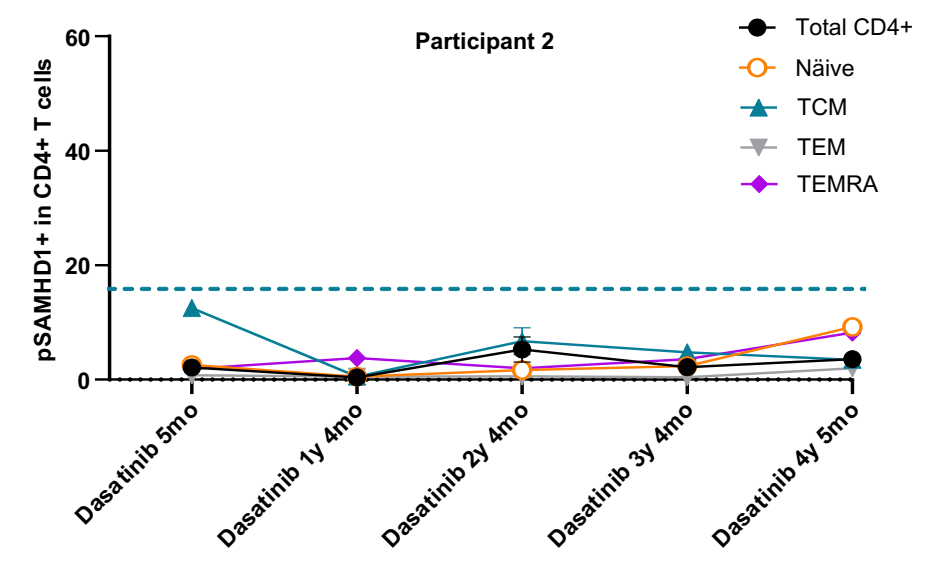
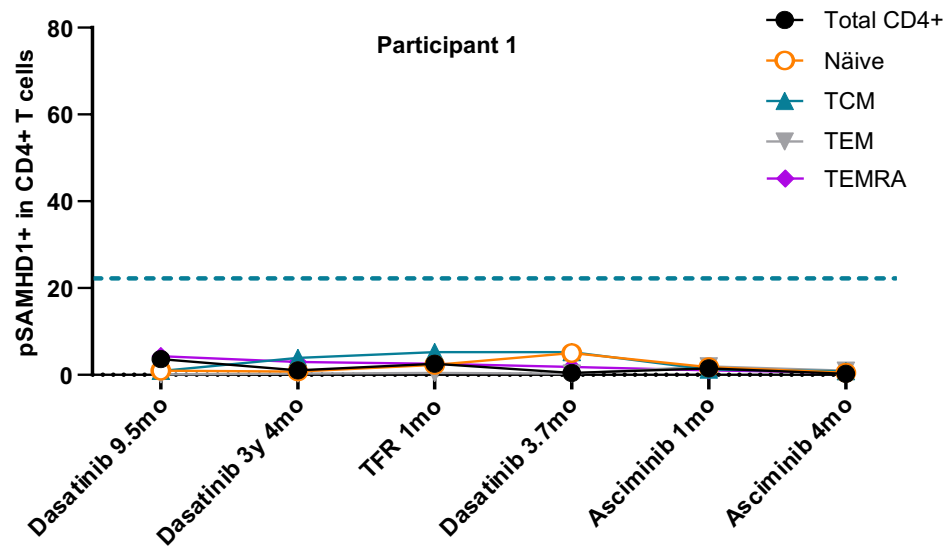
Intact proviruses were undetectable during all dasatinib treatment.

RESULTS: proviral reactivation



Proviral reactivation in both participants was below TCM proviral reactivation of controls

RESULTS: SAMHD1 phosphorylation



SAMHD1 remained in its active form in both participants during all dasatinib treatment

CONCLUSIONS

- Dasatinib treatment changed the reservoir landscape towards a more favorable scenario in which there was a reduction in intact and defective proviruses.
- Detectable p24-gag during proviral reactivation may proceed from defective proviruses.
- SAMHD1 remained in its active form during all dasatinib treatment, keeping its antiviral function that may interfere with proviral reactivation and HIV-1 integration
- Treatment with ART and low-dose dasatinib might help in reducing reservoir size and in controlling its reactivation, improving the possibilities for a functional cure in people with chronic HIV-1 infection.

ONGOING CLINICAL TRIALS

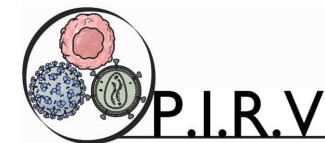
- **Phase II clinical trial NCT05527418 PI José María Miró and Juan Ambrosioni (Barcelona, Spain):** 24 ART-naïve individuals with recent HIV-1 infection, randomized into two arms to receive 4 weeks of 70 mg/day dasatinib or placebo.
- **NIH ACTG trial A5413, PI Adam Spivak (Utah):** randomized clinical trial that will administer dasatinib or placebo for 12 weeks to PWH (n=18) with chronic infection
- **Phase II clinical trial NCT05780073 PI José Moltó, Beatriz Mothe (Badalona, Spain):** PWH on suppressive ART >3 years (n=60) will be randomized into two arms to receive ART and dasatinib 70 mg daily or placebo for 24 weeks.
- **Clinical trial ICI24CIII/00003 Mayte Coiras (Madrid, Spain):** Evaluation of the safety and efficacy of dasatinib to reduce HIV-1 reservoir, inflammation and senescence in people with HIV on long-term antiretroviral treatment.

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Equipo de patogenia inmune
y reservorio viral



PIRV_isciii

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To all participants!