# PERSISTENT ANTIVIRAL EFFECT INDUCED BY TYROSINE KINASE INHIBITORS

00283

**Lorena Vigón**[1], Sara Rodríguez-Mora[1], Elena Mateos[1], Valentín García[2], Juan Ambrosioni[3], Virginia Sandonís[4], Guiomar Bautista[5], Pilar Pérez-Romero[6], José Alcamí[1,3], Juan Luis Steegmann[7], José M Miró[3], Vicente Planelles[8], María Rosa López Huertas[1], Mayte Coiras[1]

[1] AIDS Immunopathology Unit, National Center of Microbiology, Instituto de Salud Carlos III, Madrid, Spain; [2] Hematology Service, Hospital Universitario Ramón y Cajal, Madrid, Spain; [3] Infectious Diseases Service, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Hospital Clínic, University of Barcelona, Barcelona, [4] Infectious Diseases Service, Instituto de Investigación Hospital 12 de Octubre, Universidad Complutense, Madrid; [5] Hematology Service, Hospital Universitario Puerta de Hierro, Madrid, Spain; [6] Viral Infections and Immunity, National Center of Microbiology, Instituto de Salud Carlos III, Madrid, Spain; [7] Hematology Service, Hospital Universitario La Princesa, Madrid, Spain; [8] Division of Microbiology and Immunology, Department of Pathology, University of Utah School of Medicine, Salt Lake City, Utah, USA

## BACKGROUND

- Tyrosine kinase inhibitors (TKIs) are used in clinic to treat chronic myeloid leukemia (CML), They should be taken for life but some patients stop treatment due to antileukemic deep molecular response (DMR)
- Some TKIs may also induce a potent immune response against CMV
- Our group described an inhibition of HIV infection *in vitro* and *in vivo.*
- TKIs activity against HIV:

1. Cytostatic effect and inhibition of cytokine-dependent proliferation, possibly affecting reservoir establishment and replenishment
2. Maintenance of SAMHD1 antiviral activity
3. Sustained cytotoxic activity to control the growth of cancerous cells

## OBJECTIVES

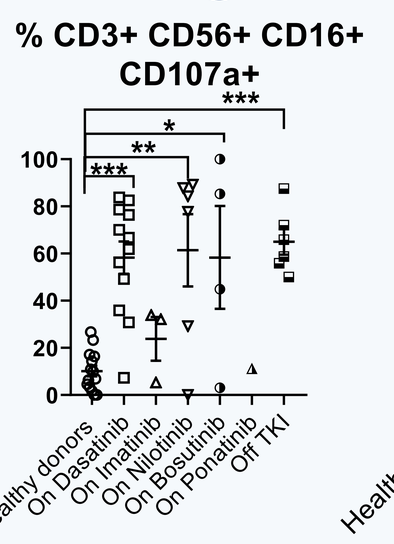
1. To analyze cytotoxic effect in CML patient cell population during TKI treatment and after withdrawal
2. To determine the susceptibility to HIV infection of CD4 T cells from CML patient off TKI treatment

# A possible transient use of Tyrosine Kinase Inhibitors in HIV-infected patients to establish a persistent antiviral activity

