NK cells are preserved by early ART in HIV-infected children with lower reservoir

Sonia Zicari[1], Margherita Doria[1], Sara Domínguez-Rodríguez[2], Nicola Cotugno[1], Alfredo Tagarro[2], Pablo Rojo Conejo[2], Eleni Nastouli[3], Kathleen Gartner[3], Nigel Klein[4], Caroline Foster[5], Savita Pahwa[6], Anita De Rossi[7], Carlo Giaquinto[7], Paolo Rossi[1], Paolo Palma[1], for the EPIICAL consortium*

[1]Bambino Gesù Children's Hospital, Rome, Italy, [2]Hospital Universitario 12 de Octubre, Madrid, Spain, [3]Great Ormond Street NHS Foundation Trust, London, UK, [4] London School of Hygene & Tropical Medicine, London, UK, [5] Imperial College Healthcare NHS Trust, London, UK, [6] University of Miami Miller School of Medicine, Miami, FL, USA, [7]University of Padova, Padova, Italy

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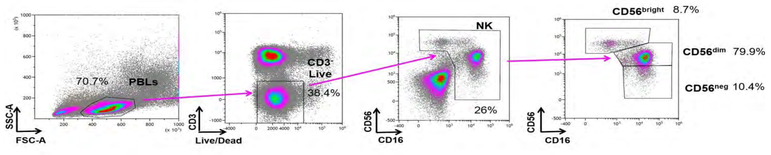
Background

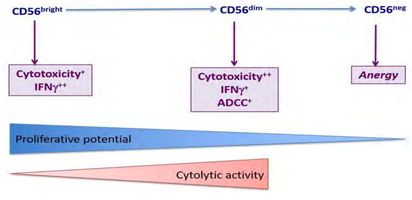
HIV infection causes pathological changes in the natural killer (NK) cell compartment that can be only partially restored by antiretroviral therapy (ART). We studied NK cells phenotype and function in perinatally HIV-infected children (PHIV) enrolled in a multicenter cross-sectional study (CARMA, EPIICAL consortium), who started ART at different ages (early treated, ET ≤ 6 months; late treated, LT > 6 months to 2 years).

Methods

40 PHIV who started ART< 2 years of life and had undetectable viremia (< 50 HIV copies/mL) for at least 5 years, were enrolled in 7 European research centers. HIV-1 DNA copies/10^6 PBMCs were measured by real-time PCR. NK cells were analyzed by flow cytometry for % of $CD56^{bright}$, $CD56^{dim}$, $CD56^{neg}$ subsets, receptor expression, maturation profile, degranulation capacity (CD107a expression) in the presence or not of K562 cells, and IFNγ production after stimulation or not with a cocktail of cytokines. Data were analyzed by Spearman correlation plots and multivariable Poisson regression model (adjusted for baseline %CD4 and RNA HIV viral load and for age at ART start as interaction term, either ET or LT) to explore the association between NK cell parameters and HIV reservoir modulated by age at ART start.

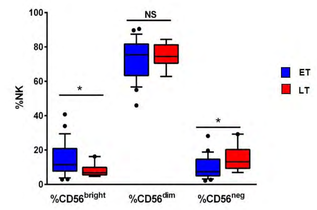
Gating strategy

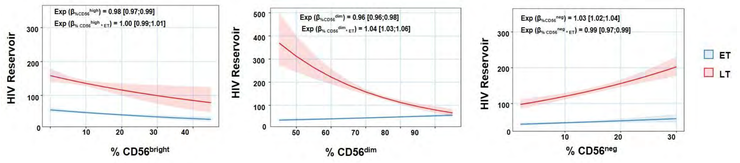


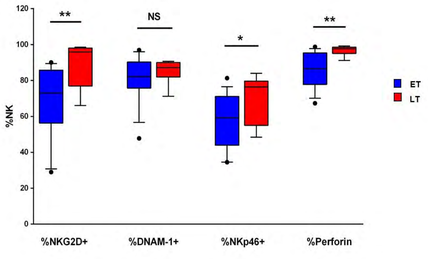


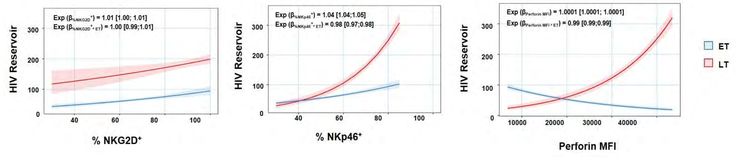
Results

Later treatment in PHIV leads to a shift of NK cells to the anergic $CD56^{neg}$ subset that is associated with an increase of HIV reservoir size. For each 1% increase in $\%CD56^{neg}$, 3% upregulation of HIV reservoir is found and this effect is reduced in ET. LT display a persistent "activated" phenotype (i.e. NKp46+, NKG2D+, high Perforin expression) that is not present in ET: for each 1-unit increase in % of NKG2D+, % of NKp46+ or Perforin mean fluorescence intensity, there is an enrichment of 1%, 4% or 0,01% in HIV reservoir, respectively.

