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Immune Reconstitution Patterns Following Early Antiretroviral Therapy Initiation

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Abstract

Whether and when to start antiretroviral therapy (ART) has been settled by randomized trial evidence, but the immunological consequences of that timing decision are more layered than the trials' clinical endpoints alone convey. This article synthesizes the literature on immune reconstitution following early ART initiation, drawing on the START and TEMPRANO trials and the cohort studies that preceded and followed them. We trace how CD4 T-cell counts and the CD4/CD8 ratio recover on different timescales and to different ceilings depending on when treatment starts, how thymic output and peripheral T-cell homeostasis jointly drive that recovery, and how gut mucosal CD4 depletion, microbial translocation, and lymphoid tissue fibrosis are established within the earliest weeks of infection and only partially reversed by treatment initiated later. We review evidence that the latent HIV reservoir is seeded early enough that even treatment within days of infection rarely prevents rapid viral rebound after treatment interruption, and we examine the population of immunological non-responders whose reconstitution remains incomplete despite years of viral suppression, along with the related risk of immune reconstitution inflammatory syndrome in patients who start treatment late. Read together, the evidence supports early ART initiation as substantially, but not completely, protective of long-term immune health, and identifies the precise biological window for that protection, the mechanisms of persistent non-response, and the biology of rare post-treatment control as the central open questions for the field.

Keywords: immune reconstitution; early antiretroviral therapy; CD4/CD8 ratio; HIV reservoir; immunological non-response

1. Introduction

Antiretroviral therapy (ART) does more than stop HIV replication: it hands the immune system an opportunity, and sometimes only a partial one, to rebuild what the virus has taken from it. For most of the epidemic's history, clinicians started ART only after CD4 counts had fallen to a threshold judged to signal meaningful immunodeficiency, first 200 cells/mm³, later 350, later still 500. That staged, CD4-triggered approach was a reasonable response to the toxicity and pill burden of early regimens, but it also meant that most people spent months to years with untreated viremia, ongoing CD4 depletion, and a slowly accumulating burden of immune damage before treatment ever began. Two landmark randomized trials, START and TEMPRANO, changed that calculus decisively by showing that starting ART immediately, regardless of CD4 count, reduced serious illness and death compared with waiting for a CD4-based threshold [1,2]. Guidelines worldwide have since moved to a treat-all posture, and the practical question for clinicians and immunologists shifted from "when should we start" to "what does the immune system actually do once we start early, and how completely does it recover."

That second question turns out to be considerably harder to answer than the trials' headline mortality and morbidity results might suggest. Immune reconstitution under ART is not a single number going up; it is a set of partially independent processes running on different clocks. Peripheral CD4 T-cell counts typically rise briskly in the first three to six months, driven largely by redistribution of memory cells out of lymphoid tissue, and then more slowly over years, driven by a mix of homeostatic proliferation and genuine new T-cell production from the thymus [3,4]. The CD4/CD8 ratio, a marker that has emerged as arguably more clinically informative than the CD4 count alone, recovers still more slowly and, in many people who start ART late, never fully normalizes [5,6]. Markers of chronic immune activation and inflammation, gut mucosal integrity, and the size and composition of the latent viral reservoir all follow their own trajectories, some of which respond dramatically to earlier treatment and some of which appear to be set, in part, by events that occur in the first weeks of infection and are only partially reversible thereafter [7,8].

This article synthesizes what a large and still-growing

literature has established about immune reconstitution following early ART initiation. We organize the discussion around five themes: the clinical trial evidence that early ART initiation improves outcomes and the mechanistic questions that evidence leaves open; the kinetics and determinants of CD4 T-cell and CD4/CD8 ratio recovery; the role of thymic output and T-cell homeostasis in sustaining that recovery; the intersection of early treatment with residual immune activation, gut mucosal damage, and the HIV reservoir; and the population of people, a minority but not a negligible one, whose immune reconstitution remains incomplete despite years of virologic suppression. We close with a discussion of the open questions we think matter most for clinical practice and for the research agenda going forward.

