# Immunosenescence in HIV infection

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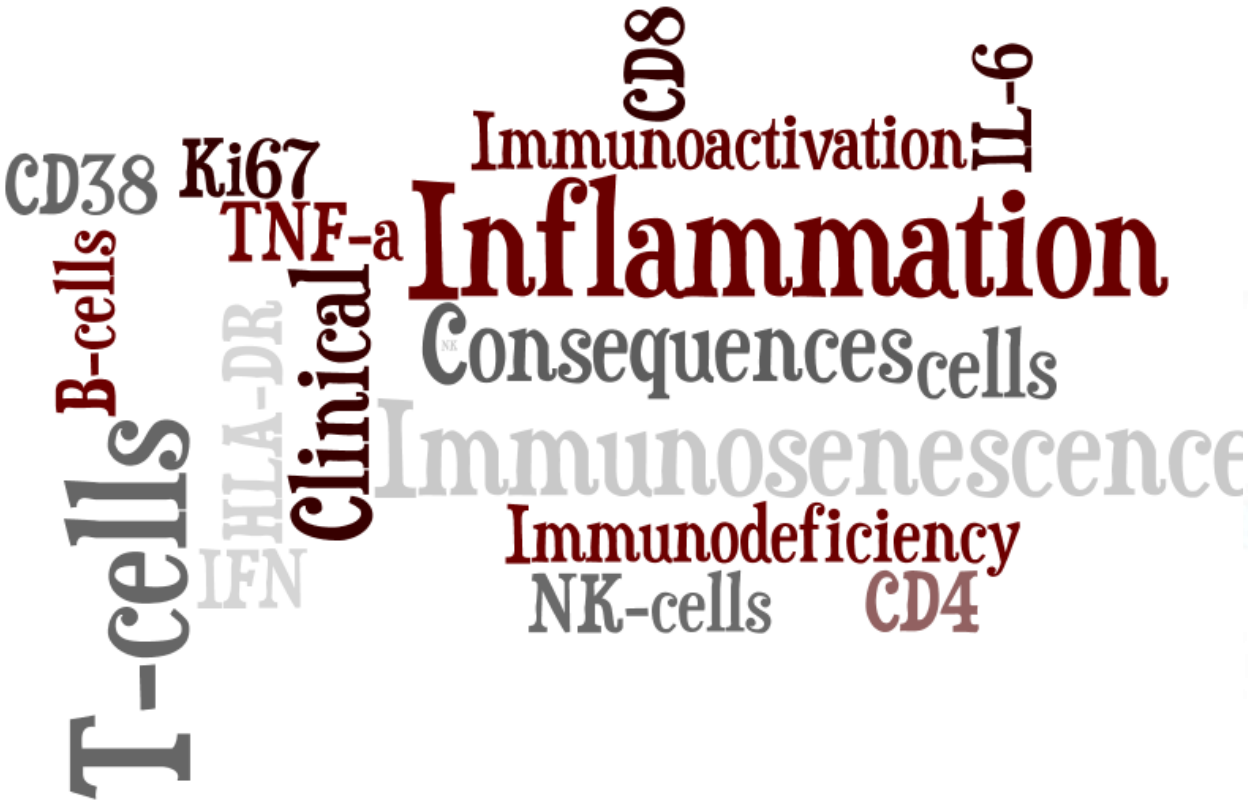
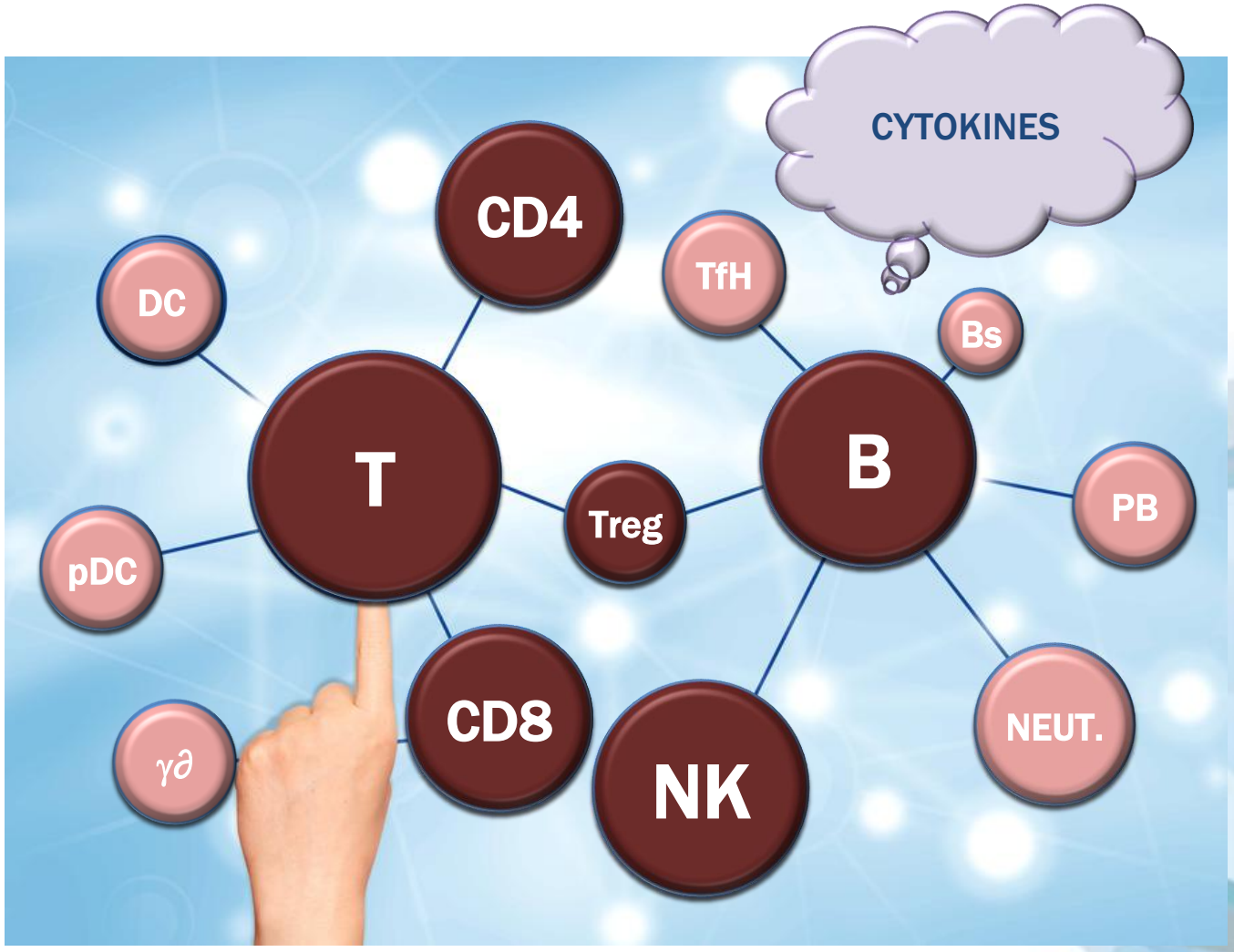
# HIV infection: a double attack to the immune system

