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The Unfinished Agenda: Pursuing Durable Protection Against Pneumococcal Disease in People Living with Human Immunodeficiency Virus

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ABSTRACT

Background: The syndemic of the human immunodeficiency virus and *Streptococcus pneumoniae* infections remains a significant global health challenge. Despite effective antiretroviral therapy, people living with the human immunodeficiency virus face a 20- to 100-fold higher risk of invasive pneumococcal disease due to persistent, multifaceted immunodeficiency affecting both innate and adaptive immunity. This includes dysfunction of alveolar macrophages and neutrophils, compromised mucosal barriers, depletion of CD4+ T-cells particularly T-follicular helper cells and B-cell dysregulation, creating a perfect storm for invasive infection. The evolution from polysaccharide to conjugate vaccines represents a major advancement. Pneumococcal conjugate vaccines, by enabling T-cell-dependent responses, generate higher-quality antibodies, robust memory B-cells, and demonstrate superior immunogenicity and effectiveness in people living with the human immunodeficiency virus compared to the 23-valent pneumococcal polysaccharide vaccine. Evidence from immunogenicity studies, observational data, and the herd effects from childhood pneumococcal conjugate vaccines programs confirms that pneumococcal conjugate vaccines significantly reduce vaccine-type pneumococcal disease. However, challenges like serotype replacement, waning immunity, suboptimal response despite antiretroviral therapy, and the aging of the people living the human immunodeficiency virus population impede optimal protection.

Conclusion: While conjugate vaccines have transformed prevention, durable protection against pneumococcal disease in people living with the human immunodeficiency virus remains an unfinished agenda. Future success hinges on developing novel vaccines (e.g., protein-based), optimizing strategies with adjuvants and boosters, defining correlates of protection, and ensuring global equity in vaccine access. A multifaceted approach combining research, clinical innovation, and public health policy is essential to significantly reduce this burden.

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Introduction

The intersection of the human immunodeficiency virus (HIV) pandemic and infections caused by *Streptococcus pneumoniae* represents a significant and persistent syndemic challenge to global public health, particularly in regions with high HIV prevalence and limited access to healthcare resources (1). HIV infection causes progressive depletion and functional impairment of CD4+ T lymphocytes, coupled with chronic immune activation and dysregulation of B-cell function, leading to a state of profound and multifaceted immunodeficiency (2). This immunocompromised state dramatically increases susceptibility to a wide range of opportunistic infections, with pneumococcal disease being one of the most common and severe bacterial complications, contributing substantially to morbidity and mortality among people living with HIV (PLWH) (3, 4).

The burden of invasive pneumococcal disease (IPD) is disproportionately high among PLWH. Even in the era of effective antiretroviral therapy (ART), which has successfully restored CD4+ counts and reduced the incidence of many opportunistic infections, the risk of IPD (e.g., pneumonia, bacteremia, and meningitis) remains 20- to 100-fold higher in PLWH compared to the general population (5, 6). This persistent vulnerability underscores the complex nature of HIV-associated immune dysfunction, which extends beyond mere CD4+ depletion. ART does not fully normalize immune function; residual defects in neutrophil activity, macrophage phagocytosis, memory B-cell maturation, and polysaccharide-specific antibody responses create a permissive environment for pneumococcal colonization and invasion (7). Furthermore, chronic inflammation and microbial translocation associated with HIV may damage the respiratory epithelium, facilitating bacterial adhesion and dissemination (8).

Vaccination has emerged as a cornerstone strategy to mitigate this excess risk. The evolution from the 23-valent pneumococcal polysaccharide vaccine (PPSV23) to more immunogenic pneumococcal conjugate vaccines (PCVs) represents a major advancement in preventive care for PLWH (9, 10). Pure polysaccharide vaccines like PPSV23, which elicit a T-cell-independent response, often result in short-lived immunity with poor immunological memory and are less effective in immunocompromised individuals who lack robust B-cell function (11). In contrast, conjugate vaccines, by coupling capsular polysaccharides to a protein carrier (e.g., CRM197), effectively recruit T-cell help. This T-cell-dependent response induces isotype switching, generates high-affinity antibodies, and establishes long-lasting memory B cells—precisely the responses that are often deficient in PLWH (12, 13).