It is worth being explicit about what this synthesis does and does not claim. Early ART initiation is now standard of care essentially everywhere ART is available, and the trial evidence for its clinical benefit is about as strong as evidence gets in HIV medicine. What remains genuinely contested, and what this article focuses on, is the more granular immunological question of how much of the damage HIV does before treatment starts is actually reversible, on what timescale, and for which specific immune compartments, given that "immune reconstitution" is really shorthand for several partially independent recovery processes that do not all respond to earlier treatment in the same way or to the same degree.

2. Clinical Trial Evidence for Early Initiation

The case for early ART initiation rests on two large randomized controlled trials conducted in different populations under different designs, which is part of why their concordant conclusion carries so much weight. The INSIGHT START trial randomized more than 4,600 ART-naïve adults with CD4 counts above 500 cells/mm³ to immediate ART or to deferral until the CD4 count fell to 350 cells/mm³ or an AIDS-defining event occurred, across 35 countries. The trial was stopped early by its data safety monitoring board because the immediate-treatment group had a 57% lower rate of the primary composite endpoint, serious AIDS events, serious non-AIDS events, or death, than the deferred group, a difference that was significant for both AIDS-related and non-AIDS-related event categories, including a reduction in cancers that are not classically

AIDS-defining [1]. The TEMPRANO trial, conducted entirely in Cote d'Ivoire in a population with a much higher background burden of tuberculosis and other opportunistic disease, used a two-by-two factorial design comparing early ART versus WHO-guideline-timed ART, each with or without six months of isoniazid preventive therapy. It found that early ART reduced the composite rate of severe HIV-related illness, non-AIDS cancer, and death by 44% relative to deferred initiation, an effect that held even in participants who started with CD4 counts above 500 cells/mm³ [2]. A subsequent long-term follow-up analysis of the START cohort, extending observation years beyond the original trial's early stopping, confirmed that the benefits of immediate initiation persisted and that the immediate-treatment group continued to show lower rates of cancer specifically over roughly nine years of additional follow-up, addressing the natural concern that a benefit detected at trial stoppage might not hold up over a longer horizon [9].

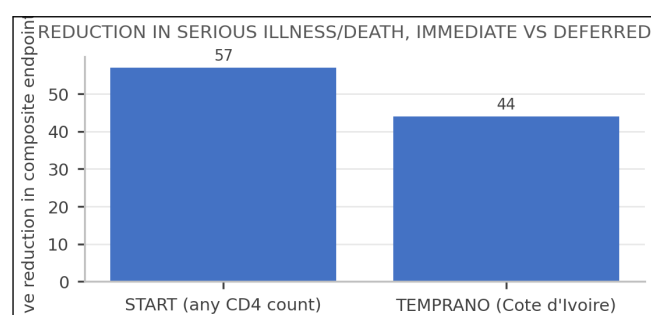


Figure 1: Relative reduction in the composite endpoint of serious AIDS events, serious non-AIDS events, and death with immediate versus deferred antiretroviral therapy in the two pivotal randomized trials establishing early ART initiation as standard of care: START (hazard ratio 0.43, any baseline CD4 count) and TEMPRANO (Cote d'Ivoire, including participants with CD4 counts above 500 cells/mm³) [1,2].

These two trials did not appear out of nowhere; they followed a decade of accumulating observational evidence pointing the same direction. The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), pooling data from more than twenty individual cohorts, found that patients who deferred ART until their CD4 count fell below 500 cells/mm³, and separately those who deferred until it fell below 350, had significantly higher mortality than those who started earlier, evidence that predated START and TEMPRANO by several years and that helped motivate running those trials in the first place [10]. In populations with a high burden of active tuberculosis, the timing question had an added dimension, because starting ART during active TB treatment raises the risk of