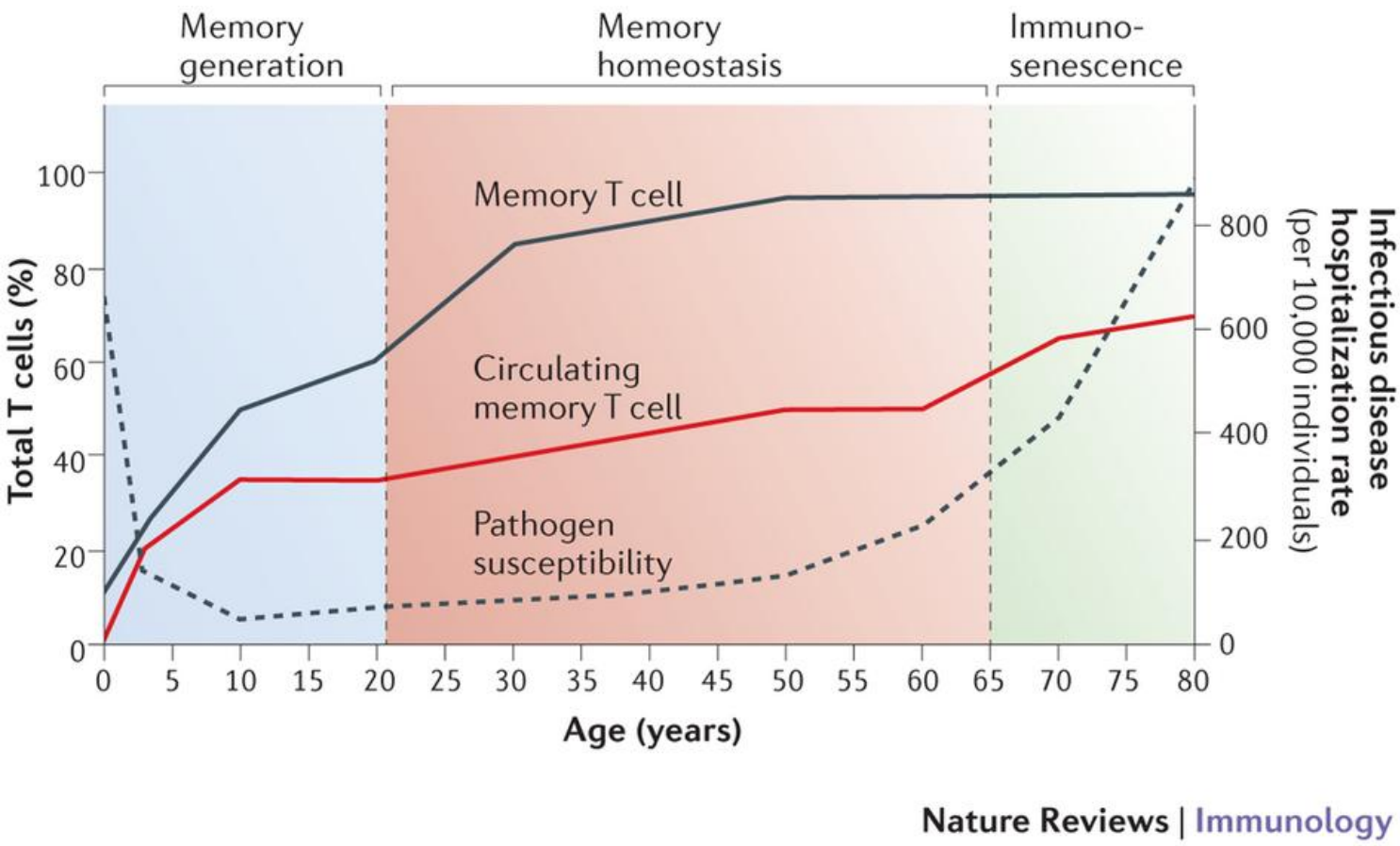


# THE SOCIAL NETWORKS: EVERYTHING IS LINKED

# THE IMMUNE SYSTEM: EVERYTHING IS LINKED

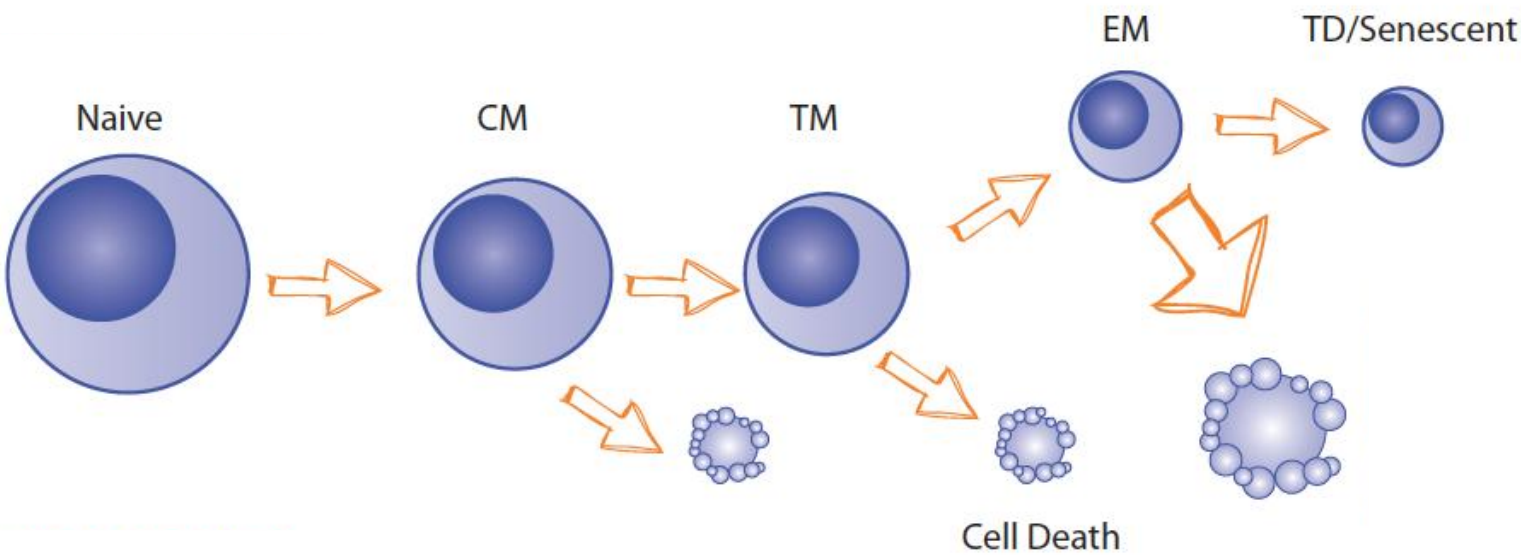


# Immunosenescence. A natural process



# The life and death of a T cell

**Inflammation (inflam-aging)**
**Pathogens: Viruses (CHRONIC CMV), bacteria (MICROBIOTA?)**



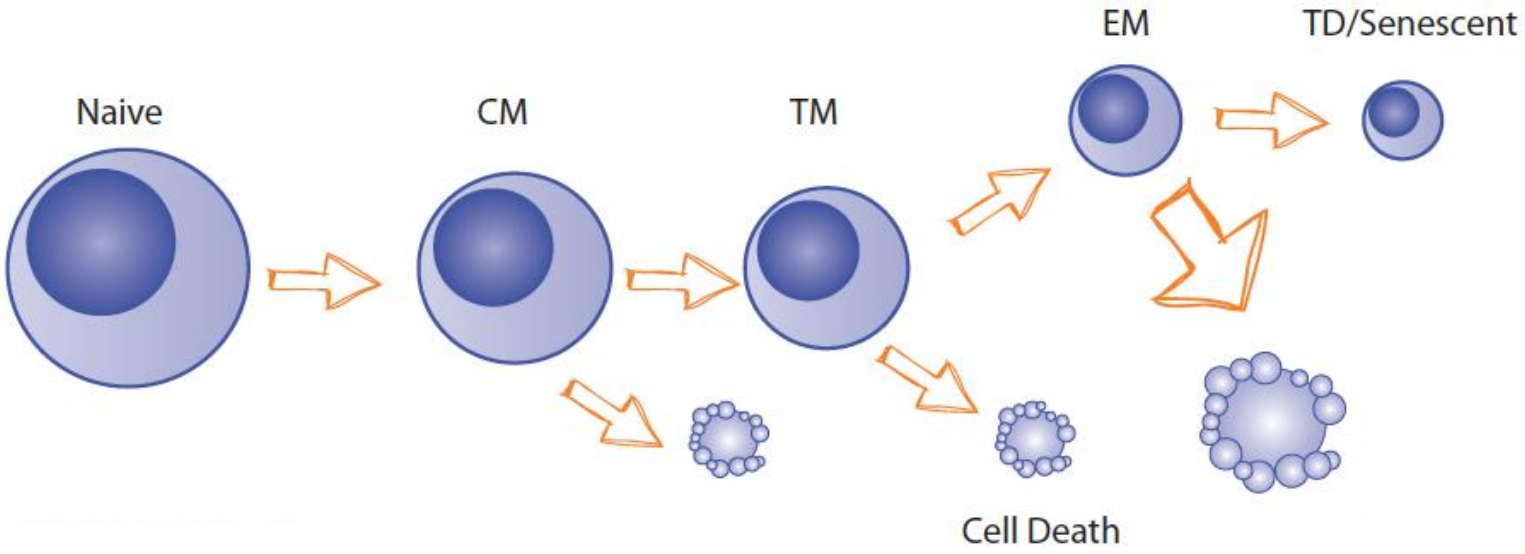
# Immunosenescence. A natural process

Cells undergo a limited number of divisions. This