The introduction of higher-valent conjugate vaccines (PCV15 and PCV20) has further expanded serotype coverage, offering protection against a broader range of clinically significant strains. However, critical challenges remain, including the emergence of non-vaccine serotypes (NVTs) due to serotype replacement, the optimal timing of vaccination in relation to ART initiation to maximize immunogenicity, and the potential need for booster doses to sustain protection (14, 15).

This review aims to synthesize current knowledge on the epidemiology and immunological pathogenesis of pneumococcal disease in the context of HIV infection. Furthermore, it will critically evaluate the clinical evidence for the efficacy and effectiveness of both polysaccharide and conjugate pneumococcal vaccines in this high-risk population. It will discuss the molecular mechanisms underpinning vaccine-induced protection, address the ongoing challenges in achieving optimal and durable immunity, and to explore future directions for research and public health policy to reduce the burden of pneumococcal disease in the global HIV syndemic.

Unraveling the Weak Links: Immunopathogenesis of Pneumococcal Disease in HIV

The heightened susceptibility to *S. pneumoniae* in people living with HIV (PLWH) stems from a profound and multi-layered erosion of the body's defenses, compromising both the immediate innate response and the more specialized adaptive immunity (16).

Innate immune dysfunction represents the first critical failure. HIV infection severely disrupts the first line of defense in the lungs. Alveolar macrophages, which are paramount for engulfing and destroying pneumococci, display a markedly reduced phagocytic and bactericidal ability. This dysfunction is a direct consequence of HIV-induced chronic activation and alteration of their normal state (17). Furthermore, neutrophil activity is significantly impaired, with documented deficiencies in its ability to migrate toward infection sites (chemotaxis), consume pathogens (phagocytosis), and form neutrophil extracellular traps (NETs) to ensnare bacteria, even in individuals on antiretroviral therapy (18). Compounding these cellular deficits, the physical integrity of the respiratory epithelial barrier is weakened. The relentless state of HIV-associated inflammation and immune activation damages the mucosal lining, which facilitates the adherence of bacteria and their subsequent translocation into the bloodstream, setting the stage for invasive disease (19).

The dysfunction extends catastrophically to the adaptive arm of the immune system, culminating in adaptive immune failure. The defining depletion of CD4+ T-cells, with a particularly devastating impact on T-follicular helper (Tfh) cells residing in germinal centers, cripples the generation of a targeted antibody response (20). These Tfh cells are indispensable, as they provide the necessary signals for B cells to undergo critical processes: class-switch recombination (to produce more effective antibody types), somatic hypermutation (to refine antibody affinity), and ultimate differentiation into either memory B cells or antibody-secreting plasma cells (21). The absence of this robust T-cell help renders the immune response to T-cell-independent antigens, such as the polysaccharide capsule that encapsulates *S. pneumoniae*, profoundly weak and transient (22).

This is exacerbated by a state of general B-cell dysregulation caused by HIV (23). The B-cell compartment exists in a paradox of chronic hyperactivation, leading to elevated levels of non-specific antibodies (hypergammaglobulinemia), but this occurs at the expense of targeted efficacy (24). This hyperactivation leads to B-cell exhaustion and an impaired ability to mount strong responses to new, specific antigens. Consequently, PLWH often exhibit reduced reservoirs of naïve B cells and a paucity of memory B cells specifically tuned to polysaccharide antigens (25). This results in inadequate antibody titers against pneumococci and feeble recall responses upon encounter, which directly explains the limited clinical efficacy observed with pure polysaccharide vaccines in this population (26).

In essence, this cumulative immunodeficiency creates a perfect storm for invasive pneumococcal disease: the initial clearance by innate immune cells is sluggish, the physical mucosal barriers are breached, and the system fails to generate high-affinity, pathogen-specific antibodies and long-lasting memory responses. This sequential failure allows *S. pneumoniae* to easily transition from a state of harmless colonization in the nasopharynx to a life-threatening invasive infection (27).