immune reconstitution inflammatory syndrome (IRIS), discussed further below, and clinicians had to weigh that risk against the mortality benefit of not delaying ART. Two independently conducted trials addressing this specific setting reached compatible conclusions: the SAPiT trial in South Africa found that integrating ART into TB treatment, rather than waiting until TB treatment finished, reduced mortality substantially, with earlier integration (within the first weeks of TB therapy) safe for patients with low CD4 counts specifically [11], and a companion trial randomizing the precise timing of ART initiation relative to TB treatment onset refined this further by showing that the survival benefit of earlier integration was concentrated in patients with CD4 counts below 50 cells/mm³, while patients with higher CD4 counts could safely wait until TB treatment was underway without a mortality cost. Beyond individual clinical outcomes, the HPTN 052 trial demonstrated an entirely separate reason to treat early: among serodiscordant couples, starting the HIV-positive partner on ART immediately, rather than waiting for CD4-based criteria, reduced linked HIV transmission to the uninfected partner by 96%, establishing treatment as prevention as a public health rationale for early initiation independent of any individual clinical benefit [12].

Pediatric data reinforce the same conclusion in a population where the stakes of delay are especially high. The CHER trial randomized HIV-infected infants in South Africa, diagnosed and enrolled before 12 weeks of age with generally preserved CD4 percentages, to immediate ART or to deferred ART pending clinical or immunological criteria, and found that early time-limited treatment reduced early mortality by 76% relative to deferral, a difference large enough that the trial's data safety monitoring board stopped the deferred arm early on ethical grounds [13]. Because infant immune systems are still developing thymic and peripheral T-cell compartments at the time of infection, the CHER results are also relevant to the mechanistic questions taken up in the sections that follow: starting treatment before extensive immune damage accumulates appears to matter more, not less, in a population whose immune system has the least existing reserve to draw on.

3. CD4 and CD4/CD8 Ratio Recovery Kinetics

The rise in CD4 T-cell count after ART initiation has a

well-characterized two-phase shape. Le and colleagues, studying a cohort of Thai participants enrolled during acute HIV infection through the RV254/SEARCH010 program and followed after immediate ART initiation, showed that CD4 counts recovered within six months to a range statistically indistinguishable from HIV-negative controls when treatment began in Fiebig stages I through III, the earliest, pre-seroconversion phase of acute infection, while later initiation (Fiebig IV or beyond) was associated with a slower, less complete rise even though viral suppression was equally effective across groups [3]. This finding is one of the most direct pieces of evidence that the timing of ART initiation, not just its eventual success at suppressing viremia, independently shapes the ceiling on CD4 recovery, and it has been influential in motivating acute-infection testing and immediate-treatment programs precisely because it demonstrated that a narrow, weeks-wide window early in infection has outsized consequences for the immunological trajectory that follows.

Table 1: Selected quantitative findings linking pre-treatment immune status and treatment timing to CD4 count and CD4/CD8 ratio recovery, drawn from cohort and trial data cited in this section.

Source	Cohort / Design	Exposure Compared	Reported Effect on Recovery
Kelley et al. [15]	Long-term suppressed adults, US cohort	Pre-ART CD4 count <100 vs 100-200 vs ≥300 cells/mm3	44% vs 25% vs 5% failed to reach CD4 >500 cells/mm3 after years of suppression
Le et al. [3]	RV254/SEARCH010 acute-infection cohort, Thailand	ART started Fiebig I-III vs Fiebig IV or later	CD4 count statistically normal by 6 months only in the Fiebig I-III (earliest-treated) group
Serrano-Villar et al. [14]	Virologically suppressed adults, Spanish cohort	Per-quartile decrease in CD4/CD8 ratio	OR 2.9 (95% CI 1.3-6.2) for non-AIDS morbidity; OR 2.8 (95% CI 1.5-5.3) for non-AIDS mortality
Thornhill et al. [5]	Adults treated at primary HIV infection	Earlier vs later ART initiation during primary infection	Earlier initiation independently associated with greater CD4/CD8 ratio normalization