number is controlled by the quality of the chromosome ends (TELOMERS)

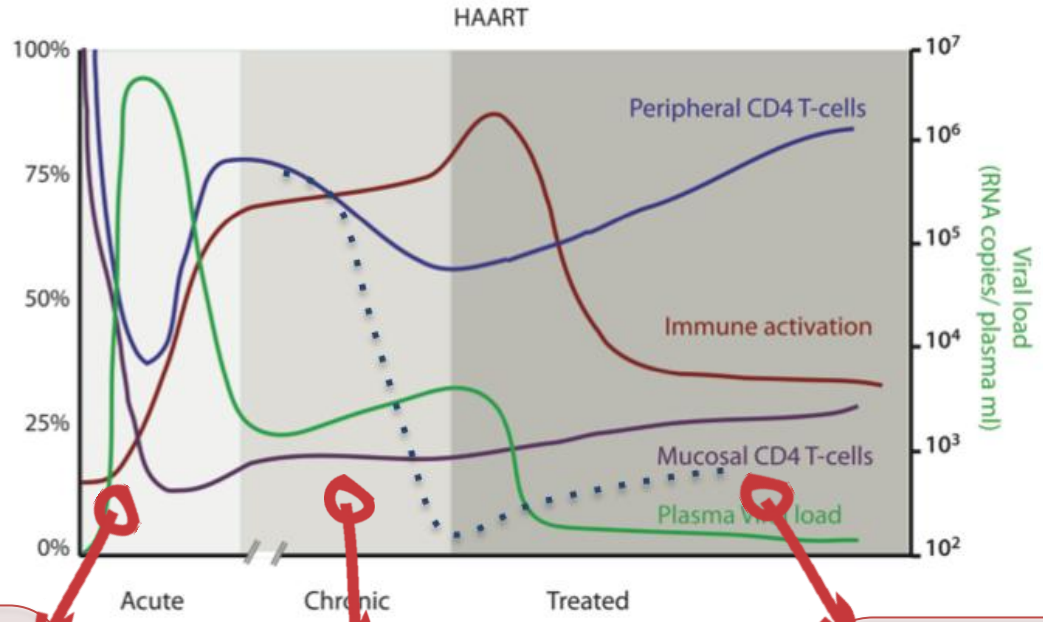
Cells with damaged (short) telomers undergo apoptosis or become refractory to division signals (senescence)

# The life and death of a T cell

| NAIVE | CM | TM | EM | TD | |
|---|---|---|---|---|---|
| + | + | - | - | - | CCR7 |
| + | + | + | + | - | CD27 |
| + | + | + | + | - | CD28 |
| - | - | - | + | + | PD1 |
| - | - | - | - | + | CD57 |



