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REVIEW

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Pneumococcal vaccine hyporesponsiveness in people living with HIV: A narrative review of immunological mechanisms and insights from minimally invasive lymph node sampling

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ABSTRACT

Despite highly effective antiretroviral therapy, people living with HIV (PLWH) remain at elevated risk for invasive pneumococcal disease. Clinical studies show that, even with high $CD4^+$ counts, PLWH exhibit diminished serological responses and rapid antibody decline following pneumococcal vaccination, plausibly due to underlying immune dysfunction. Germinal centers (GCs), located within lymph nodes, are essential for generating high-affinity antibodies, but are structurally and functionally disrupted in PLWH. These local impairments, combined with systemic immune dysregulation, contribute to vaccine hyporesponsiveness in PLWH. This narrative review links immunological findings from experimental and in vivo studies to clinical pneumococcal vaccine trials, to investigate mechanisms that may be leveraged to strengthen vaccine-induced immunity in PLWH. We also highlight the application of fine needle aspiration (FNA) of the lymph node as a way to study pneumococcal vaccine hyporesponsiveness in the GC and provide potential direction to improve responses for next-generation pneumococcal conjugate vaccines in PLWH.

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Introduction

The acquired immunodeficiency syndrome (AIDS) was first recognized in 1981 in the United States, with HIV identified as the causative agent 2 years later.[1,2] Over the past four decades, significant progress has been made in understanding the pathogenesis of HIV and developing treatment and prevention strategies, notably through the introduction of combined antiretroviral therapy (cART). This has transformed HIV from a fatal disease into a chronic inflammatory disease.[3–5] As of 2024, over 39 million people are living with HIV (PLWH), with 76% receiving cART of which 72% are virally suppressed, defined as <1000 copies/mL by the WHO.[6] Despite this viral suppression, HIV infection continues to alter immune function, leaving PLWH vulnerable to certain infections. One such infection is pneumococcal disease, caused by the bacterium *Streptococcus pneumoniae*, which remains a leading cause of morbidity and mortality in PLWH. Pneumococcal-related mortality rates reach as high as 25% for PLWH even in the modern cART era.[7–9] The seven-fold risk increase of invasive pneumococcal disease (IPD) compared to the general population underscores the urgent need for effective vaccination methods for this at-risk group.[7,10,11]

To date, over 100 *S. pneumoniae* serotypes have been identified based on their capsular polysaccharide.[12] A subset of these polysaccharide capsule antigens is targeted by the two types of available pneumococcal vaccines: the pneumococcal polysaccharide vaccine (PPV) and the pneumococcal conjugate vaccine (PCV).[13] PPV, introduced in 1983, consists of 23 different serotypes and induces a T-cell-independent response.[14] Importantly, this T-cell independent immune response offers no protection in infants and limited memory B cell formation and is therefore only used in at-risk adults.[15] However, its effectiveness in at-risk adult populations, such as older adults and PLWH, against pneumococcal pneumonia and IPD has been questioned, with various studies showing varying long-term protection outcomes 13–60 months post vaccination.[13,16] The other licensed vaccine is the more recently developed PCV, first introduced in the early 1990s. PCV induces a robust, T-cell dependent immune response via a conjugated carrier protein in both adults and children.[14,17] Current PCV formulations cover 7 to 21 pneumococcal serotypes associated with the highest disease burden.[18] Moreover, higher-valency PCV formulations are in development, aiming to broaden serotype coverage up to 31 serotypes.[19–21] The implementation of PCVs into national infant immunization programs dramatically changed the epidemiology of IPD, with significant herd-protection (70% reduction in IPD incidence) in healthy adults.[22] However, studies found a mere 25% reduction of IPD cases in PLWH in the USA following the introduction of the national pediatric PCV7 vaccination campaign 5 years prior.[10,23,24] This highlights the insufficiency of infant-

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only vaccination programs in protecting high-risk populations and underscores the need for direct immunization of PLWH.[25]

Various international guidelines advise a single dose of the conjugated PCV13, PCV15 or PCV20 vaccine for PLWH, regardless of viral load or $CD4^+$ cell count.[16,26,27] Yet, supporting data on the optimal vaccine strategy remain limited, with studies showing variable efficacy and significant heterogeneity in study design, patient characteristics, vaccine responses and follow-up periods. Initial data on the immunogenicity of the new PCV20 vaccine in PLWH demonstrated robust serotype-specific immune responses at 30 days post vaccination, but long-term immunogenicity and clinical effectiveness remain to be established.[26,28]

Despite viral suppression and high $CD4^+$ cell counts in PLWH, vaccine hyporesponsiveness persists for both pneumococcal vaccines, as we describe below.[29,30] This has also been previously described for other vaccines, such as hepatitis B and Influenza, and indicates that vaccine hyporesponsiveness in PLWH has a profound, vaccine-platform independent basis.[31] This is thought to be influenced by the impairment of cellular immunity and memory B cell depletion, resulting in suboptimal antibody responses.[11,32–34] Of particular interest for vaccine responses are the germinal centers (GCs) located within lymph nodes, which are crucial for generating high-affine antibodies and developing long-term immunity after vaccination. These regions are also primary sites of HIV replication, with prior studies showing that viral reservoirs form within hours after infection.[35]

In this narrative review, we explore the pneumococcal vaccine immunogenicity in PLWH, emphasizing the key immunological disruptions in GCs that may contribute to vaccine hyporesponsiveness. To investigate these immune defects in more depth, novel tools have been optimized that allow direct sampling of vaccine-draining lymph nodes. Fine-needle aspiration (FNA) is a minimally invasive technique that enables longitudinal assessment of germinal center (GC) dynamics in humans.[36] By allowing direct access to vaccine-draining lymph nodes, FNA facilitates real-time, tissue-specific immune monitoring, previously restricted to animal models. We also outline future strategies to enhance vaccine efficacy based on the reported immunological alterations in PLWH.

Methods

This narrative review incorporates data from clinical pneumococcal vaccine trials, clinical lymph node FNA studies, as well as fundamental research. The systematic search for clinical trials was restricted to articles published from January 1, 1995, until December 31 2024 in the databases of PubMed, Embase and Google Scholar, corresponding with the introduction of cART, which significantly transformed HIV management. The search for clinical and fundamental studies was done separately and systematically. The full search strings can be found in *Appendix 1* and entailed the following keywords for study population*: "HIV positivity," "People living with HIV," "HIV-infected," "Adults living with HIV"* AND *"pneumococcal vaccination," "PCV7," "PCV10" "PCV13," "PCV15," "PCV20," "PCV21," "PPSV23," "PPV23," "polysaccharide pneumococcal vaccine"* and *"conjugate pneumococcal vaccine." A separate search for FNA studies included the keywords: "lymph node fine-needle aspiration" or "lymph node FNA" and "vaccination" or "vaccine response" or "vaccine kinetics"* The full search string for the fundamental studies entailed the following keywords: *"HIV positivity," "People living with HIV," "HIV-infected" AND "immunological changes," "immune alterations," "immune dysfunction," "immune activation," "chronic inflammation," "immune exhaustion," "immune dysregulation"* and *"germinal centers."* Only systematic reviews, randomized controlled trials (RCTs) and cohort studies from 1995 to 2024 were included in the search for clinical studies with both cART-naïve and cART-treated PLWH populations, regardless of $CD4^+$ cell count or viral load. Fundamental studies included both *in vivo*, *in vitro* studies and reviews. Study selection was performed by a single reviewer who screened titles, abstracts and full texts for relevance and eligibility.

Clinical trials on pneumococcal vaccines in PLWH

The clinical trial search yielded 426 articles of which 5 were included based on the in- and exclusion criteria, see *Appendix 1*. This included three cohort studies, one RCT and one systematic review. Summarized in Table 1, Garrido et al. compiled 39 clinical studies, RCTs and cohort studies from 2000 to 2020, researching the immunogenicity of both PCV and PPV, in which 4649 PLWH and 250 hIV negative controls were included.[30] This systematic review found that the combination of PCV+PPV yielded higher seroconversion-rates (SCRs) 1–3 months post vaccination, than PPV alone with an odds ratio (OR) of 2.24 (95% CI, 1.41–3.58).[30] Seroconversion was defined here as a > 2-fold increase in pooled IgG levels from baseline.[30] No significant differences were observed in log-transformed geometric mean concentrations (GMCs) when comparing a single dose of PCV with PPV. The pooled overall SCRs based on a subset of included articles, were 44%, 42% and 57% for PLWH who received PCV, PPV or a combination of PCV/PPV, respectively. Although overall SCRs were not reported for the HIV-negative control group, serotype-specific SCRs ranged from 50% to 70% for PPV23 and 80–90% for PCV13 across studies.