The CD4/CD8 ratio has increasingly displaced the CD4 count alone as the marker clinicians and researchers pay closest attention to, because it captures something the CD4 count misses: the extent to which CD8 T-cell expansion, itself a marker of chronic immune activation,

persists despite adequate CD4 recovery and viral suppression. Thornhill and colleagues, studying participants treated during primary HIV infection, found that earlier ART initiation was independently associated with a greater degree of CD4/CD8 ratio normalization than later initiation, even after accounting for the CD4 count trajectory itself, implying that the ratio is tracking something about ongoing CD8 T-cell dynamics that CD4 recovery alone does not capture [5]. This matters clinically because a persistently low CD4/CD8 ratio, generally defined as below 1.0, has been repeatedly associated with excess risk of non-AIDS morbidity and mortality even among people with well-controlled viral loads and adequate CD4 counts. Mussini and colleagues, in a large observational cohort of virologically suppressed patients, found that achieving CD4/CD8 ratio normalization (above 1.0) was associated with a substantially lower rate of serious non-AIDS events compared with patients whose ratio remained low, and, notably, that later ART initiation was one of the strongest predictors of failing to normalize the ratio even after years of suppressive treatment [6]. Serrano-Villar and colleagues reached a similar conclusion in an independent cohort, showing that a persistently low CD4/CD8 ratio was an independent predictor of serious non-AIDS events including cardiovascular disease and non-AIDS malignancy, with an association that held even among patients whose CD4 count had normalized above 500 cells/mm3, underscoring that CD4 count recovery and CD4/CD8 ratio recovery are genuinely separable outcomes with separable clinical consequences [14].

Kelley and colleagues' study of incomplete CD4 restoration adds an important quantitative anchor to this picture: among patients on long-term suppressive ART, roughly 15 to 20 percent failed to reach a CD4 count above 500 cells/mm3 even after years of undetectable viremia, and lower CD4 nadir, the lowest CD4 count reached before treatment, was the single strongest predictor of this incomplete recovery [15]. That dependence on nadir is, in effect, the clinical-epidemiology version of the same mechanistic point Le and colleagues made at the cellular level: whatever damage accumulates before treatment starts appears to set a partial ceiling on how completely the immune system can subsequently recover, which is precisely the rationale for shifting treatment initiation as early as possible rather than treating the CD4 threshold

debate as settled purely by trial endpoints for morbidity and mortality.

4. Thymic Output and T-Cell Homeostasis

The mechanisms underlying CD4 recovery are not uniform across the recovery curve, and distinguishing them matters because they respond differently to the timing of treatment. In the earliest months after ART initiation, most of the CD4 rise reflects redistribution: memory T cells sequestered in lymphoid tissue during active viral replication move back into peripheral blood as inflammation subsides, producing a rapid numerical increase that does not represent genuinely new T-cell production. The slower, longer-term phase of CD4 recovery depends much more heavily on actual new T-cell generation, and the thymus is the principal organ responsible for that generation. Douek and colleagues' foundational work using T-cell receptor excision circles (TRECs), a molecular byproduct of T-cell receptor gene rearrangement that marks recently thymus-derived cells, established that the thymus remains functionally active into adulthood and that its output increases measurably after ART initiation, providing direct evidence that treated HIV infection permits genuine thymopoiesis to resume rather than relying solely on peripheral expansion of pre-existing cells [4]. This finding reframed immune reconstitution from a purely peripheral, redistribution-based phenomenon into one with a real central, thymic-output component, and it helps explain why CD4 recovery in adults, whose thymic reserve is already limited by age-related involution, is generally slower and less complete than in children and adolescents, whose thymic output is substantially higher to begin with.

The practical upshot of the redistribution-versus-thymopoiesis distinction is that the two phases of CD4 recovery carry different prognostic weight and respond differently to when treatment starts. Rapid early redistribution happens whether ART starts at a CD4 count of 50 or 500, because it mainly reflects reversal of acute lymphoid-tissue trafficking abnormalities; the slower thymopoietic phase, by contrast, is the one plausibly constrained by cumulative thymic damage from years of untreated viremia, and it is this second phase that appears to track most closely with how early treatment began. This distinction is part of why CD4 nadir, rather than CD4 count at any single later time point, has proven to be

such a robust predictor across multiple independent studies of both CD4 count and CD4/CD8 ratio recovery: nadir is, in effect, a proxy for how much thymic and peripheral T-cell reserve was still intact at the moment treatment interrupted further decline [15,5].