# HIV infection




**Viral spread**
- Massive replication
- GALT destruction

**VIRAL DISEASE**

**Partial Immune control**
- Partial control of viral replication
- Tissue damage
- **Persistent inflammation**

**VIRO-IMMUNO DISEASE**

**Pharmacological control**
- Viral persistence
- Incomplete tissue repair

**INFLAMMATORY DISEASE?**

**HIV PERSISTENCE**

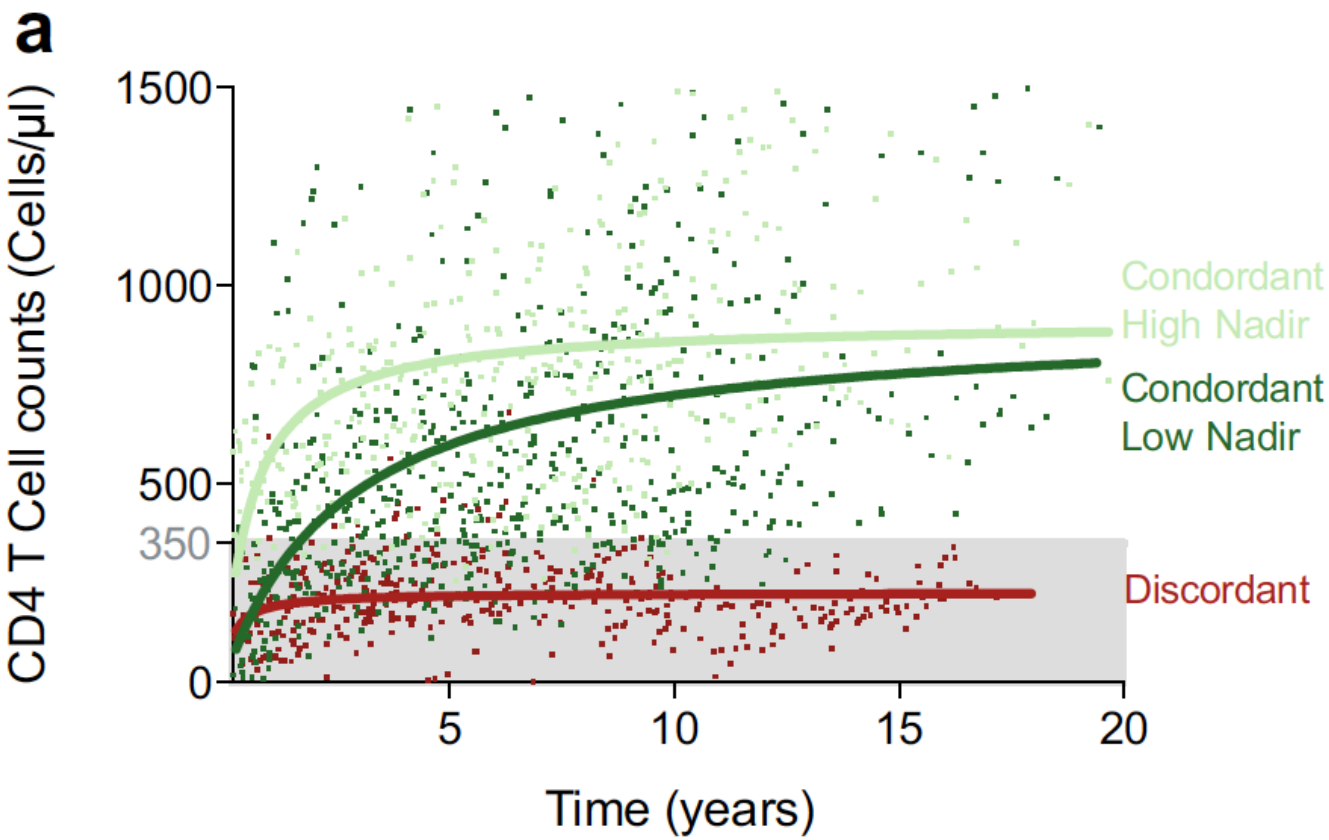
# APOP VI II STUDY

CROSS SECTIONAL STUDY TO ASSESS :