Another RCT studying the immunogenicity of a successive PCV13 and PPV23 vaccination schedule for PLWH showed that 49% of PLWH (39/80) and 82% (28/34) of controls achieved seroprotection, defined by a protective cutoff of 1.3 ug/L IgG.[29] They conclude that although IgG levels for all vaccine serotypes increased significantly in both PLWH and controls, only a minority of PLWH achieved seroprotection after the successive regime. Seroprotection rates did not differ by baseline $CD4^+$ count (<500 vs > 500 cells/mm^3). However, PLWH with a nadir $CD4^+$ count >200 cells/mm^3 had a significantly higher overall seroprotection rate at 4 months and 12 months after enrollment than those with a nadir $CD4^+$ count <200 cells/mm^3. Furthermore, a rapid decline in protective immunity was observed in PLWH, with protective IgG-titers dropping from 49% to 23% between 4 and 12 months post-vaccination, compared to a decline from 82% to 63% in the control group.[29]

Table 1. Summary and details of included clinical studies on pneumococcal immunogenicity in PLWH. *RCT; randomized controlled trial, SR; systematic review, GMT: Geometric mean titer, GMC: geometric mean concentration, OPA: opsonophagocytic activity.*

Baseline characteristics and findings of studies on pneumococcal vaccine immunogenicity in PLWH										
Author	Country	Design	Sample size	Sampling timepoints	Vaccine regimens	Groups	Treatment regimen	Definitions and measurements	Outcome	Key findings
Kroon et al. [40]	Netherlands	Cohort study	*N* = 50 PLWH *N* =10 controls	Day 0, 30 and 60, yearly until year 5.	PPV23	Group A (26): $CD4^+$ count < 200 cells/µl. Group B (24): $CD4^+$ count ≥ 200 cells/µl.	Majority on cART, treatment regimen varied.	**Definition seroconversion**: increase in IgG antibody concentration > 1µg/mL or 2-fold increase. **Measurements**: IgG antibodies (PS14/18C/19F/23F)	**IgG antibodies mean PS 14** Controls: ~ 7 µg/mL (initial), maintained > 3 µg/mL (year 5). $CD4^+$ ≥ 200: ~ 6 µg/mL (initial), declined to ~2 µg/mL (year 5). $CD4^+$ < 200: ~ 3 µg/mL (initial), declined to < 1 µg/mL (year 3). **IgG antibodies mean PS 18C** Controls: ~ 8 µg/mL (initial), maintained ~ 2–3 µg/mL (year 5). $CD4^+$ ≥ 200: ~ 5 µg/ml (initial), declined to < 1 µg/mL (year 3). $CD4^+$ < 200: ~ 3 µg/mL (initial), declined to < 1 µg/mL (year 2). **IgG antibodies mean PS 19F** Controls: ~ 10 µg/mL (initial), declined to ~ 3 µg/mL (year 5). $CD4^+$ ≥ 200: ~ 6 µg/mL (initial), declined to ~ 1 µg/mL (year 5). $CD4^+$ < 200: ~ 3 µg/ml (initial), declined to < 1 µg/mL (year 3). **IgG antibodies mean PS 23F** Controls: ~ 4 µg/mL (initial), maintained > 1 µg/mL (year 5). $CD4^+$ ≥ 200: ~ 3 µg/mL (initial), declined to < 1 µg/mL (year 3). $CD4^+$ < 200: ~ 2 µg/mL (initial), declined to < 1 µg/mL (year 1).	Vaccine responses varied depending on $CD4^+$ counts, with a more rapid decline in IgG antibodies observed in individuals with lower $CD4^+$ -cell counts, highlighting the importance of early immunization in people living with HIV H(PLWH)
Garrido et al.[7]	Multiple	SR with meta-analysis Years: 2000 – 2020	39 studies *N* = 4649 PLWH *N* = 250 controls	Various	PCV or PPV23 or PCV +PPV23	People living with HIV (all $CD4^+$ cell counts, all viral loads included)	23/39 studies > 75% of PLWH being on cART. 3/39 studies 100% on cART. 7/18 studies showed higher immunogenicity on cART.	**Definitions**: An IgG level above 1.00 µg/ml and/or two-fold increase in IgG level from baseline **Measurements**: 1) Seroconversion rate 1–3 months after vaccination 2) Geometric mean concentration (GMC) IgG 3) OPA-titers	PCV+PPV23 had higher seroconversion (73%) than PCV (61%) or PPV23 (57%). There were no significant differences in the log-transformed GMCs between PLWH who received PCV compared to PPV23.	The combination of PCV and PPV23 demonstrated higher seroconversion rates (73%) in PLWH compared to PCV (61%) or PPV23 (57%), with no significant differences in antibody concentrations between PCV and PPV23.

(*Continued*)

Table 1. (Continued).

Baseline characteristics and findings of studies on pneumococcal vaccine immunogenicity in PLWH

Author	Country	Design	Sample size	Sampling timepoints	Vaccine regimens	Groups	Treatment regimen	Definitions and measurements	Outcome	Key findings
Romaru et al.[13]	France	Cohort study	*N* = 40 PLWH (no control group)	Day 0, 1 month and 12 months post vaccination.	Single dose PCV13	PLWH with $CD4^+$ count ≥ 200 cells/mm^3	37/38 on cART therapy at time of vaccination. VL < 40 copies/ml for 86.8% of participants.	**Definition protection by ELISA**: 2x fold increase in specific IgG antibody titers **Definition protection by OPA**: 4x increase in OPA titer from baseline, for at least 5 serotypes.	**Month 1 post PCV13:** 57.9% achieved seroprotection by ELISA. 63.2% achieved seroprotection by OPA. **Month 12 post PCV13:** 64.7% achieved seroprotection by ELISA. 55.9% achieved seroprotection by OPA. GMCs: increase of 2.4–3.5-fold for all serotypes (ELISA). GMTs: 9.3–21.7-fold increase for all serotypes (OPA).	PCV13 induced substantial seroprotection and increases in GMCs/GMTs in PLWH, with a modest decline after 12 months, although protective levels were retained in more than half of the participants
Garrido et al.[29]	The Netherlands	Cohort study	PLWH *N* = 120 *N* =34 controls	Day 0, 2 months after PCV13, 4 months after PCV13, 6 months and 12 months.	PCV13 at baseline followed by PPV23 at month 2.	PLWH with $CD4^+$ count <500 cells/mm3 PLWH with $CD4^+$ count ≥ 500 cells/mm^3	All on cART	**Definition(s) protection**: proportion of patients with a post-immunization IgG concentration of >1.3 µg/mL for >70% of all serotypes of PCV13/PPV23 **Measurement(s)**: Serotype specific IgG concentrations (2 months post full vaccination schedule).	**Month 4 post-vaccination:** PLWH: 49% (39/80) achieved seroprotection. Controls: 82% (28/34) achieved seroprotection. *No differences in seroprotection between PLWH with $CD4^+$ count < 500 cells/mm3 and > 500 cells/mm3 **Month 12 post-vaccination:** PLWH: 23% (18/79) of PLWH remained seroprotected. Controls: 63% (22/35) remained seroprotected.	Only 23% of PLWH maintained seroprotection 12 months post-vaccination.

(*Continued*)

Table 1. (Continued).