From Polysaccharides to Conjugates: A Revolution in Vaccine Strategy

The development of pneumococcal vaccines for people living with HIV (PLWH) represents a crucial journey of overcoming immunological limitations through innovative vaccine design, marking a significant evolution from polysaccharide-based to conjugate vaccine platforms (28).

The limitations of polysaccharide vaccines present a fundamental challenge in

immunocompromised hosts (29). The 23-valent pneumococcal polysaccharide vaccine (PPSV23), while covering a broad spectrum of serotypes, suffers from a critical immunological flaw in the context of HIV infection due to its T-cell-independent mechanism of action (30). This vaccine directly stimulates B cells without engaging T-cell help, resulting in several key shortcomings: rapid decay of antibody levels typically within 3-5 years, absence of a robust booster response upon revaccination (a phenomenon known as hyporesponsiveness), and failure to generate long-term immunological memory (31). Meta-analyses have consistently demonstrated that while PPSV23 shows effectiveness in reducing invasive pneumococcal disease in the general population, its efficacy in PLWH remains modest at best, highly variable, and ultimately provides unreliable protection for this vulnerable population (32).

In contrast, the advent of conjugate vaccines represents a paradigm shift in vaccine strategy. Pneumococcal conjugate vaccines (PCVs) achieve their superior immunogenicity through covalent linking of capsular polysaccharides to an immunogenic protein carrier, such as CRM197, diphtheria toxoid, or tetanus toxoid (33). This design fundamentally converts the immune response from T-independent to T-dependent, enabling several crucial immunological advantages that directly address the deficits seen in PLWH. The conjugate design allows for effective engagement of CD4+ T-cells, as the protein carrier is processed and presented by antigen-presenting cells, activating T-cells that subsequently provide essential help to antigen-specific B cells (34). This T-cell help drives the formation of long-lived memory B cells and plasma cells, enabling rapid and potent anamnestic responses upon future pathogen exposure (35). Furthermore, the response is characterized by isotype switching to IgG1 and IgG3, affinity maturation, and production of mucosal IgA—all features essential for effective opsonophagocytosis and neutralization of pneumococci (36).

The strategic approach of sequential vaccination has been explored to leverage the respective advantages of both vaccine types. The prime-boost strategy, involving initial vaccination with a conjugate vaccine followed by administration of a polysaccharide vaccine, aims to combine the superior memory induction of PCVs with the broader serotype coverage of PPSV23(37). However, evidence supporting the superior effectiveness of this approach compared to PCV vaccination alone remains limited and continues to evolve, particularly in the context of HIV-associated immunodeficiency (38).

Clinical Evidence: Evaluating Vaccine Efficacy and Effectiveness in PLWH

Numerous clinical studies have evaluated the real-world impact of PCVs on PLWH, with evidence supporting their use stemming from immunogenicity trials, direct effectiveness studies, and observations of indirect herd effects (39). The key findings from these studies are summarized in Table 1.

Immunogenicity Studies form the foundational evidence. Consistently, clinical trials have demonstrated that PCVs are significantly more immunogenic than PPSV23 in PLWH. Vaccination with PCV (e.g., PCV7, PCV13) results in higher geometric mean concentrations (GMCs) of serotype-specific IgG antibodies and higher opsonophagocytic activity (OPA) titers, a functional correlate of protection (40, 41). A critical finding is that the timing of vaccination matters profoundly; administering PCV after ART initiation and after some degree of immune reconstitution (e.g., CD4+ >200 cells/μL) yields a superior antibody response compared to vaccinating in the setting of severe immunodeficiency (42).