- IMMUNOSENESCENCE AND MATURATION MARKERS IN ART TREATED HIV INFECTED INDIVIDUALS.
- THE IMPACT OF CD4 T CELL RECOVERY

Massanella et al, JTM, 2015, 13:230

# DEFINITION OF IMMUNE RECOVERY

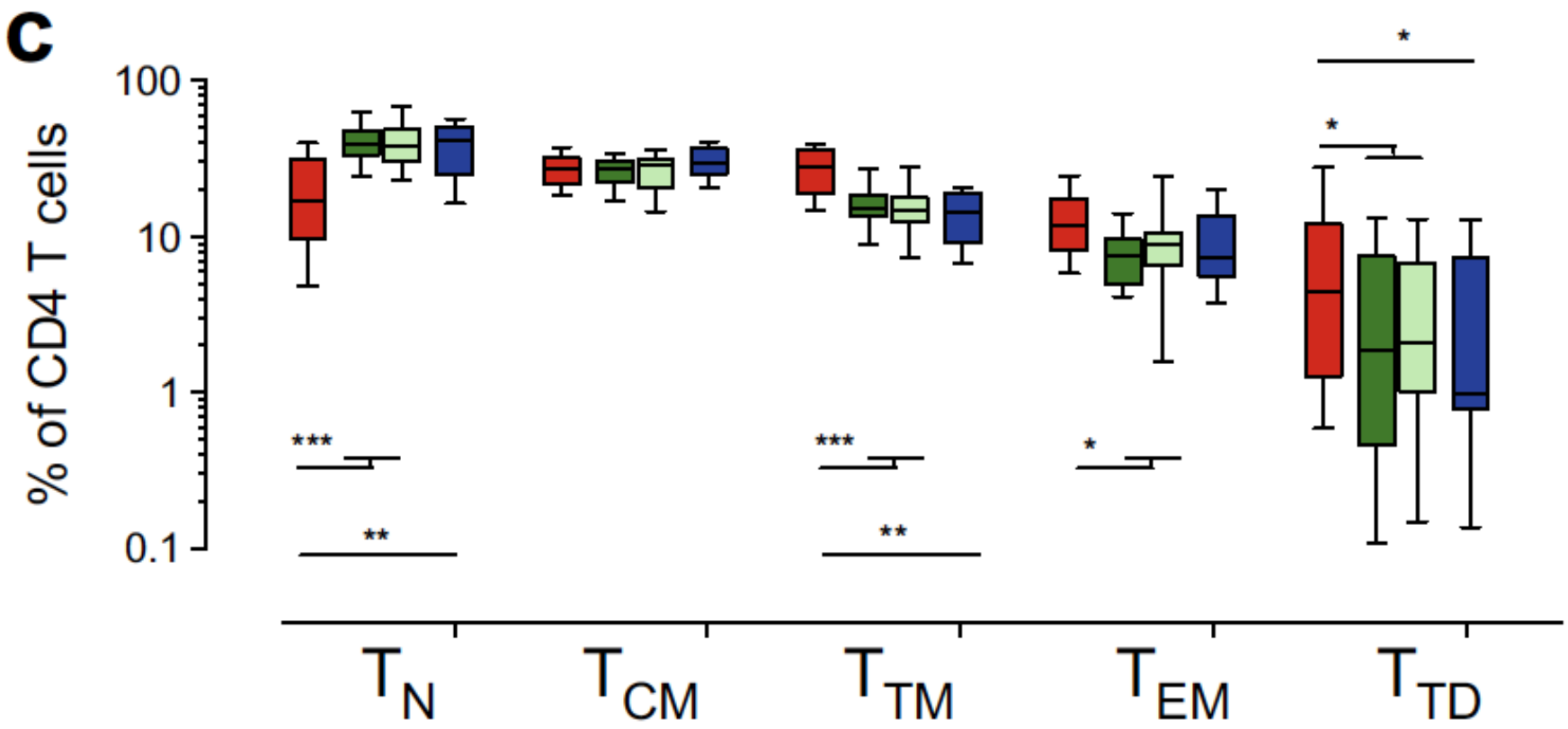


| | Discordant (n = 23) | a | Concordant | | | b | Uninfected (n = 11) |
|---|---|---|---|---|---|---|---|
| | | | All (n = 33) | Low Nadir (n = 17) | High Nadir (n = 16) | | |
| Age (years), Median [IQR] | 48 [45–50] | ns | 45 [38–49] | 48 [42–52] | 42 [37–45] | ns | 38 [34–47] |
| Gender (% of male) | 91 | ns | 85 | 76 | 94 | ns | 55 |
| Time since HIV diagnosis (years), Median [IQR] | 10.1 [4.1–20.4] | ns | 11.8 [7.5–16.6] | 12.2 [8.9–17.4] | 11.6 [4.9–13.4] | ns | – |
| Time on HAART (years), Median [IQR] | 5.2 [3.5–11.4] | ns | 11.2 [7.4–12.6] | 11.4 [8.8–12.6] | 10.6 [3.7–12.8] | ns | – |
| Current HAART (% PI-based) | 70 | * | 33 | 41 | 25 | * | – |
| HCV coinfection (%) | 35 | ns | 21 | 36 | 15 | * | 0 |
| Ratio CD4/CD8, Median [IQR] | 0.23 [0.17–0.33] | * | 0.87 [0.60–1.11] | 0.76 [0.54–0.87] | 1.06 [0.86–1.1] | ns | 1.64 [1.31–1.81] |
| CD4 T cell counts (cells/μL), Median [IQR] | 220 [192–253] | * | 798 [600–998] | 703 [600–896] | 881 [672–1,075] | ns | 779 [629–1,072] |
| Nadir (cells/μL), Median [IQR] | 64 [15–122] | * | 239 [76–345] | 76 [19–185] | 351 [280–429] | * | – |
| CD4 T-cell gain (cell/μL/year HAART), Median [IQR] | 27 [9–54] | * | 53 [46–102] | 53 [46–93] | 53 [36–124] | ns | – |
| CD4 T cell (% of lymph), Median [IQR] | 14 [10–17] | * | 31 [27–39] | 29 [27–33] | 37 [29–40] | ns | 42 [36–45] |
| CD4 T-cell death (%), Median [IQR] | 9.3 [7.5–15.1] | * | 4.6 [3.3–5.9] | 4.9 [4.4–5.6] | 4.3 [2.9–6.1] | ns | 4.0 [3.2–4.7] |
| $CD38^{+}CD45RA^{-}$ (% of CD4 T cells), Median [IQR] | 37 [29–41] | * | 25.7 [20–32] | 26.5 [20–32] | 25.1 [20–31] | ns | |
| $HLA\text{-}DR^{+}CD95^{+}$ (% of CD4 T cells), Median [IQR] | 16 [7.7–21.6] | * | 4.5 [3.7–6.7] | 4.7 [4.2–6.3] | 4.4 [3.2–7.1] | ns | 2.0 [1.5–2.7] |
| CD8 T cell counts (cells/μL), Median [IQR] | 940 [754–1,146] | ns | 908 [771–1,239] | 1,118 [855–1,380] | 811 [637–1,121] | ns | 459 [433–548] |
| CD8 T cell (% of lymph), Median [IQR] | 56 [51–61] | * | 38 [34–46] | 39 [36–47] | 36 [32–40] | ns | 24 [23–27] |
| CD8 T cell death (%), Median [IQR] | 7.1 [4.8–10.3] | ns | 6.5 [5.0–12.4] | 8.8 [6.1–11.0] | 6.1 [4.8–14.9] | ns | 3.9 [3.4–4.9] |
| $CD38^{+}CD45RA^{-}$ (% of CD8 T cells), Median [IQR] | 31 [23–36] | * | 23 [19–35] | 25 [21–36] | 21 [19–26] | ns | 9 [5–13] |
| $HLA\text{-}DR^{+}CD95^{+}$ (% of CD8 T cells), Median [IQR] | 12.6 [6.9–22.4] | ns | 9.1 [5.6–13.0] | 9.8 [5.4–13.6] | 8.5 [5.6–13.0] | ns | |
| sCD14 (μg/mL), Median [IQR] | 8.4 [7.7–10.2] | ns | 8.8 [7.2–9.7] | 9.2 [7.6–10.1] | 8.0 [7.1–9.2] | ns | 4.2 [3.9–4.6] |

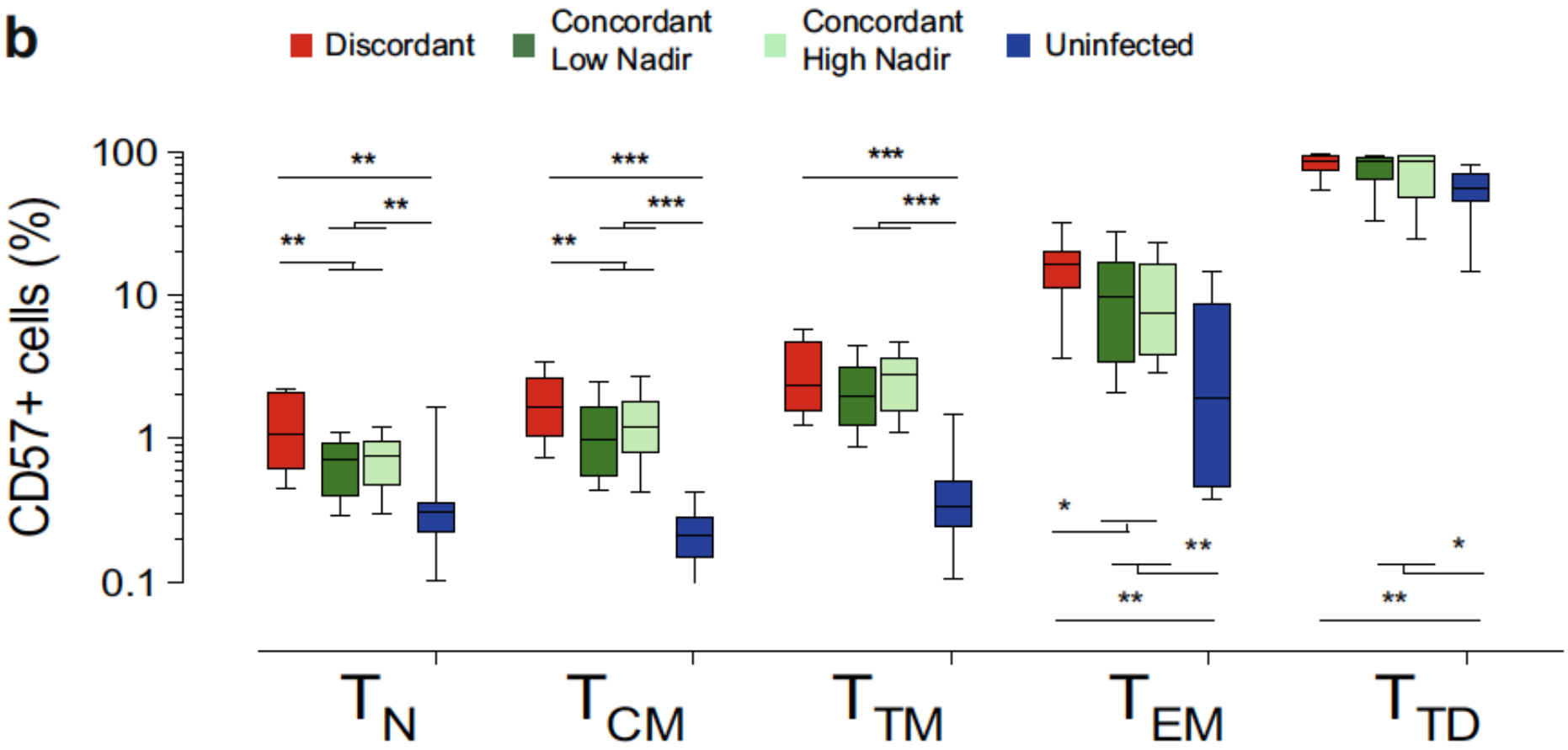
*a* Comparison of concordant and discordant subjects. * denotes $p < 0.05$; *ns* non significant (Mann–Withney U or Fisher exact test).