Baseline characteristics and findings of studies on pneumococcal vaccine immunogenicity in PLWH

Author	Country	Design	Sample size	Sampling timepoints	Vaccine regimens	Groups	Treatment regimen	Definitions and measurements	Outcome	Key findings
Mohapi et al.[27]	USA, France, Peru, South-Africa and Thailand.	RCT	*N* = 292 PLWH (no control group)	Day 0, Day 30, Week 12	PCV13 vs PCV15 followed both by PPV23 8 weeks afterwards.	PLWH with a $CD4^+$ cell count of >50 cells/µl + HIV RNA < 50.000 copies/ml on cART (Only 4 participants with $CD4^+$ cell count ≤ 200 cells/µl)	Stable on cART regime 6 weeks prior to inclusion.	**Definition protection by ELISA**: 4x fold increase in specific IgG antibody titers between day 0 and day 30. **Definition protection by OPA**: 4x increase in OPA titer from baseline between day 0 and day 30. **Measurements**: 1) Serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMT's) and geometric mean fold-rise (GMFR) for all 15 serotypes at day 30. 2) Serotype-specific IgG geometric mean concentrations (GMC's) OPA GMT's and IgG GMCs at week 12.	**Day 30 opsonophagocytic activity (OPA):** Comparable OPA geometric mean titer (GMT) increase overall. Higher OPA GMT in PCV15 for: Serotype 3: 116.8 vs 72.3 (PCV13) Serotype 18c: 3002.2 vs 1560.3 (PCV13) Serotype 4: 1465.5 vs 824 (PCV13) **Day 30 IgG geometric mean concentration (GMCs):** Comparable IgG responses for most shared serotypes. Higher GMC in PCV13 for: Serotype 1: 4.27 µg/ml vs 3.16µg/ml (PCV15) Serotype 4: 2.00µg/ml vs 1.14 µg/ml (PCV15) Higher GMC in PCV15 for: Serotype 18c: 5.58 µg/ml vs: 5.07 µg/ml **Geometric mean fold-rise (GMFR) for OPA (day 1 to day 30):** Serotype 4: 22.4 for PCV13 vs 15.5 for PCV15 Serotype 18C: 6.9 for PCV13 vs 13.8 for PCV15 **PCV15 unique serotypes:** Serotype 22F: 54.4 for PCV15 compared to 1.5 for PCV13 Serotype 33F: 5.5 for PCV15 compared to 1.2 for PCV13	Both PCV13 and PCV15 were effective, with PCV15 eliciting superior OPA responses for unique serotypes (22F and 33F), while PCV13 showed stronger responses for shared serotypes such as serotype 4.

The immunogenicity of a single dose of PCV13 in PLWH with a $CD4^+$ count ≥200 cells/μl was assessed by Romaru et al.[13] At one-month post-vaccination, 58% of study participants were above the threshold of protection, measured via enzyme-linked immunosorbent assay (ELISA) and 63.2% via the functional opsonophagocytosis assay (OPA). Protection was defined as either a 2-fold increase in specific IgG antibody titers or 4-fold increase in OPA titer compared to baseline, see Table 1. At 12 months post-vaccination, more than half (64.7%, 55.9% via ELISA and OPA respectively) of the study participants remained above the threshold for protection. Mohapi et al. found that PCV15 induced robust immune responses for all serotypes in pneumococcal vaccine-naïve PLWH with similar safety and immunogenicity profiles to that of the PCV13 vaccine, but with higher OPA titers for serotypes 4 and 18C.[27] More so, they found that PCV15 followed by PPV23 at 8 weeks, broadened serotype coverage effectively. However, the follow-up period was only 12 weeks, giving limited insights into long-term immunity.

Few studies assessed the durability of vaccine-induced immunity in PLWH. One study, which investigated long-term immunogenicity after single PPV23 vaccination found that the proportion of patients with a ≥ 2-fold antibody increase to serotype 14 declined from 43.8% at 1 year to 30.0% at 5 years, for serotype 19F from 35.4% to 19.4%, and for serotype 23F from 22.5% to only 7.5%.[37] This finding supports the recommendation for repeating PPV vaccination every 5 years. Two studies investigated the long-term immunogenicity of PCV, one comparing a single or prime/boost regime of PCV7 (4 weeks apart) and another which compared the long-term immunogenicity between PCV13 and PPV23 after 5 years.[38,39] The first study reported sustained high SCRs 5 years post-vaccination, with higher SCRs in the group that received two PCV7 doses (76% vs 62%). In contrast, the second study showed that SCRs declined from 22% to 4.8% 5 years post-vaccination with no significant differences between the PCV and PPV groups. However, all of these studies lacked a control group providing little insight into how these responses were affected by HIV. An older study by Kroon *et al*., showed that PLWH with $CD4^+$ counts ≤200 cells/μl had significantly lower GMCs, which declined faster over time, falling below the protective value (1 μg/ml) more quickly compared to a healthy control group.[40] Unfortunately, no other studies reported long-term immunity outcomes of the PCV/PPV23 combination beyond 5 years.

These findings demonstrate that the initial serological response to various pneumococcal vaccination regimes in PLWH on cART is sufficient to achieve a certain degree of protection, while the scarce data available on long-term vaccine responses indicate that antibodies tend to wane rapidly over time. Notably, a single study suggests that repeated doses of PCV may be able to induce long-term immunity in PLWH.[38] The lower peak response and durability is observed even in those on optimal cART therapy, and plausibly suggests that specific immunological mechanisms may play a role in vaccine hyporesponsiveness in PLWH. GC responses play a pivotal role in generating robust and long-lasting antibody responses which are generated within secondary lymphoid organs (SLOs) such as the spleen and lymph nodes. These SLOs represent a reservoir and important site for HIV replication. Notably, HIV infection has been shown to disrupt SLO biology and GC responses. Below, we dissect the GC biology in the context of HIV and aim to provide insights into the mechanisms responsible for rapid waning of protective immunity after pneumococcal vaccination in PLWH. Furthermore, we explore potential targets to improve vaccine responsiveness for PLWH.

Immunological basis of pneumococcal vaccine responses

T cell-independent response following PPV

The pneumococcal polysaccharide vaccine (PPV) elicits a type II, T cell-independent (TI-2) response which bypasses GC formation, see Figure 1.[41,42] Instead, B cell receptors undergo cross-linking due to the repeated saccharide structures, leading to B cell proliferation and antibody production without the involvement of T cell assistance. Prior studies indicate that dendritic cells, NK cells and innate lymphoid cells play a role in supporting the TI-2 response.[43,44] Indeed, cytokines, including Interleukin 1-alpha and interferon-gamma have been identified, in addition to B cell antigen receptor (BCR)-mediated protein Kinase C (PKC)-gamma signaling, as essential factors in inducing rapid B cell activation, proliferation and plasmablast differentiation.[45] Prior studies found that polysaccharide vaccination induces a strong increase in plasmablasts within 7 days, with their frequency increasing from 3% at baseline to 19% of total peripheral blood B cells.[46,47]

In mice, marginal zone (MZ) B cells and B1b cells are the primary subsets involved in TI-2 responses, particularly in response to polysaccharide vaccines.[41] In humans, the equivalent B cell subset is debated, but IgM^+, IgD^+, $CD27^+$ B cells are thought to play a significant role in supporting TI-2 immunity.[47] BCR sequencing reveals that these circulating cells in peripheral blood are diverse and, after vaccination, can produce highly mutated antibodies.[47] This phenomenon was attributed to the activation of pre-diversified and pre-amplified B cells that are primed in mucosal tissues by cross-reacting with bacterial species from the gut microbiota.[47] However, it cannot be ruled out that asymptomatic carriage of *S. pneumoniae* may have contributed to the activation of these diversified MZ B cells. Repeated administration of polysaccharide vaccines fails to enhance immune responses and may even lead to hyporesponsiveness upon re-exposure.[48,49]

Germinal centers

T-cell dependent germinal center response following PCV

GCs, first described in 1884, are microanatomical structures within SLOs.[50] GCs are critical for generating memory B cells, long-lived plasma cells and high-affinity antibodies through affinity maturation, see Figure 2.[51] GCs are generally temporary, lasting weeks to months before dissipating once the infection or antigen causing their formation is cleared.[52] However, in certain tissues, GCs can persist chronically.[53,54]

GCs can be divided into a dark zone and a light zone, see Figure 2. The dark zone is the site of B cell proliferation and is