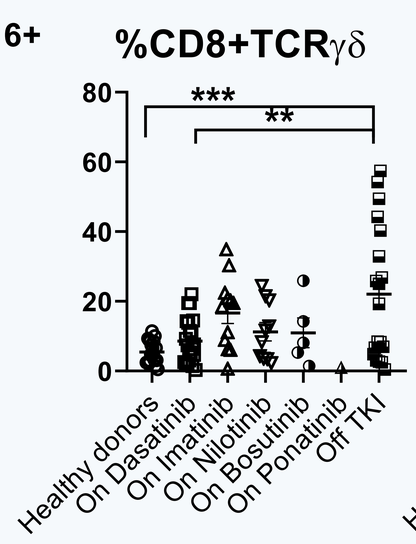
## RESULTS

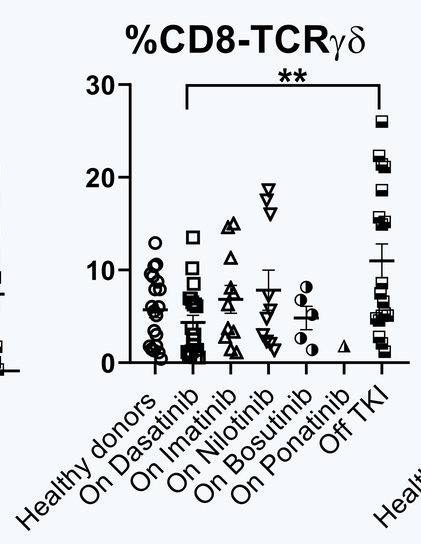
1. **Active NK cells CD56+CD16+CD107a+ were increased >6-fold in patients on treatment with all TKIs, except Imatinib, compared to control. This population remained >5-fold enhanced after withdrawal**
2. **CD8±TCRγδ lymphocytes were increase >2-fold in patients on treatment and remained >3-fold greater in patient off treatment**
3. **Synthesis of IFNγ in response to *in vitro* CMV pp65 was increased >2-fold in CD8+CD69+ T cells from patients off treatment**
4. ***In vitro* treatment with TKI Dasatinib and IL-15 for 5 days increased >2.5 fold the IFNγ secretion from NKs**
5. **PBMCs from patient off treatment showed <12-fold proviral integration after *in vitro* infection**

1

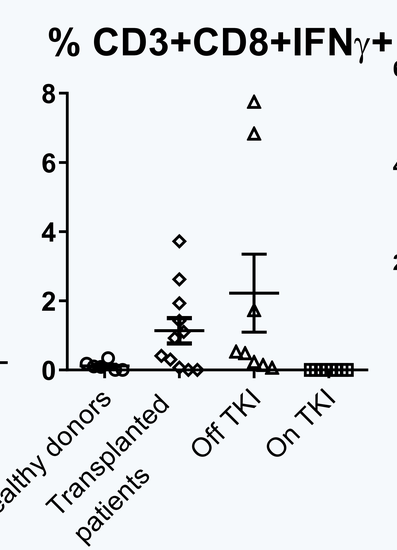



2

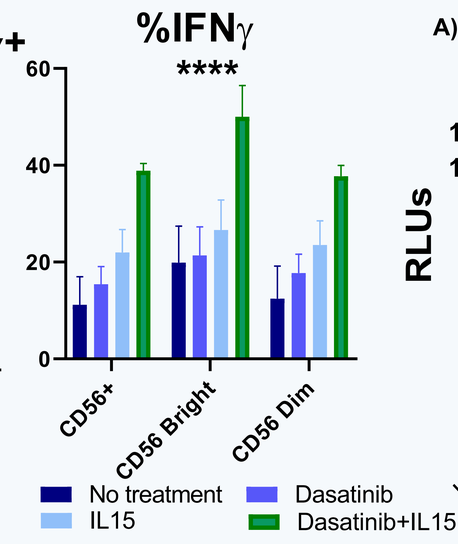


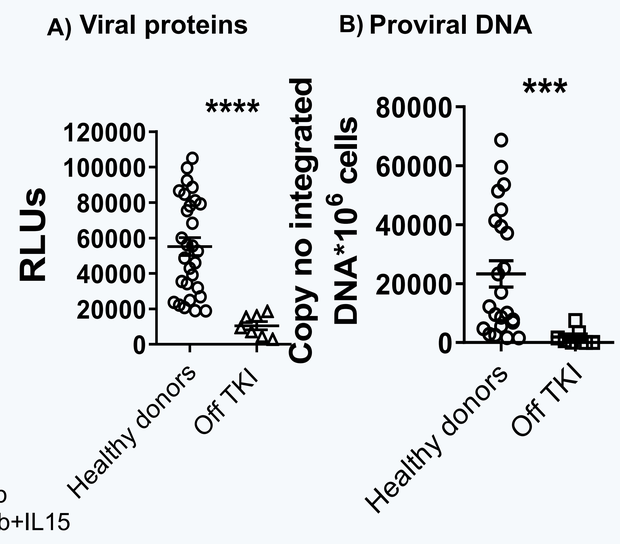

3




4




5




## METHODS

- PBMCs from:
  - CML patients on TKI treatment for avg 3.8±0.5y (Dasatinib n=20; Imatinib n=11; Nilotinib n=9; Bosutinib n=5; Ponatinib n=1)
  - CML patients Off TKI treatment for avg, 2.3±0.3y due to DMR (last TKI:Dasatinib n=4; Imatinib n=7; Nilotinib n=6)
  - Healthy donors (n=20)
- PBMCs and IFNγ synthesis analyzed by flow cytometry
- Proviral integration was analyzed by Alu-qPCR

## CONCLUSIONS

- TKIs induce mechanisms with antiviral activity that may be used against HIV infection
- Populations of active NK cells and IFNγ–secreting CD8 cells may persist in CML patients even after treatment withdrawal, as well as CD4 cells resistant to HIV infection

## ACKNOWLEDGEMENTS

Thanks to the patients