*b* Comparison of concordant subjects with low and high nadir. * denotes $p < 0.05$; *ns* non significant (Mann–Withney U or Fisher exact test).

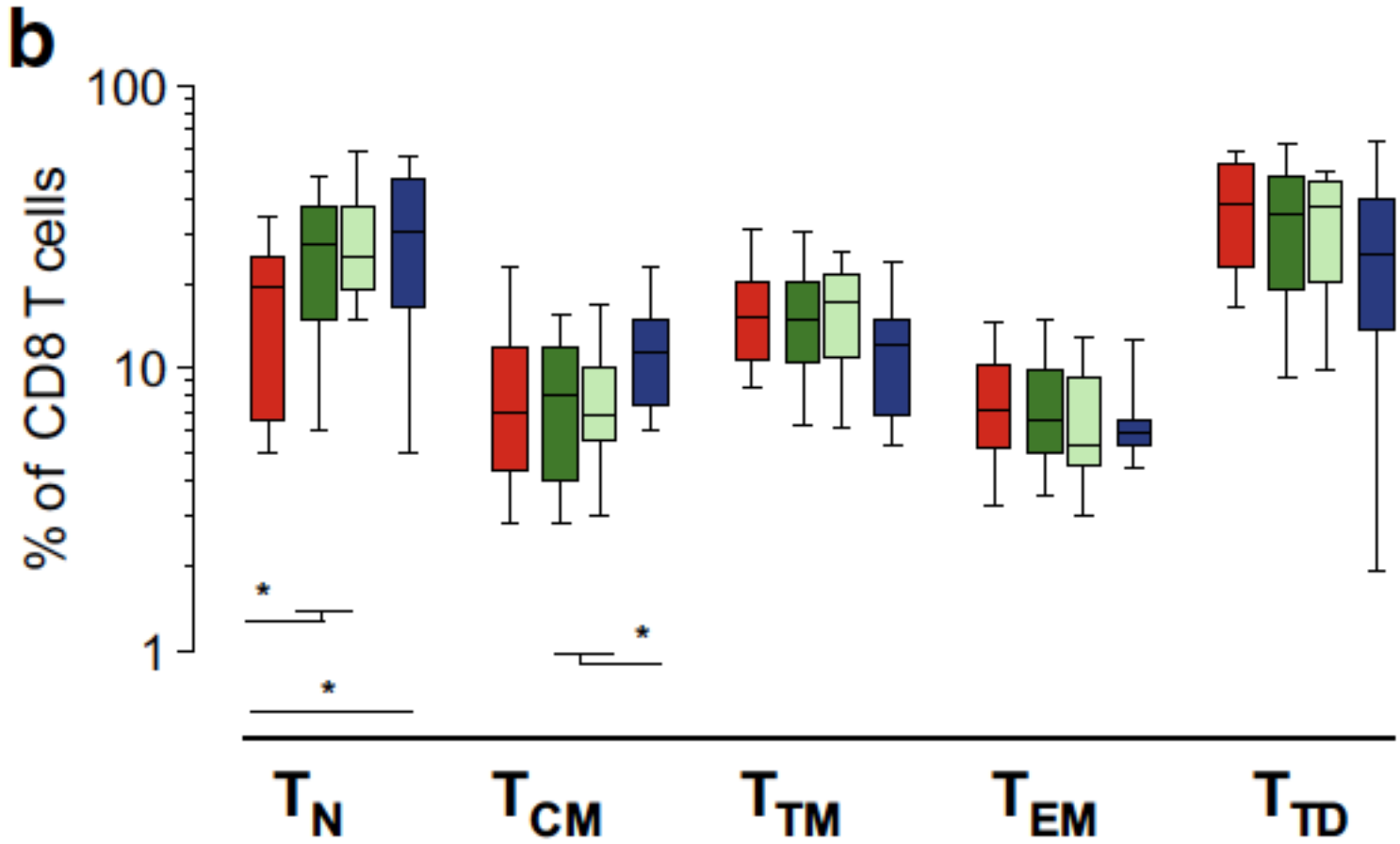
# MATURATION OF CD4 T cells



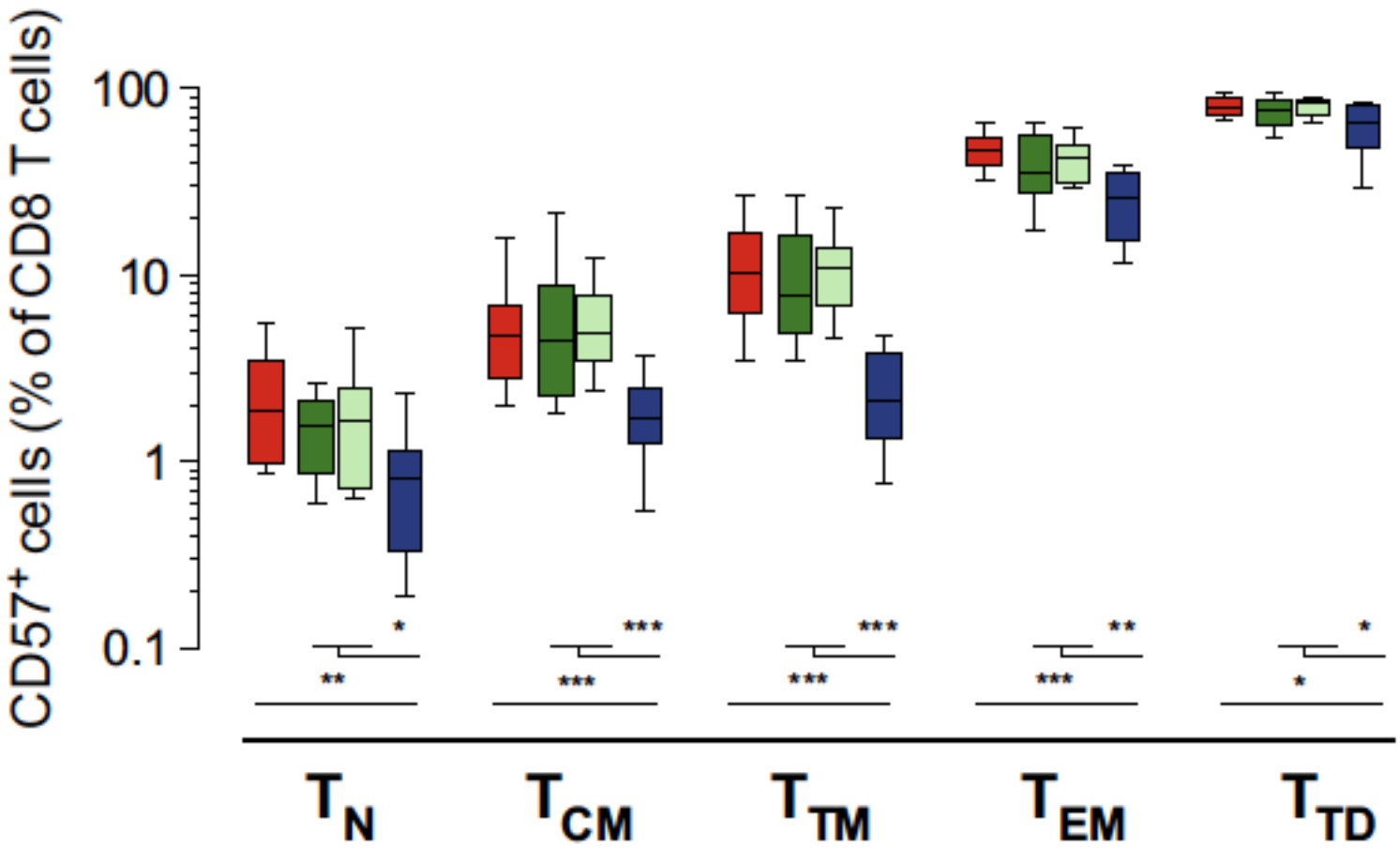
# SENESCENCE (CD57 EXP) IN CD4 T CELLS



# MATURATION IN CD8 T CELLS



# SENESCENCE (CD57 EXP) IN CD8 T CELLS



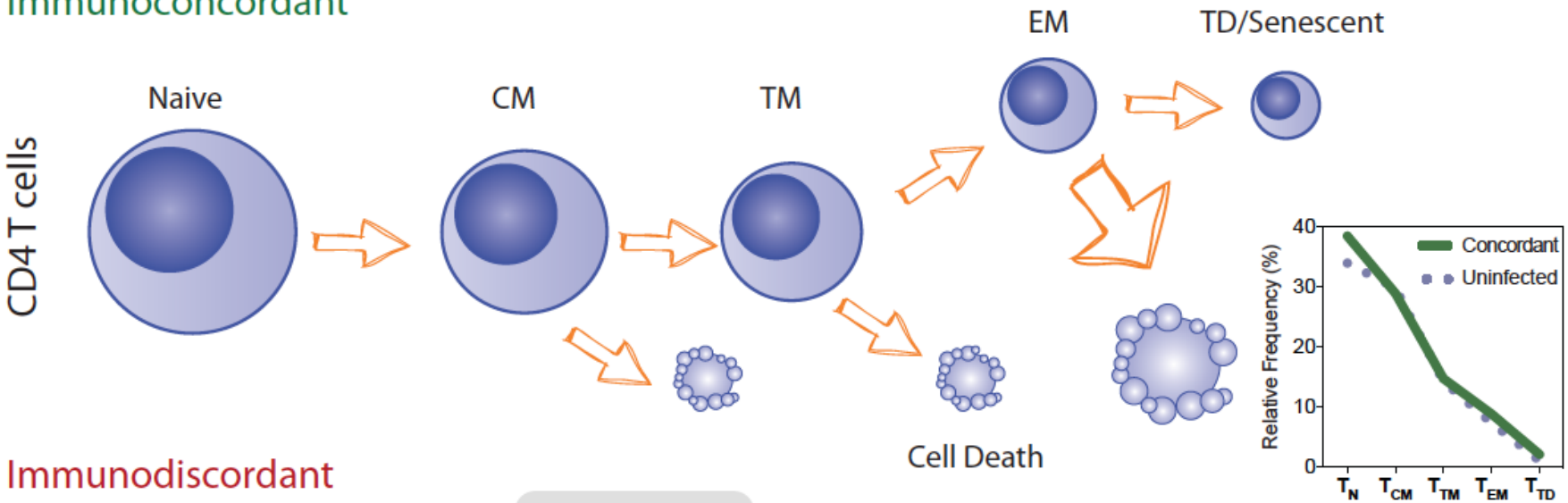
# CONCUSIONS

- CD4 T CELL MATURATION MARKERS ARE STRONGLY ALTERED IN IMMUNODISCORDANT INDIVIDUALS. AN APPARENT FULL RECOVERY OCCURS IN IMMUNOCONCORDANT INDIVIDUALS