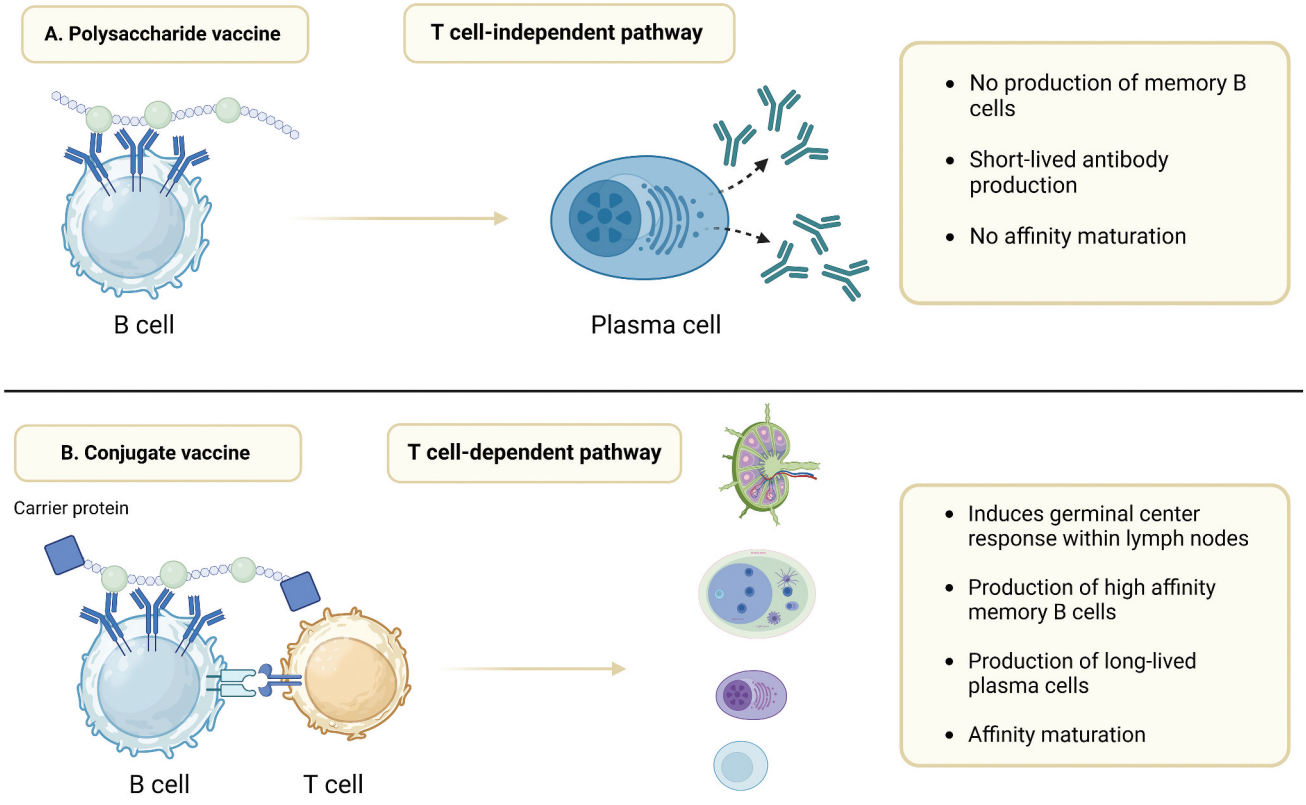

Figure 1. Differences in T cell-dependent (PCV) vs T cell-independent (PPV) pneumococcal vaccine responses in humans. This figure was created using BioRender software.

almost exclusively composed of germinal center B (B_{gc}) cells.[50,55,56] Here, naïve B cells proliferate, undergo somatic hypermutation and class switching.[50,57] The light zone is located near the lymph node capsule and contains a mixture of B_{gc} cells, $CD4^+$ T follicular helper cells (T_{fh}) and a network of stromal cells called follicular dendritic cells (FDCs) that display antigen.[55,56] In the light zone, affinity-driven B cell selection takes place and differentiation toward long-lived plasma cells or memory B cells occurs in response to encountered antigens and signals provided by T_{fh} cells.[53,55] The carrier protein coupled to the polysaccharides is presented to T_{fh} cells and thus enables the formation of GC responses following PCV. B_{gc} cells can shuttle between the light and dark zone, engaging in multiple cycles of somatic hypermutation (SHM) and selection. This process serves to enhance the overall affinity of the B cell receptor (BCR) toward its cognate antigens.[54]

In murine models, GCs are established within a few days to several weeks following primary immunization.[58] During vaccination, B cells become activated and migrate to the draining lymph node, more specifically the center of B cell follicles, where GCs are formed.[59] In the GCs, B cells compete for a pool of signals originating from T cells, such as cytokines and co-stimulatory receptors, which propel their transition from the light zone to the dark zone, trigger B cell apoptosis, or differentiation and GC exit.[60–62] B cells that gathered beneficial mutations in the genes encoding the antigen-binding part of their B cell receptor in the dark zone are more likely to seize and present antigens to T cells when they move back to the light zone, expediting their transformation into either memory B cells or plasma cells.[59] These are the end products of the germinal center reaction and are essential for durable humoral immunity.[54] In the following section, we will describe in more detail the cellular players involved in GC responses and how they are affected by HIV infection.

Impact of HIV infection on germinal center dynamics

Alterations in germinal center structure in HIV infection

Although initiation of cART in PLWH results in viral suppression and $CD4^+$ cell recovery, residual immune deficiency persists.[63] Indeed, Jeger-Madiot *et al.* reported that HIV infection affects GC architecture within lymph nodes.[50] Within hours of infection, the virus roots within lymph nodes, residing predominantly on the surface of follicular dendritic cells (FDCs) and within $CD4^+$ cells in GCs.[64,65] This leads to follicular changes over time such as hyperplasia of GCs, lysis of FDCs, and follicular atrophy.[35,66,67] Emerging evidence indicates that, despite viral suppression, structural abnormalities often persist in lymphoid tissue, and low-level viral replication can still be detected in these sites during the chronic disease phase, see Figure 3.[62,68]

Two possibly related processes have been observed in GCs of PLWH that might explain these changes.[50,64] Firstly, immunohistochemical analysis shows fragmentation and elimination of both FDCs and fibroblastic reticular cells, resulting in disruptions of the GC microarchitecture with less distinct dark and light zones.[64,69] This disruption impairs the ability of FDCs to coordinate positioning of B_{gc} and T_{fh} cells thereby affecting the selection and maturation of high-affinity B cells into long-lived plasma cells.[30,50] The elimination of FDCs in PLWH is not yet fully understood