The introduction of PCVs into childhood immunization programs has had a dramatic Indirect (Herd) Effectiveness on IPD incidence in PLWH. By reducing nasopharyngeal carriage of vaccine-type pneumococci in vaccinated children,

transmission to susceptible adults, including PLWH, is drastically reduced (43). This has led to significant declines in vaccine-type IPD among PLWH in countries with mature pediatric PCV programs, even before adult recommendations were widespread (44). However, this herd effect also underscores a critical challenge, serotype replacement (44). As vaccine-type carriage decreases, non-vaccine serotypes (NVTs) have expanded to fill the ecological niche (45). Consequently, PLWH remain vulnerable to IPD caused by these NVTs, a persistent limitation that highlights the need for broader-valency vaccines and continued surveillance (46).

Regarding Direct Effectiveness against Clinical Outcomes, while randomized controlled trials (RCTs) powered to directly measure efficacy against IPD are ethically challenging in the ART era, large observational cohort and case-control studies have provided compelling real-world evidence (47). These studies consistently show that PCV vaccination is associated with a significant reduction in the risk of all-cause pneumonia and confirmed IPD among PLWH, confirming that the robust immunogenicity translates into meaningful clinical protection (47, 48).

Ongoing Challenges in Achieving Optimal Protection

Despite the clear benefits of conjugate vaccines, several significant challenges impede the goal of achieving optimal and durable protection against pneumococcal disease in people living with HIV (49).

The timing of vaccination presents a complex clinical dilemma (50). The immunogenicity of pneumococcal conjugate vaccines is strongly influenced by the degree of immune reconstitution achieved with antiretroviral therapy (51). Vaccinating individuals with low CD4+ counts often results in blunted antibody responses and suboptimal protection (52). While current guidelines recommend vaccination after ART initiation, the precise optimal window balancing the need for early protection with achieving maximum immunogenicity remains an active area of investigation (53). Determining the exact point at which immune recovery is sufficient to mount a robust vaccine response while minimizing the period of vulnerability represents a critical challenge in clinical management (54).

Waning immunity and the potential need for booster doses constitutes another significant hurdle (55). Despite the superior memory response induced by PCVs compared to polysaccharide vaccines, studies consistently demonstrate that antibody levels in PLWH decline more rapidly than in immunocompetent hosts (56). This observation has sparked considerable debate regarding the potential need for and timing of booster vaccinations (57). The question of whether to revaccinate with another dose of PCV or switch to PPSV23 for broader serotype coverage lacks a definitive evidence-based answer, leading to variations in national guidelines and clinical practice (58). The optimal interval for revaccination and the most effective booster strategy remain important unanswered questions in the field (59).

Serotype replacement and non-vaccine serotypes represent an evolving challenge in pneumococcal prevention (60). The remarkable success of PCVs in reducing vaccine-type carriage and disease has led to the emergence of non-vaccine serotypes that now cause a growing proportion of invasive pneumococcal disease cases in PLWH (61). This ecological phenomenon necessitates the continuous development of higher-valency vaccines and underscores the limitation that current vaccines do not provide universal protection against all pneumococcal serotypes (62). The dynamic nature of serotype distribution requires ongoing surveillance and vaccine development efforts to address this evolving threat (63).

Table 1. Summary of clinical evidence for pneumococcal conjugate vaccine (PCV) in people living with HIV (PLWH).

Type of Evidence	Study Design and Findings	Key Implications for PLWH
Immunogenicity	Randomized Controlled Trials (RCTs): Consistently show PCV induces higher Geometric Mean Concentrations (GMCs) of serotype-specific IgG and higher Opsonophagocytic Activity (OPA) titers compared to PPSV23. Finding: Optimal response when vaccinated after ART initiation and immune reconstitution (e.g., CD4+ >200 cells/μL) (40, 41, 42).	Demonstrates PCV's ability to generate a functional immune response despite immunodeficiency. Timing with ART is crucial for maximizing immunogenicity.
Indirect (Herd) Effectiveness	Observational Surveillance Studies: Document a significant decline in vaccine-type IPD among PLWH following the introduction of pediatric PCV immunization programs. Finding: Reduction in IPD incidence in unvaccinated adults due to reduced transmission from vaccinated children (43, 44).	Highlights the critical public health value of childhood PCV programs in protecting immunocompromised adult populations like PLWH.
Direct Effectiveness against Clinical Outcomes	Cohort & Case-Control Studies: Show PCV vaccination is associated with a significant reduction in the risk of all-cause pneumonia and confirmed IPD. Finding: Direct RCTs are limited, but real-world evidence confirms a protective benefit (48, 49).	Provides robust evidence that the improved immunogenicity of PCV translates into meaningful clinical protection against disease.
Limitation: Serotype Replacement	Population-level Surveillance: Monitoring shows a decrease in vaccine-type carriage and disease but a concomitant increase in colonization and IPD caused by Non-Vaccine Serotypes (NVTs) (45).	Underscores that current PCVs are not universal solutions. PLWH remain at risk from NVTs, driving the need for higher-valency vaccines (PCV15, PCV20).