- CD4 T CELL IMMUNOSENESCENCE IS HIGHER IN LONG TERM SUPPRESSED HIV INFECTED INDIVIDUALS COMPARED TO CONTROLS
- CD4 T CELL IMMUNOSENESCENCE IS ASSOCIATED WITH THE LEVEL OF CD4 T CELL RECOVERY

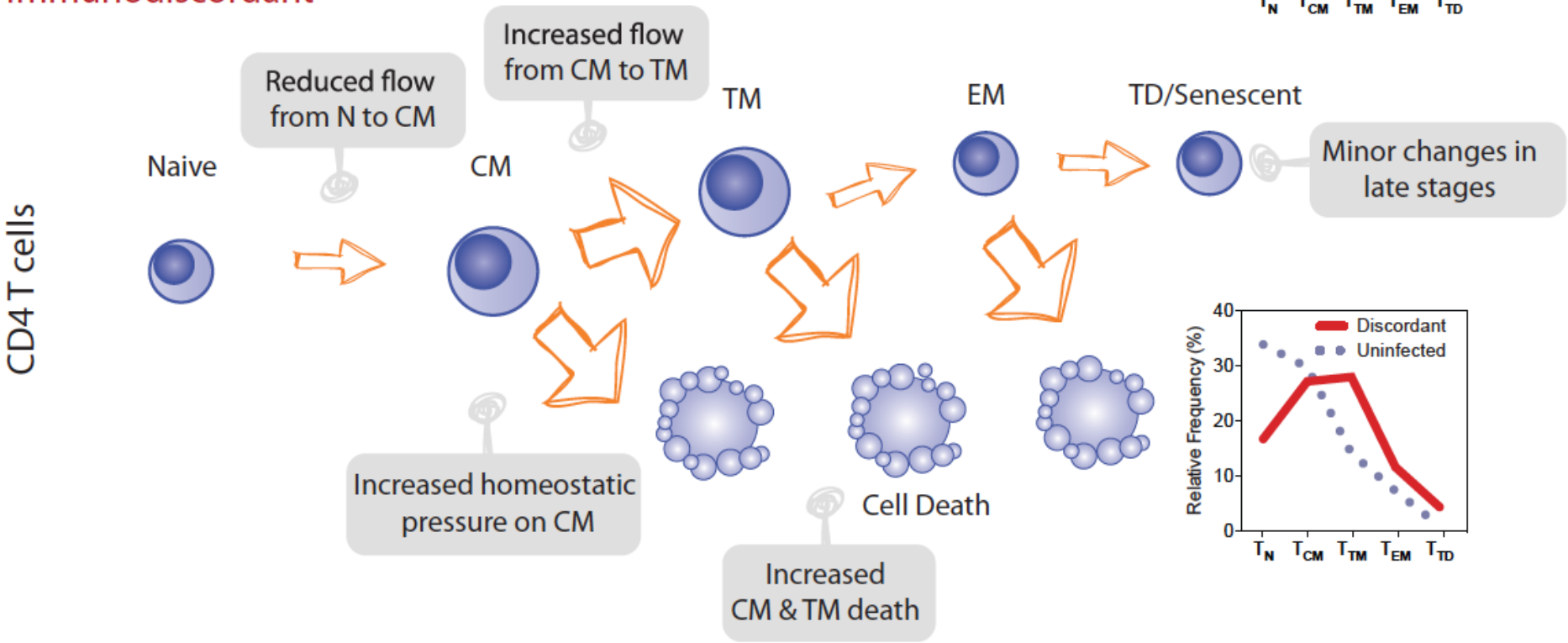
# CONCUSIONS

- CD8 T CELL MATURATION MARKERS SHOW SLIGHT DIFFERENCES IN ART TREATED HIV INFECTED INDIVIDUALS COMPARED TO CONTROL INDIVIDUALS.
- CD8 T CELL IMMUNOSENESCENCE IS HIGHER IN LONG TERM SUPPRESSED HIV INFECTED INDIVIDUALS COMPARED TO CONTROLS
- CD8 T CELL IMMUNOSENESCENCE IS LARGELY INDEPENDENT OF THE LEVEL OF CD4 T CELL RECOVERY