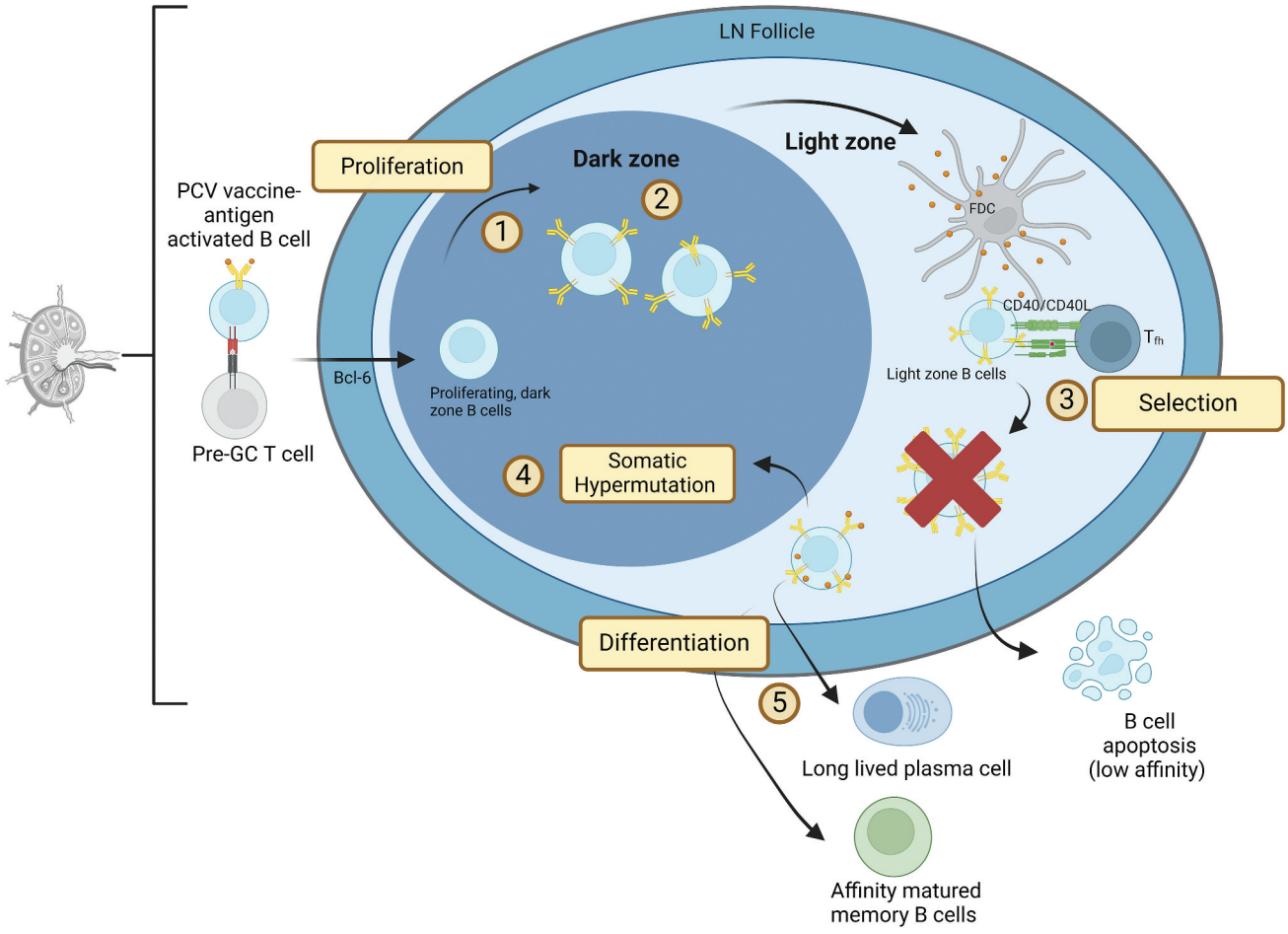

Figure 2. Schematic overview of GC formation. 1) Early GC formation and clonal expansion occurring within weeks after initial contact with antigens. 2) Somatic hypermutation in the dark zone. 3) Selection in the light zone, B cells move into the light zone, where their modified B cell receptors are tested for improved antigen binding with help from T_{fh} cells and follicular dendritic cells. B cells with higher BCR affinity capture more antigen, receiving more T cell help, resulting in positive selection. B cells with unfavorable BCRs undergo apoptosis. 4) Recirculation and further mutation. Positively selected B cells undergo immunoglobulin class-switch recombination and are instructed to recirculate to the dark zone. In the dark zone, these B cells proliferate and undergo further SHM, generating higher affinity antibodies. 5) Final differentiation: antigen-selected B cells differentiate into memory B cell precursor cells and plasmablasts. This figure was created using BioRender software.

but might be a result of cell destruction mediated by CD45RA low $CD8^+$ T cells. Indeed, an abundance of cytotoxic granule-containing $CD8^+$ lymphocytes infiltrate germinal centers during active HIV-1 infection, initially aimed at eliminating infected cells. However, their accumulation in close proximity to viral antigen depositions and follicular atrophy suggests that they might be contributing to the progressive destruction of FDCs.[70] Secondly, collagen depositions in the T cell zone can be found, which disrupts cell homing affecting $CD4^+$ and $CD8^+$ T cells.[71] The formation of collagen depositions can be explained by the fact that T regulatory cells (T_{regs}) accumulate within the lymph node due to persistent inflammation, a key component of HIV infection. These cells produce TGF-β1 which leads to an increase in collagen production.[72] Interestingly, lymph node fibrosis at time of diagnosis seems to be inversely correlated with the number of $CD4^+$ cells in peripheral blood, as well as the degree of $CD4^+$ T cell recovery after cART therapy initiation.[73] Thus, fibrotic remodeling, impaired cell interactions and limited cytokine access, collectively impair the survival, growth and trafficking of $CD4^+$ cells.[73]

Alterations in germinal center populations in HIV infection

T-follicular helper (T_{fh}) cells

T-follicular helper (T_{fh}) cells, discovered around the turn of the century as a recognizable subset of $CD4^+$ T cells, have since been extensively studied.[64,74,75] T_{fh} cells residing in lymph nodes and spleen are identified by their expression of CXCR5, PD-1, CD40L and Bcl-6.[56,62,76,77] These T cells facilitate GC reactions through expression of CD40L, as well as cytokines such as IL-21. CD40L is a member of the tumor necrosis factor (TNF) family and interacts with CD40 receptors on B_{gc} cells, thereby initiating B cell proliferation and assisting in the production of high affinity and long-term humoral responses, see Figure 3.[61,78]

Previous studies have demonstrated that T_{fh} cells are also a major HIV reservoir. They harbor the highest levels of HIV

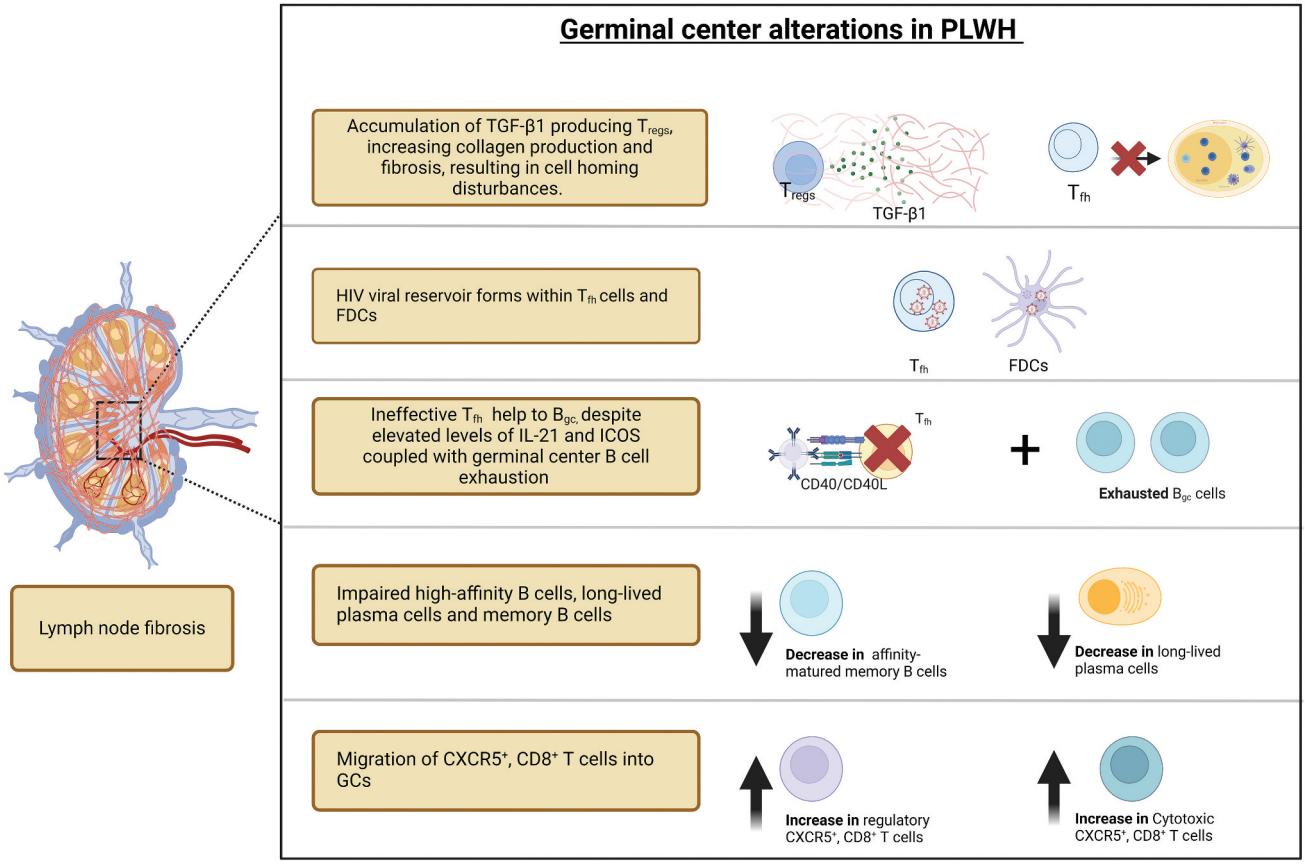

Figure 3. Schematic overview of germinal center changes in PLWH. FDC = follicular dendritic cells. T_{regs} = T follicular regulatory cells. T_{fh} = T follicular helper cells. B_{gc} = germinal center B cells. This figure was created using BioRender software.

