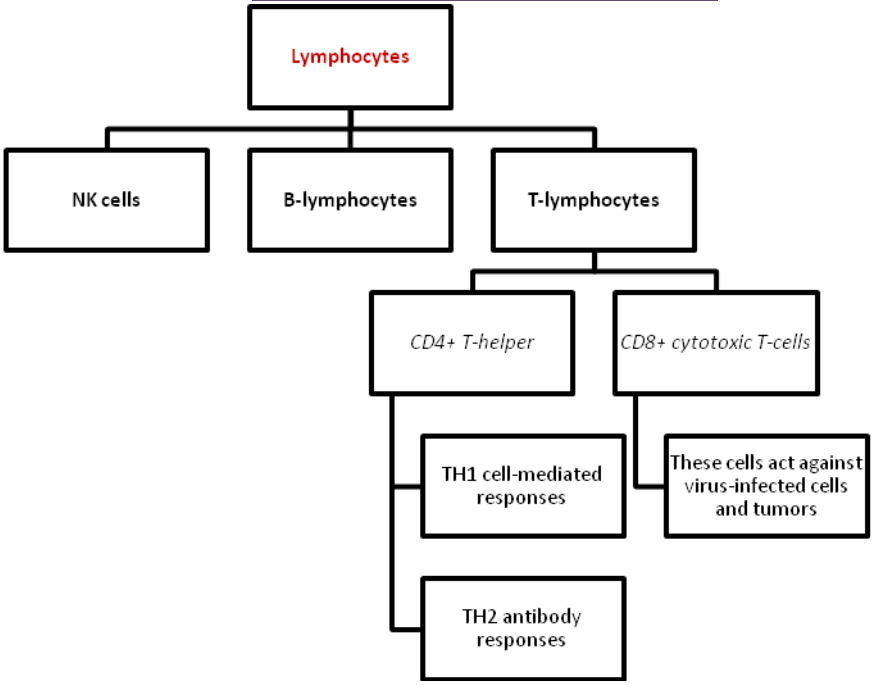
T-LYMPHOCYTE SUBSETS & FUNCTION



- **CD4+ functions:**
  - **Macrophage activation** → intracellular parasite killing.
  - **NK cell activation** → killing virus-infected cells and tumor cells.
  - **B-lymphocyte response** → leading to the production of antibodies.
  - **Activating cytotoxic T-cells by secreting IL-2** → this will lead to the killing of virus-infected cells and tumor cells.
- **B and T lymphocyte interaction with antigen:**
  - **B-cell receptors** will interact with the antigen in its native form (the normal tertiary structure).
  - **T-Cell-Receptors (TCR)** will interact with small peptides presented on MHC molecules carried on antigen presenting cell (antigen will be internalized and processed by APC to small peptides).
- **Restriction of T-cell interaction:**
  - **CD8** → they will interact with antigens presented on MHC class-I molecules carried by all nucleated cells in the body including platelets.
  - **CD4** → they will interact with antigens presented on MHC class-II molecules carried by antigen presenting cells (macrophages, B-lymphocytes and dendritic cells).
- **MHC molecules:**
  - **MHC-I** → it will present intracellular antigens (viruses and tumors). It will be recognized by CD8 cytotoxic T-cells which will kill the infected cells.
  - **MHC-II** → it will present extracellular antigens (ex. Bacteria) → it will be recognized by CD4 helper T-cells which will mediate the production of immunoglobulins (by converting B-lymphocytes to plasma cells) and they will stimulate CD8 cells by secreting IL-2.
- **CD4 cell interaction with APC:**
  - TCR presented on CD4 cells will interact with MHC class-II molecule presented on APC.
  - LFA-1 presented on CD4 cells will interact with ICAM-1 presented on APC.
  - CD28 presented on CD4 cells will interact with B7 presented on APC.
  - CD40L presented on CD4 cells will interact with CD40 presented on APC.
- **Activation of CD8 cytotoxic T-cells:**
  - APC has the antigen presented on MHC class-I which will be recognized by CD8 cells (they are activated). In addition, the APC has the antigen also presented on MHC class-II which will be recognized by CD4 cells (they are activated). CD4 cells will provide the second signal of activation of CD8 cells (by producing IL-2).