5. Immune Activation, Gut Mucosal Damage, and the Reservoir

Untreated HIV infection drives a state of chronic, generalized immune activation that persists, at reduced but still measurable levels, even after years of suppressive ART, and this residual activation is now understood to be a major independent driver of the excess non-AIDS morbidity, cardiovascular disease, certain cancers, and accelerated aging phenotypes, seen in treated people with HIV compared with the general population [16]. Kuller and colleagues, analyzing biomarker data from the SMART trial cohort, found that elevated levels of interleukin-6 and D-dimer, both markers of inflammation and coagulation activation, were strongly associated with all-cause mortality among HIV-infected patients, including among those with well-controlled viral loads, establishing that residual inflammation is not a benign laboratory finding but a clinically consequential state in its own right [17]. Brenchley and colleagues identified one of the principal drivers of that residual activation: HIV infection causes massive, largely irreversible depletion of CD4 T cells in the gut-associated lymphoid tissue within the first weeks of infection, compromising the integrity of the intestinal epithelial barrier and allowing microbial products, principally bacterial lipopolysaccharide, to translocate from the gut lumen into systemic circulation, where they chronically stimulate the innate and adaptive immune system [7]. This microbial translocation model reframed chronic immune activation in HIV from a mysterious epiphenomenon into a mechanistically tractable process rooted in a specific, anatomically localized site of damage that occurs extremely early in infection.

That early timing is precisely why the timing of ART initiation matters so much for this particular axis of immune reconstitution. Estes and colleagues showed that the lymphoid tissue architecture itself, not just the cells within it, sustains lasting damage during untreated infection: collagen deposition and fibrosis in lymph nodes and gut-associated lymphoid tissue physically degrade the structural niche that T cells depend on for survival and homeostatic signaling, and the extent of this

fibrosis, once established, limits the ceiling on immune reconstitution even after years of otherwise successful ART [18]. Because gut CD4 T-cell depletion and the fibrotic scarring that follows it both begin within the earliest weeks of infection, before most people are even diagnosed under conventional testing algorithms, the window in which ART could plausibly prevent rather than merely limit this damage is narrow. Ananworanich and colleagues tested this directly in a cohort treated during acute infection, most within Fiebig stages I through III, and found that immediate ART initiation substantially limited gut CD4 T-cell depletion and reduced HIV DNA levels in gut tissue relative to what is typically observed in chronically infected, later-treated patients, providing direct evidence that treating within days to a few weeks of infection can meaningfully preserve gut mucosal immune architecture that later treatment cannot restore [19]. Jain and colleagues extended this observation using a well-characterized cohort of adults with precisely estimated infection dates, showing that ART initiated within six months of infection was associated with significantly lower T-cell activation markers and a smaller measured HIV DNA reservoir size than ART initiated later, even after adjusting for time on treatment, reinforcing that both immune activation and reservoir size are shaped by a genuine biological window rather than simply by how long a person has subsequently been on suppressive therapy [8].

The reservoir itself, the pool of latently infected, long-lived cells that persists despite fully suppressive ART and that rebounds viremia almost immediately if treatment is stopped, is also shaped by treatment timing in ways directly relevant to immune reconstitution. Buzon and colleagues identified a subset of the reservoir residing in T memory stem cells, an unusually long-lived, self-renewing CD4 T-cell population, and found that this stem-cell-like reservoir component persists proportionally even in patients treated relatively early, suggesting that some degree of reservoir seeding into extremely durable cellular compartments may occur very early in infection and resist even prompt treatment [20]. Colby and colleagues' analytic treatment interruption study in the RV254 cohort found that even among people who began ART within days of infection (Fiebig I), most experienced rapid viral rebound after treatment was stopped, typically within four weeks, demonstrating that early treatment, while it clearly

limits reservoir size and immune damage, is not on its own sufficient to prevent reservoir establishment or to achieve durable post-treatment control in most people [21]. Against that largely discouraging backdrop, a small number of case reports and cohort studies have identified rare individuals, most extensively characterized in the French ANRS VISCONTI cohort, who maintain viral control for years after stopping ART that was started during early infection and continued for a substantial period before interruption; Saez-Cirion and colleagues characterized these post-treatment controllers as having a smaller, less easily reactivated reservoir and a distinct immunological profile compared with typical early-treated patients who rebound promptly, though the mechanisms distinguishing post-treatment controllers from the majority who do not achieve this state remain incompletely understood [22]. Similarly, Hocqueloux and colleagues had earlier described a comparable phenomenon in a smaller set of patients treated during primary infection and later interrupting treatment, establishing that durable post-treatment control, while rare, was not a single-cohort artifact [23].