RNA among $CD4^+$ T cell subsets, efficiently support viral replication in vitro and contain replication-competent virus even in non-progressors with low viremia.[79,80] This, together with the limited access of HIV-eliminating NK cells to GCs and reduced antiretroviral drug penetration in lymph nodes, helps explain why the lymph nodes are a sanctuary for HIV replication, even when on cART.[79,81,82]

Graff-Dubois *et al.* and others have linked HIV infection to alterations in T_{fh}-dependent B cell development, showing that T_{fh} cells, although often increased in numbers, provide insufficient B cell help *in vitro*.[83,84] Moreover, increased expression of the cell surface markers Inducible costimulator (ICOS), PD-1 and signaling lymphocytic activation molecule (SLAM) by T_{fh} cells can be found in PLWH, which are molecules involved in B cell regulation, activation and exhaustion.[85] Additionally, Petrovas *et al.* demonstrated that $SLAM^{high}$ T_{fh} cells from Simian immunodeficiency virus (SIV)-infected nonhuman primates produce significant amounts of IL-10, a regulator of T_{fh} cell responses, and exhibit a greater capacity for *in vivo* proliferation, when compared to $SLAM^{low}$ T_{fh} cells. This phenotypic shift within the T_{fh} compartment suggests that HIV-associated chronic immune activation may alter T_{fh} function and subset dynamics, ultimately resulting in a reduced GC-associated vaccine response.[85,86] Thus, targeting pathways that restore T_{fh} cell function, such as modulation of IL-21 or CD40L signaling, may enhance B cell help and improve germinal center vaccine responses in PLWH.

Circulating T follicular helper (cT_{fh}) cells

Circulating T follicular helper (cT_{fh}) cells are composed of heterogeneous $CXCR5^{high}$, $CD4^+$ T cells. This subset of $CD4^+$ T cells, also named peripheral T_{fh} cells, share functional characteristics with T_{fh} cells, with the ability to provide B cell help and facilitate SHM and class-switch recombination, highlighting their potential role in stimulating vaccine-induced immunity.[62,74,87–89] Although their exact connection to T_{fh} cells is not yet fully understood, their high expression of CCR7 indicates the capacity to traffic to SLOs.[90,91] As opposed to T_{fh} cells, cT_{fh} cells express much lower amounts of PD-1 and do not express Bcl-6.[62,89] T-cell receptor (TCR) sequencing has demonstrated clonal overlap between cT_{fh} and lymph node T_{fh} cells, though their precise and potentially distinct roles in vaccine immunology remain under investigation.[92]

In relation to HIV infection, Pallikkuth et al. found that cT_{fh} cells exhibit a high susceptibility to HIV, similar to the lymph node counterparts, showing that they can maintain latent viral reservoirs despite effective cART.[90] Additionally, PLWH not only have an impaired quantity of cT_{fh} cells but they also show an impaired function, with reduced IL-21 production in response to the Influenza A (H1N1) vaccine, a crucial cytokine for B cell activation and antibody generation.[93]

T follicular regulatory (T_{fr}) cells

T follicular regulatory (T_{fr}) cells form a small population of cells within GCs.[50,56] Sharing features with both regulatory T and T_{fh} cells, T_{fr} cells can be identified by their expression of CXCR5, PD-1, Bcl-6 and FOXP3.[94,95] Although the full scope of T_{fr} cell function is not entirely understood, early studies suggest that they facilitate isotype switching and regulate antigen specificity, making them an important regulatory element within the GC reaction.[50,61] Others have demonstrated that T_{fr} cells hinder proliferation of T_{fh} and B_{gc} cells in murine models, by inhibiting ICOS expression and IL-4 and IL-21 production by the T_{fh} cells.[95–97]

In the context of HIV, earlier research showed that T_{fr} cells restrict the quantity and functionality of T_{fh} cells, which are necessary for effective antibody production. This inhibition occurs through suppression of cytokine IL-21, and molecules such as ICOS, both vital for generating adequate B cell help and the generation of high-affinity antibodies.[97,98] By restraining T_{fh} cell activity, T_{fr} cells may contribute to the maintenance of the HIV reservoir within B-cell follicles, thus posing a barrier to achieving viral clearance.[95] Jeger-Madiot *et al.* investigated the T_{fh}/T_{fr} cell ratio during HIV disease progression and showed that an initial increased T_{fh}/T_{fr} ratio can be found, related to GC activation.[50] Subsequent expansion of T_{fr} cells progressively decreases this ratio. Nevertheless, the T_{fh}/T_{fr} ratio remains elevated as disease progresses, indicating ongoing GC dysregulation in PLWH.[50]

While selectively inhibiting T_{fr} cell activity could relieve constraints on B cell activation and enhance pneumococcal conjugate vaccine responses in PLWH, the broader immunological consequences remain unclear. Given the critical role of T_{fr} cells in preventing autoreactivity, their depletion may not only alter vaccine responses but also exacerbate immune activation, inflammation, or even affect HIV pathogenesis. Further research is needed to better understand and clarify the potential of this subpopulation.

Follicular $CXCR5^+$, $CD8^+$ T cells

$CD8^+$ T cells have traditionally not been considered central to GC reactions.[56,61] In chronic HIV infection, they show limited capacity to access GCs, in contract to earlier stages of infection where, as discussed above, their infiltration contributes to follicular dendritic cell damage.[62,99,100] However, a distinct subset of $CXCR5^+$ $CD8^+$ T cells has been identified within B cell follicles and GCs during chronic viral infections, including Epstein–Barr Virus (EBV), SIV and HIV.[101] Ferrando *et al.* described this subset in SLOs of SIV^+ non-human primates.[102] Subsequent studies confirmed the presence of follicular $CD8^+$ ($fCD8^+$) T cells in lymph nodes of PLWH.[50,103] Although the exact function of this subset has not yet been unraveled, emerging evidence suggests that they may serve regulatory roles in SIV infection. Indeed, $fCD8^+$ T cells suppress T_{fh} effector functions and induce T_{fh} cell apoptosis via an HLA-E pathway.[104] Alongside their regulatory activity, a cytotoxic subset of $CXCR5^+$ $CD8^+$ T cells has been characterized with high *ex vivo* expression of granzyme B and perforin. One study, which employed an anti-HIV/anti-CD3 bispecific antibody in a redirected killing assay, demonstrated that $fCD8^+$ T cells exhibited superior killing activity compared to non-$fCD8^+$ T cells.[50,103] This was further expanded by findings that this subpopulation of $CD8^+$ T cells is more prevalent among spontaneous HIV controllers than non-controllers.[105] Their ability to selectively target HIV-infected cells positions them as potential contributors to viral clearance.[101] Although their direct involvement in pneumococcal vaccine responses or GC remodeling remains unexplored, their regulatory impact on Tfh cells suggest they may indirectly modulate vaccine-induced immunity in PLWH.

Harnessing or expanding follicular CXCR5+ CD8+ T cells with cytolytic capacity may offer benefits such as purging the HIV viral reservoir within GCs, thereby stimulating lymph node GC reconstitution and ultimately enhancing PCV responses.