- **Activation of B-lymphocytes:**
  - Antigens will be presented on MHC class-II molecules carried on APC → CD4 cells will activate the B-lymphocytes and stimulate their conversion to plasma cells so they can secrete immunoglobulins.

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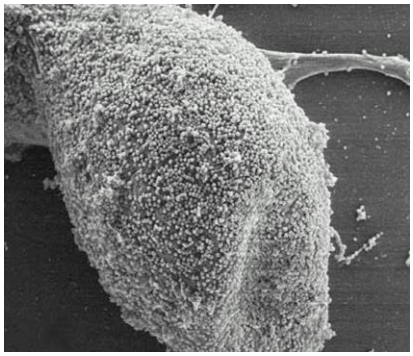
HIV INFECTION EFFECTS ON THE IMMUNE SYSTEM

- **Life cycle:**



  - The gp120 which is present on the envelope of HIV virus will attach to CD4 receptors present on the host cell.
  - Then, gp120 will interact with chemokine receptors (CCR5 or CXCR4).
  - Gp41 which is embedded in the envelope of the virus will mediate the fusion of the virus with the host cell.
  - After fusion occurs, the virus will release nucleocaspid, RNA genome & reverse transcriptase, integrase and protease in the cytoplasm of the host cell.
  - The enzyme reverse transcriptase will use the RNA genome of the virus to synthesize a DNA copy from it and an RNA-DNA complex will be formed.
  - Then, reverse transcriptase will have a ribonuclease H activity and it will remove the RNA strand from the RNA-DNA complex so double-stranded DNA genome can be synthesized.
  - The double-stranded DNA will move to the nucleus of the host cell to be integrated with the host cell DNA and this will be mediated by integrase.
  - Replication will occur and RNA will be released from the nucleus to the cytoplasm. Protease will cleave polyproteins to polypeptides and assembly them in the new viral particles.
  - Viral particles will be released from the host cell.
- **Chemokines & chemokine receptors:**
  - Chemokines are cytokines that chemoattract and activate leukocytes.
  - Their receptors belong to G-protein-coupled receptors.
  - Since the entry of HIV into host cells requires chemokine receptors, chemokine antagonists are being developed to treat AIDS.
- **Comparison between CCR5 & CXCR4 chemokine receptors:**

CCR5	CXCR4
• β chemokine receptor, (MIP-1α, MIP-1β, RANTES) • associated with primary and early infection • expressed on macrophages and T cells	• also known as"fusin" • α chemokine receptor, • natural ligand is SDF-1 • expressed on T cells and T cell lines

- Early in the infection, macrophage-tropic strains of the virus will predominate using CCR5, but later it will be switched to T-tropic strains which will utilize CXCR4 and there will be no involvement of macrophages.
- In HIV infection →CD4 helper T-cells will be infected leading to their loss (no cell-mediated immunity) → in addition, cytotoxic T-cells will lose their function due to the reduction in CD4 cells (which normally activate them by producing IL-2) → all of this will lead to the progression of the disease.

	Normal	AIDS
Total lymphs	>1000	<600 to 0
Total T cells	>60%	<30%
Absolute CD4 count	>600	<200
CD4/CD8 ratio	>1.7	<1

- **Destruction of CD4 cells:**
  - Lysis of cell caused by budding of virus.
  - Cytopathic effect of unintegrated viral RNA,DNA.
  - Apoptosis mediated by gp120 *env*.
  - Cytotoxic T-cell killing of infected cells.
  - ADCC-mediated cell lysis by NK cells.

    Note: there might be impaired production of CD4 cells by thymic dysfunction or bone marrow suppression.
- **Effect of CD4 cell cytokine dysregulation:**
  - Lack of T-cell (help) for B-cell antibody responses (TH2 cytokines):
    - ✓ Poor response to new antigens.
    - ✓ Loss of CD4 memory responses.
  - Lack of TH1 cytokine (help) to augment and sustain CTL both to HIV and other antigens.
  - Decrease in cytokine and chemokines which have direct antiviral effects.
- **HIV and lymphoid organs:**
  - HIV sticks to (Denditic Cell sign) on dendritic cells and is transported to lymph nodes.
  - Regional lymph node is the site of initial replication and expansion of HIV (act as reservoir of virus).
  - Early in infection, lymph nodes act as a trap of HIV (follicular dendritic cell network).
  - Later in infections as FDC network fails, ↑viremia.