The aging population of PLWH introduces additional complexities through immunosenescence and comorbidities (64). As antiretroviral therapy has transformed HIV into a chronic condition, the population of people living with HIV is experiencing natural aging processes (65). The combined effect of HIV-associated immune dysfunction and age-related immunosenescence may further increase susceptibility to pneumococcal disease and diminish vaccine responses (66). This dual immune compromise creates a unique immunological environment that requires focused study and potentially tailored vaccination strategies for older adults living with HIV (67).

Future Directions for Research and Public Health Policy

Addressing the persistent challenges in pneumococcal protection for people living with HIV requires a comprehensive and multi-faceted approach that spans basic science investigation, clinical research advancement, and public health implementation strategies (68).

The development of novel vaccine strategies represents a promising frontier in overcoming current limitations (69). Research efforts are increasingly focused on protein-based vaccines targeting highly conserved pneumococcal proteins such as pneumolysin and pneumococcal surface protein A (PspA) (70). These next-generation vaccines offer the potential for serotype-independent protection, which could fundamentally overcome the challenge of serotype replacement and provide broader protection

against diverse pneumococcal strains (71). By targeting antigens common across multiple serotypes, these vaccines may provide more universal protection that is not limited by the changing epidemiology of circulating strains (72).

Advancements in adjuvant technology and vaccine formulations present another critical research direction (73). The investigation of novel adjuvants in combination with existing conjugate vaccines offers significant potential for enhancing the magnitude, breadth, and durability of immune responses in immunocompromised populations (74). Specifically designed adjuvants could help overcome the particular immune deficits seen in PLWH, potentially mitigating the issue of waning immunity and reducing the need for frequent booster doses (75). The development of tailored formulations that optimize immune responses in the context of HIV-related immune dysfunction represents an important area of translational research (74, 75).

Establishing precise correlates of protection remains an essential prerequisite for evaluating new interventions (76). While opsonophagocytic activity is generally accepted as a correlate of protection in immunocompetent populations, its precise protective thresholds and clinical relevance in PLWH require further elucidation (77). Defining population-specific immunological correlates that accurately predict clinical protection would significantly accelerate vaccine development and evaluation (78). Such correlates would enable more efficient assessment of new vaccine candidates and vaccination strategies without requiring large-scale clinical endpoint studies (79).

Implementation science and global access initiatives constitute the crucial bridge between scientific advancement and public health impact (80). From a policy perspective, improving vaccine uptake requires integrating pneumococcal vaccination into routine HIV care packages and developing effective reminder systems (81). Importantly, ensuring equitable access to the latest conjugate vaccines in low- and middle-income countries represents an ethical imperative and practical necessity. Addressing barriers to vaccine access, distribution, and administration in resource-limited settings is essential for achieving meaningful reductions in global pneumococcal disease burden among PLWH ((82, 83).

Conclusion

As a conclusion the future of pneumococcal prevention lies in the development of broader-spectrum vaccines, boosters and adjuvants, and an unwavering commitment to global health equity. Through a concerte effort combining basic research and clinical innovation, the goal of reducing the burden of pneumococcal disease among people with HIV is an achievable imperative.

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