Germinal center B (B_{gc}) cells

B_{gc} cells are the predominant immune cell population in GCs and are among the fastest dividing cells in humans.[56] Unlike naïve B cells, B_{gc} cells exhibit high proliferation rates, with a cell cycle time of only 5-6 h.[54] This rapid division combined with the expression of the enzyme activation-induced cytidine deaminase (AID) leads to somatic mutations that generate sequence diversity for antigen affinity-based selection.[54] Bcl-6, a primary transcriptional suppressor, is selectively upregulated in GCs and orchestrates the B_{gc} program. Expression of key surface markers-including proapoptotic Fas and S1P2-distinguishes B_{gc} cells from their naïve counterparts. Bcl-6 is crucial for the GC B cell program, influencing genes that contribute to the B_{gc} cell characteristics. Specifically, Bcl-6 suppresses MYC and PRDM1 (which encodes Blimp-1) and thereby elevates the thresholds for positive selection and plasma cell differentiation.[61]

In PLWH, B_{gc} exhibit a functional impairment, namely increased expression of PD-L1, a marker of cellular exhaustion, suggesting HIV-induced dysregulation of this population.[7,40,106,107] This, combined with the intrinsic elevated levels of PD-1 expression on T_{fh} cells in HIV, adversely affects T_{fh} cell function and results in insufficient T_{fh} cell assistance to B_{gc} cells.[76] As a result, the T_{fh}-B_{gc} axis is disrupted, contributing to poor antibody responses following pneumococcal conjugate vaccination.[108]

Systemic immunological alterations in HIV infection affecting vaccine response

Beyond GC disruptions, systemic immunological changes in PLWH also contribute to impaired vaccine responses, see Figure 4. This is further evidenced by reduced responses to T-cell independent vaccines like PPV, underscoring the role of systemic dysfunction. Firstly, $CD4^+$ cell depletion is a hallmark of acute HIV infection, particularly affecting mucosal sites shortly after infection, and is not fully reversible by cART. While early cART improves $CD4^+$ cell recovery, persistent immune activation, driven in part by microbial translocation due to gut barrier damage, sustains $CD4^+$ cell loss.[109] Secondly, chronic inflammation is a key feature of HIV infection, driven

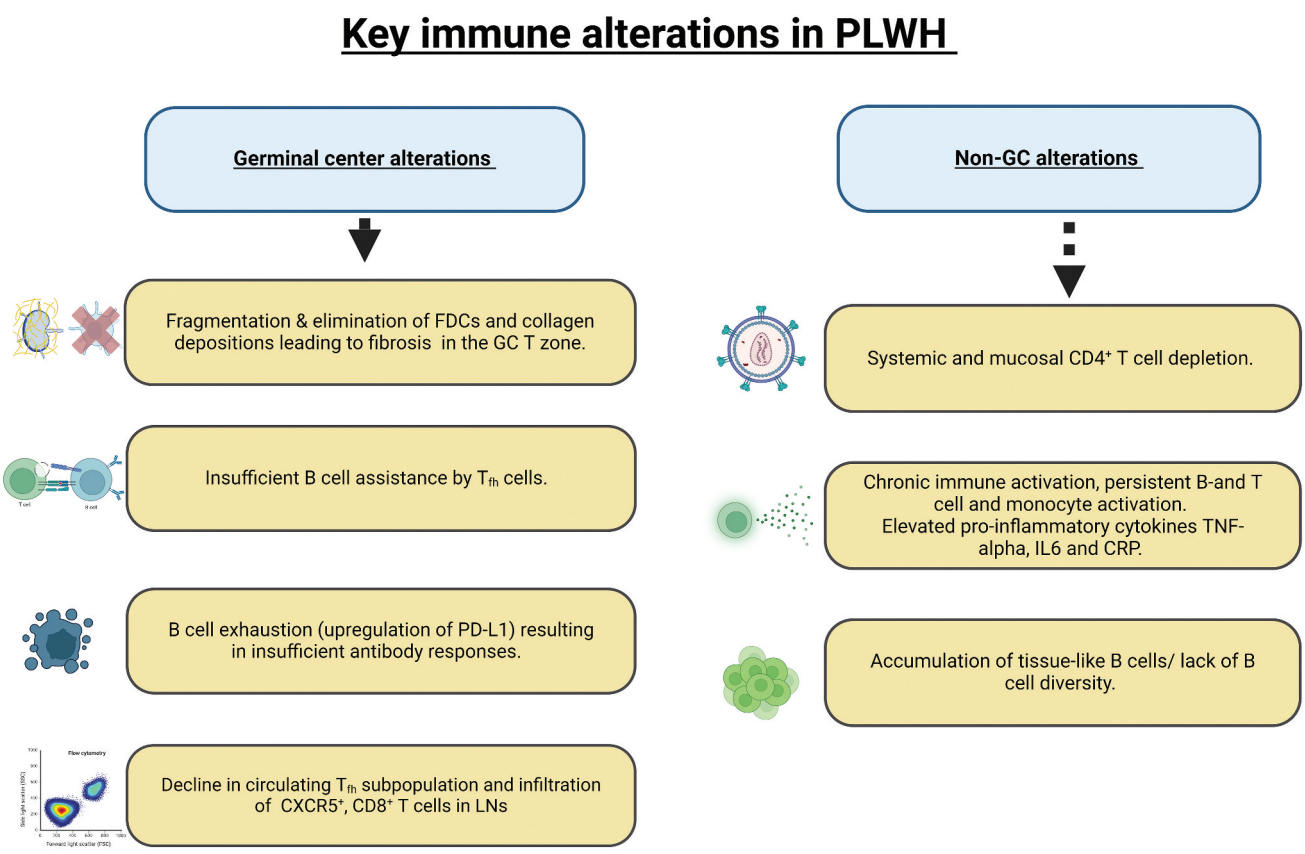

Figure 4. GC and non-GC related immunological alterations in PLWH affecting vaccine responses. This figure was created using BioRender software.

by the persistent activation of T cells, B cells and monocytes, as well as elevated pro-inflammatory cytokines such as TNF-alpha, IL-6 and CRP.[110] Immune activation is exacerbated by persistent viral replication, co-infections and as described above, microbial translocation. HIV reservoirs under cART are not solely found within lymph nodes, but also within several other tissues, such as the urinary tract, skin, lungs and central nervous system, inducing a state of chronic inflammation and ultimately leading to exhaustion of the immune system.[111–113] This increased inflammation also influences the innate immune response to vaccines, altering the immune activation thresholds and cellular responses necessary for effective immunogenicity. This was observed by George *et al.*, who found that elevated pro-inflammatory markers, C-C chemokine receptor-2 (CCR2) and plasma-soluble tumor necrosis factor receptor-1 (sTNFR1), at baseline were associated with impaired Influenza vaccine responses in PLWH.[114] Thirdly, B cells display significant dysfunction characterized by chronic activation and exhaustion, impairing their ability to respond effectively to antigens.[115] There is a shift from durable resting memory B cells to exhausted non-conventional subsets such as tissue-like memory (TLM) and activated memory B cells, which are more apoptosis-prone and less responsive to antigenic stimulation.[34] While limited data are available, it is plausible that these changes in B cell function, limit their ability to generate specific, high-affinity antibodies, contributing to pneumococcal vaccine hyporesponsiveness.[115–117] More so, while purified polysaccharide vaccines do not rely on T cell help and GC formation, B cell dysfunction in PLWH may still impair the polysaccharide vaccine effectiveness via the T cell independent route. The accumulation of TLM B cells and the loss of B cell diversity could help explain why PLWH exhibits weaker responses, even to polysaccharide vaccines.[34,118,119] Lastly, mitochondrial dysfunction, insulin resistance and intracellular lipid accumulation due to cART have been described previously.[120,121] Although the exact implications of these alterations for vaccine hyporesponsiveness remain undefined, it is credible that they might also influence the vaccine response.[122]

Reducing chronic inflammation may help restore immune homeostasis, thereby lowering the activation threshold of immune cells and improving the quality of vaccine-induced responses. By mitigating systemic immune activation and preserving immune cell function, particularly within the B cell and T cell compartments, anti-inflammatory interventions could enhance pneumococcal vaccine responsiveness in PLWH.