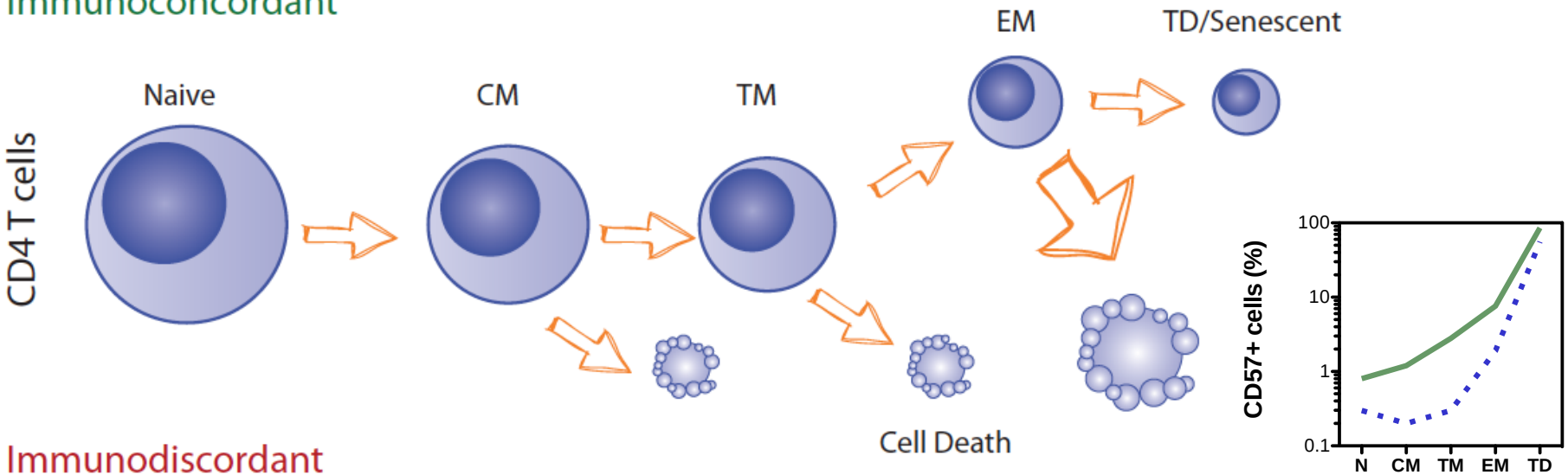
## Immunoconcordant



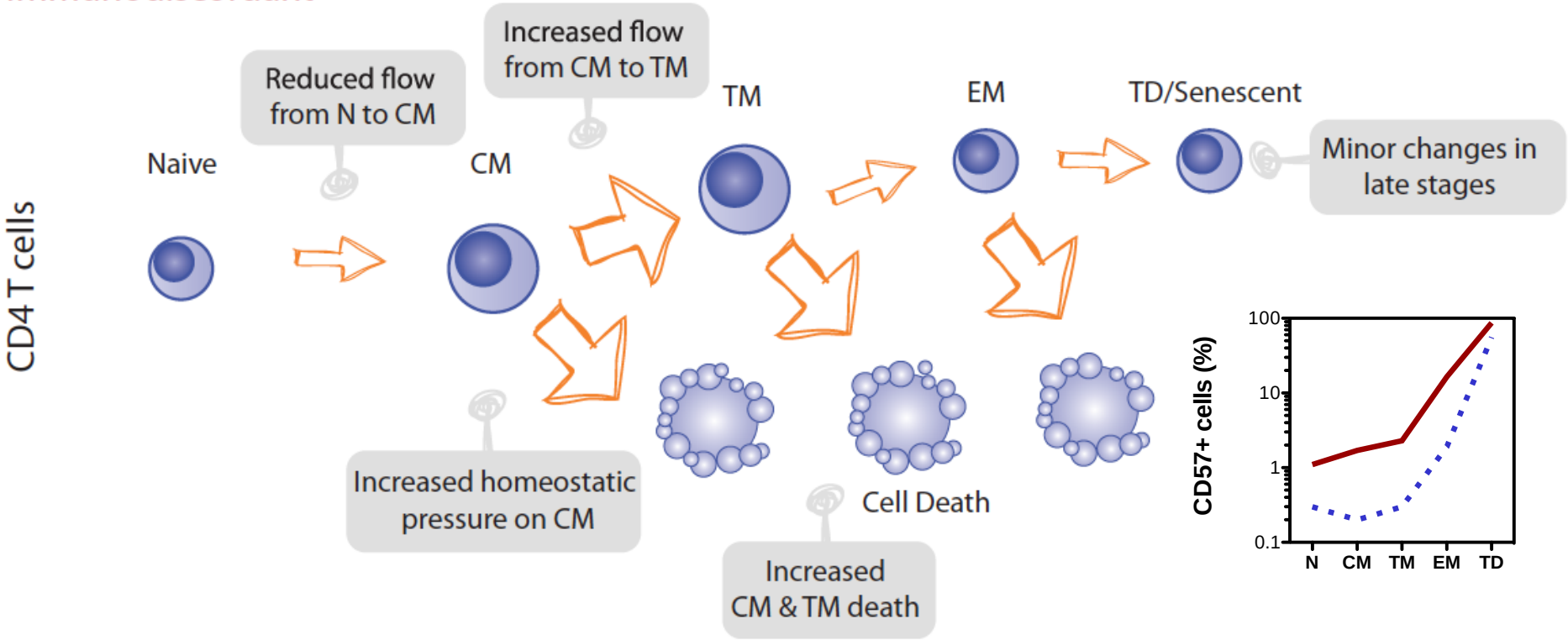

## Immunodiscordant



## Immunoconcordant




## Immunodiscordant



# CONCUSIONS

- DESPITE FULL RECOVERY OF CD4 T CELL NUMBERS, IMMUNOCONCORDANT TREATED HIV INFECTED INDIVIDUALS MAINTAIN IMMUNOLOGICAL ALTERATIONS IN ALL CD4 AND CD8 T CELL COMPARTMENTS.

- SENESCENCE ACCUMULATED DURING UNTREATED INFECTION LEAVES A IRREVERSIBLE? IMPRINT IN THE IMMUNE SYSTEM

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