6. Immunological Non-Responders and Incomplete Reconstitution

Not everyone who starts ART, even relatively early, achieves adequate immune reconstitution, and the population of so-called immunological non-responders, patients with sustained viral suppression but persistently low CD4 counts, has been the subject of substantial dedicated study because their excess morbidity and mortality risk approaches that of untreated, viremic patients despite fully controlled viral loads. Gaardbo and colleagues' review of the mechanisms behind incomplete immune recovery lays out several non-mutually-exclusive contributors: reduced thymic output, particularly in patients who started treatment at an older age or with substantial pre-existing thymic damage; ongoing low-level immune activation that drives increased T-cell turnover and apoptosis even in the setting of suppressed viremia; and lymphoid tissue fibrosis of the kind Estes and colleagues characterized, which physically limits the niche available for T-cell homeostatic proliferation regardless of how much new thymic output or peripheral expansion is occurring [24]. This multifactorial picture explains why immunological non-response is not simply a matter of starting treatment "late enough" in any

single dimension; a patient can start ART promptly after diagnosis and still be an incomplete responder if the diagnosis itself came years into an unrecognized chronic infection, or if age-related thymic involution limits the reserve available for reconstitution regardless of viral control timing.

This population is also where the clinical relevance of immune reconstitution inflammatory syndrome (IRIS) becomes most acute, because IRIS occurs precisely at the intersection of a rapidly recovering immune system and a pre-existing burden of subclinical or partially treated opportunistic infection, most classically tuberculosis, cryptococcal meningitis, or cytomegalovirus retinitis. Mayer and French's reappraisal of IRIS describes it as a paradoxical clinical worsening that occurs when a reconstituting immune system mounts an inflammatory response against antigens from a pathogen that was present, often subclinically, before ART began, and they note that the risk of IRIS is highest specifically among patients who start ART with very low CD4 counts and a correspondingly large burden of unrecognized opportunistic pathogens, which creates a genuine clinical tension: the same low-CD4, late-presenting patients who stand to benefit most from starting ART promptly are also the patients at highest risk of an IRIS event in the weeks that follow [25]. This tension is precisely what the SAPIt and companion TB-timing trials were designed to resolve, and their finding that the mortality benefit of earlier ART integration outweighed the added IRIS risk, at least for the lowest-CD4 patients, has shaped current tuberculosis-HIV co-treatment guidelines [11].

Taken together, the immunological non-responder literature and the IRIS literature point to the same underlying reality: the population that starts ART late, with substantial pre-existing immune damage, is simultaneously the population least likely to achieve complete immune reconstitution and the population most likely to experience acute inflammatory complications during the reconstitution process that does occur. Early ART initiation does not eliminate either problem, but the trial and cohort evidence reviewed throughout this article is fairly consistent in showing that it substantially reduces both the probability of incomplete long-term reconstitution and, in the tuberculosis-specific trials at least, the net clinical

risk associated with the reconstitution process itself.

7. Open Challenges

Several open questions recur across this literature and deserve to be stated plainly rather than left implicit. First, the precise biological window during which starting ART meaningfully changes the ceiling on immune reconstitution, as opposed to simply changing the starting point from which recovery proceeds, is not fully mapped. The RV254 and related acute-infection cohorts suggest this window may be measured in weeks rather than months for gut mucosal damage and reservoir seeding specifically [3,19], but most people living with HIV are diagnosed and start treatment well outside this window, which means the majority of the clinically relevant evidence base for "early" treatment in ordinary practice actually concerns initiation within months of diagnosis rather than within days of infection, and the two are not necessarily interchangeable in their immunological consequences.