Future directions; lymph node FNA and next-generation pneumococcal vaccines

Recent advances in ultrasound-guided lymph node sampling techniques have opened new avenues for understanding vaccine-induced immunity beyond traditional analyses in

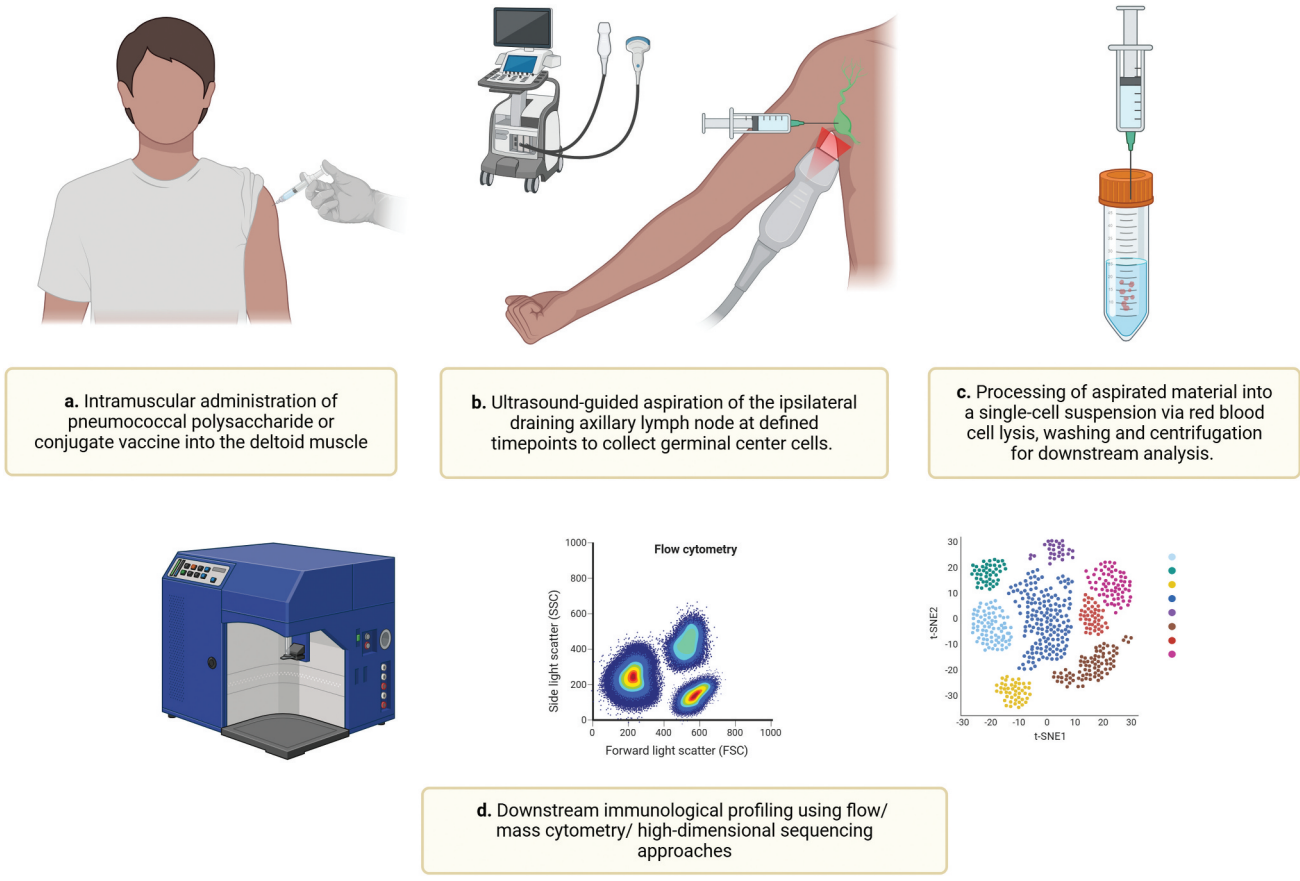

Figure 5. Detailed lymph node fine-needle aspiration procedure. This figure was created using BioRender software.

peripheral blood.[123] Fine-needle aspiration (FNA) of vaccine-draining lymph nodes is a minimally invasive method that enables direct and repeated access to germinal center (GC) activity in humans, see Figure 5. While serological studies provide information on circulating antibody titers post-vaccination, they do not capture the underlying cellular dynamics that drive long-lived immunity.[124] FNA addresses this gap by allowing characterization of B_{gc} cells and T_{fh} cells in vivo. This technique has been successfully employed to study immune responses to various vaccines, revealing that antigen-specific B_{gc} and T_{fh} cells can persist for several months post-vaccination and that their maturation correlates with the development of high-affinity memory B cells and long-lived plasma cells.[51–52,125–129] Importantly, Quinn et al. performed a seminal FNA pilot study in the PLWH population.[51] Their findings showed that while GC responses can be induced, observed in 2/2 recipients of mRNA vaccines, they were infrequent among recipients of the Ad26. COV2.S vector-based vaccine (only 1/6). These results illustrate the variability of vaccine-induced GC activity in HIV infection and offer mechanistic insight into the suboptimal and short-lived antibody responses often reported in PLWH. This and other FNA studies underscore the power of FNA to uncover cellular correlates of durable vaccine responses, unravel mechanisms of action for impaired immunity and ultimately guide the rational design and evaluation of next-generation vaccines.[51,126–128] Such studies may enable a deeper exploration of pneumococcal vaccine immunogenicity, particularly in the context of HIV-associated germinal center dysfunction (https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-510354-16-00).

Secondly, as next-generation pneumococcal conjugate vaccines (PCVs) expand in serotype coverage – such as PCV24, PCV25, and PCV31—concerns have arisen over a phenomenon known as immunogenicity creep.[21,130,131] This term refers to the observed gradual reduction in immune responses elicited against individual serotypes as the total number of serotypes in a vaccine increases.[130] While each novel vaccine passes non-inferiority testing against the most recently licensed PCV, the cumulative effect may be that at some point vaccine effectiveness drops. Immunogenicity creep may result from a combination of factors, including antigenic competition among multiple serotypes and carrier proteins and reduced per-serotype antigen doses. While this effect has been described in children and to a lesser extent in healthy adults, its impact on immunocompromised populations, particularly PLWH, is poorly understood.[131] Given their already diminished vaccine responses, PLWH may potentially be more affected by this immunogenicity creep, which should be tested and if necessary, lead to reevaluation of future vaccination strategies. Such adjustments might include favoring lower-valency vaccines with higher per-serotype immunogenicity for PLWH while leveraging population-level herd immunity via infant immunization programs, or using altered dosing schedules e.g. by spacing out PCVs (PCV20) into two separate

vaccines (PCV10s). Alternatively, a successive PCV approach also has shown promising results and should also be evaluated for newer, higher valency vaccines.[38]

Thirdly, targeting the ongoing HIV replication within lymph nodes, dysfunction in key GC cell players and chronic inflammation, might provide possibilities to improve vaccine responsiveness in PLWH. fCD8$^+$ T cells have potential to target HIV-infected cells. Utilizing this information may create opportunities to enhance adjuvants specifically for PLWH.[103,105] Future research should focus both on uncovering mechanistic insights and translating these findings into clinical solutions.

Conclusion

Despite widespread vaccine availability, PLWH remain insufficiently protected against pneumococcal disease due to persistent immune dysfunction. This review highlights how structural and functional impairments within germinal centers, combined with systemic immune alterations, compromise vaccine efficacy. As pneumococcal vaccine design evolves, addressing challenges like immunogenicity creep and leveraging advanced immune profiling tools – such as lymph node fine-needle aspiration – in PLWH will be key to optimizing pneumococcal vaccine strategies.

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Author contributions

G.E.L. conceived and designed the narrative review, conducted the literature search, interpreted the data and drafted the manuscript, including the creation of tables and figures. D.d.V. contributed to revising the manuscript and provided suggestions and insights. L.V. critically reviewed the manuscript. S.J. and A.R. supervised the project, critically reviewed the manuscript multiple times, revised the text and recommended related literature. All authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Ethical statement

This study did not involve human participants, and therefore, ethical approval was not required.

Notes on contributor

Giovanni E. Loe-Sack-Sioe is a PhD-candidate at the Leiden University Center for Infectious Diseases (LU-CID), studying vaccine hyporesponsiveness in people living with HIV. His research combines novel sampling techniques to uncover vaccine kinetics in secondary lymphoid organs.

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