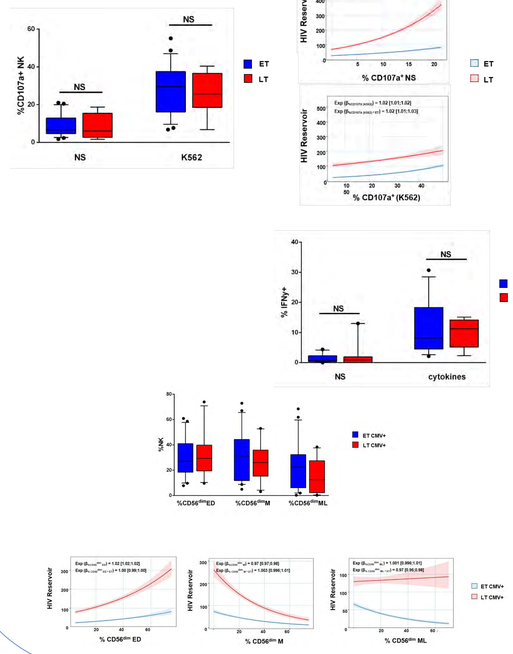








Moreover, %CD107a+ and %IFNγ+ non-stimulated NK cells show a positive association with HIV DNA, and these effects are decreased in ET. Finally, among $CD56^{dim}$ cells, the frequencies of early differentiated and mature cells are associated with HIV DNA in a positive and inverse manner, respectively, whereas these effects were lower in ET.



Conclusions

Our results demonstrate that starting ART as soon as possible in PHIV is important to preserve NK cell features. Notably, we show for the first time that a preserved NK cell compartment in PHIV is associated with lower HIV viral reservoir.

*The EPIICAL consortium

Nigel Klein, **Diana Gibb, Sarah Watters, Man Chan, Laura McCoy, Abdel Babiker** - University College London (UCL) UK; **Anne-Genevieve Marcelin**, **Vincent Calvez** - Université Pierre et Marie Curie (UPMC) France; **Maria Angeles Munoz** - Servicio Madrileño de Salud - Hospital General Universitario Gregorio Marañon (SERMAS-HGUGM) Spain; **Britta Wahren** - Karolinska Institutet (KI) Sweden; **Caroline Foster** - Imperial College Healthcare NHS Trust (ICHT), London, UK; **Mark Cotton**- Stellenbosch University -Faculty of Medicine and Health Sciences(SU) South Africa; **Merlin Robb** - The Henry M. Jackson Foundation for the Advancement of Military Medicine, Maryland, USA; **Polly Claiden** - HIV i-Base (HIViBase) UK; **Deenan Pillay** - University of KwaZulu-Natal Africa Center (UKZN/AC) South Africa; **Deborah Persaud** - Johns Hopkins University (JHU); **Rob J De Boer, Juliane Schröter, Anet J.N. Anelone** - University of Utrecht (UU) Netherlands; **Thanyawee Puthanakit** - Thai Red Cross AIDS-Research Centre (TRCARC) Thailand; **Adriana Ceci**, **Viviana Giannuzzi** - Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) Italy; **Kathrine Luzuriaga** - University of Massachusetts Medical School (UMMS), Worcester, Massachusetts, USA; **Nicolas Chomont** - Centre de Recherche du Centre Hospitalier de l'Université de Montreal – University of Montreal (CRCHUM), Canada; **Mark Cameron** - Case Western Reserve University (CWRU), Cleveland, Ohio, USA; **Caterina Cancrini** - Università degli Studi di Roma Tor Vergata (UNITOV), Italy; **Andrew Yates**, **Louise Kuhn** - Columbia University (COLUMBIA), New York, USA; **Avy Violari, Kennedy Otwombe** - University of the Witwatersrand, Johannesburg (PHRU), South Africa; **Ilaria Pepponi**, **Francesca Rocchi** - Children's Hospital "Bambino Gesu", Rome, Italy; **Stefano Rinaldi** – University of Miami, Miller School of Medicine (UM), Florida, USA; **Alfredo Tagarro** - Hospital 12 de Octubre, Universidad Complutense, Madrid, Spain; **Maria Grazia Lain**, **Paula Vaz** – Fundação Ariel Glaser contra o SIDA Pediátrico (ARIEL), Moçambique; **Elisa Lopez**, **Tacita Nhampossa** – Fundação Manhiça, Mozambique.

Author contact information: sonia.zicari@opbg.net