Second, the relative contributions of thymic output, peripheral homeostatic proliferation, and lymphoid tissue structural integrity to any given patient's CD4 and CD4/CD8 recovery trajectory remain difficult to disentangle in routine clinical practice, where TREC assays and lymphoid tissue biopsies are research tools rather than standard-of-care measurements. This limits how precisely clinicians can currently predict, at the point of treatment initiation, which patients are likely to become immunological non-responders and might benefit from closer monitoring or investigational adjunctive interventions. Third, the biology of post-treatment control remains only partially explained; Saez-Cirion and colleagues' VISCONTI cohort and Hocqueloux and colleagues' earlier description both identify early treatment as a necessary but clearly not sufficient condition for durable post-treatment control, since Colby and colleagues found that most people treated even within days of infection still rebound rapidly after treatment interruption [22,23,21], and what specifically distinguishes the rare post-treatment controllers from the majority of similarly early-treated patients who do not achieve this state is still not well characterized at the mechanistic level.

Fourth, most of the cohort evidence establishing CD4 nadir and treatment timing as predictors of long-term reconstitution comes from adult populations in relatively well-resourced health systems with reliable

longitudinal follow-up; the generalizability of these findings to pediatric populations with developing immune systems, and to resource-limited settings where diagnosis and treatment timing are frequently much later and monitoring is less intensive, is less thoroughly established even though the CHER trial data suggest the underlying timing-dependence may be at least as strong, and possibly stronger, in children [13]. Fifth, and more practically, there remains no consensus clinical algorithm for managing the genuinely incomplete immunological non-responder who has been virally suppressed for years: current guidance is largely limited to optimizing ART itself and managing non-AIDS comorbidity risk factors, rather than any reconstitution-directed intervention with strong trial evidence behind it, which leaves a real gap between how well this population's biology is now understood and how little of that understanding has translated into a specific therapeutic response.

8. Conclusion

The evidence reviewed here supports a reasonably precise, if not entirely simple, claim: early ART initiation, now firmly established as standard of care by the START and TEMPRANO trials and reinforced by a substantial body of earlier observational evidence, does more than avert AIDS-defining illness [1,2,10]. It measurably improves the ceiling on immune reconstitution across several partially independent axes, CD4 T-cell recovery, CD4/CD8 ratio normalization, thymic output, gut mucosal integrity, and residual immune activation, each of which carries its own downstream consequences for non-AIDS morbidity and mortality [5,6,16]. At the same time, the literature is candid that this benefit is one of degree rather than of complete reversal: gut CD4 T-cell depletion and lymphoid tissue fibrosis begin within weeks of infection and are only partially preserved by even fairly prompt treatment [7,18,19], the HIV reservoir is seeded early enough that even treatment within days of infection does not prevent rapid rebound after interruption in most patients [21], and a meaningful minority of patients, disproportionately those who start treatment with substantial pre-existing immune damage, remain incomplete immunological responders despite years of undetectable viremia [15,24].

None of this diminishes the clinical case for starting ART as early as diagnosis allows; if anything, the immunological literature strengthens that case by

identifying specific, biologically grounded reasons, preserved thymic reserve, intact gut lymphoid architecture, a smaller and less entrenched reservoir, why earlier is better, beyond the trial endpoints that first established the point. What the literature leaves open is how to translate "earlier is better" into a more precise clinical and public-health strategy: how aggressively to pursue diagnosis during acute infection specifically, how to identify and manage patients likely to become immunological non-responders despite reasonably prompt treatment, and how to weigh the real but generally manageable risk of immune reconstitution inflammatory syndrome against the substantial mortality benefit of not deferring treatment in patients with advanced, pre-existing immunodeficiency [25,11]. Continued follow-up of early-treated cohorts, and continued refinement of the biomarkers, CD4/CD8 ratio, inflammatory markers, reservoir assays, that track reconstitution more precisely than CD4 count alone, remain the most promising paths toward closing that gap.

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The authors declare that they have no competing interests relevant to the content of this article.

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Ethical Approval

Not applicable. This work did not involve human participants, animal subjects, or the collection of primary clinical data.

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