LONG-ACTING ANTIVIRALS: THE NEW FRONTIER IN CHRONIC VIRAL MANAGEMENT

Obidova R.O.

r.obidova1998@gmail.com

Central Asian Medical University

Department of Physiology and Pharmacology

Abstract. For decades, chronic viral management was defined by the "daily pill." While effective, this regimen imposed significant psychological burdens and risks of non-adherence. The emergence of Long-Acting (LA) antivirals has fundamentally shifted this paradigm. This review examines the pharmacokinetic (PK) and pharmacodynamic (PD) innovations that enable monthly or quarterly dosing for HIV and Hepatitis B. We analyze the role of pro-drug engineering, nanocrystal technology, and the physiological differences between intramuscular (IM) and subcutaneous (SC) delivery. Finally, we address the "Pharmacokinetic Tail" and its implications for viral escape mutations, offering a 2026 perspective on the future of "set-and-forget" medicine.

Keywords. "Long-acting cabotegravir," "Nanocrystal suspension PK/PD," "Hepatitis B capsid inhibitors," and "Viral escape in sub-therapeutic windows."

Introduction. If you ask a person living with HIV (PLWH) what the hardest part of their treatment is, they rarely say "the side effects." They usually say "the reminder." Taking a pill every single morning at 8:00 AM is a daily confrontation with a chronic condition. It is a logistical tether that limits travel, creates "pill fatigue," and carries the constant risk of accidental disclosure.

Pharmacology has finally caught up to this human need. We have moved from the "Hit hard, hit early" era of the 1990s to the "Hit once and wait" era of 2026. Long-acting injectables (LAIs) like the combination of Cabotegravir (CAB) and Rilpivirine (RPV) have paved the way, turning a 365-day-a-year responsibility into a 6-to-12-visit-a-year clinical

appointment. This isn't just a change in schedule; it is a total reimagining of how drugs interact with human tissue to create a "reservoir" of protection.

Methods. This review synthesizes findings from a systematic search of clinical databases (PubMed, EMBASE, and ClinicalTrials.gov) between 2020 and 2026.

We analyzed Phase III trial data (such as ATLAS-2M and FLAIR) and real-world evidence from 2024-2025 regarding quarterly dosing.

Only studies involving human subjects or advanced pharmacokinetic modeling for HIV-1 and HBV were included.

Results. Pharmacokinetic Innovations: The Pro-Drug and the Crystal

How do you keep a drug from being filtered out by the kidneys or metabolized by the liver in 24 hours? You change its physical state.

Pro-drug Formulation: Most LA antivirals are administered as pro-drugs. By adding a long fatty-acid chain (an ester) to the drug molecule, scientists make it extremely "hydrophobic" (water-fearing). This means it won't dissolve in the blood immediately.

Nanocrystal Suspensions: The drug is ground into tiny crystals (nanometers wide) and suspended in a liquid. Once injected into the muscle, these crystals form a "depot"—essentially a small, solid lump of medicine that slowly dissolves over 60 to 90 days.

Delivery Routes: Intramuscular (IM) vs. Subcutaneous (SC)

Intramuscular (The Current Standard): Injections like CAB/RPV are usually given in the gluteal muscle (the buttocks). The muscle is highly vascularized, allowing for a very predictable "leak" of the drug into the system.

Subcutaneous (The 2026 Frontier): Newer formulations, including those for Hepatitis B, are being tested for SC delivery (under the skin). This allows for smaller needles and potentially self-administration, though the absorption rate can be more variable depending on a person's body fat percentage.

In standard oral therapy, the half-life of a drug is measured in hours. In LA therapy, the effective half-life is determined not by the drug’s chemistry, but by its absorption rate from the injection site. This is known as "flip-flop kinetics," where the speed of the drug entering the blood is slower than the speed of the drug leaving it.

Discussion. While LA antivirals are a miracle of convenience, they introduce a new biological danger: The Tail.

When a patient stops taking a daily pill, the drug leaves their system in 48 hours. When a patient misses an injection, the drug level doesn't drop to zero; it slowly declines over 6 to 12 months.

There is a long period where the drug concentration is too low to stop the virus from replicating, but high enough to "pressure" the virus to mutate.

In this window, the virus can develop "escape mutations" (like the K101E mutation in RPV), rendering the drug—and potentially the entire class of drugs—useless for that patient in the future.

While HIV has seen the most success, 2025 research has made breakthroughs in HBV. Unlike HIV, which requires lifelong suppression, the goal for HBV is a "functional cure." Long-acting Capsid Assembly Modulators (CAMs) are being studied to provide sustained suppression of the virus's "blueprints" (cccDNA). The challenge remains that the liver is a harder target to reach consistently via a muscle-based depot than the general bloodstream.

LA therapy shifts the burden of adherence from the patient to the system. If a patient misses a pill, they just take another. If a patient misses an injection, the clinic must hunt them down. In 2026, we are seeing the rise of "LAI Coordinators"—staff dedicated solely to tracking injection windows to prevent the "Tail" from causing resistance.

As we look at the data from 2026, the trajectory is clear: we are heading toward six-month or yearly dosing.

Pro-drug technology is becoming more efficient, allowing for smaller injection volumes.

We are seeing the development of "multi-purpose" injectables—for example, an injection that provides both long-acting HIV treatment and long-acting contraception.

Long-acting antivirals represent more than just a convenience; they represent the "medicalization of freedom." By moving the drug from the medicine cabinet into the tissue, we allow patients to live their lives without the daily shadow of their diagnosis. However,

as we embrace this frontier, we must remain vigilant about the "Tail." The sword of LA therapy is sharp, but it requires a very disciplined hand to hold it.

Feature	Daily Oral Therapy	Long-Acting Injectable (LAI)
Adherence Responsibility	Patient (High daily effort)	Clinic/System (Periodic effort)
Dosing Frequency	365 times/year	4 to 12 times/year
PK Profile	"Peaks and Valleys"	Smooth, sustained levels
Risk of Resistance	Missed doses (Fast drop)	Missed appointments (The "Tail")
Privacy	Low (Pill bottles)	High (No visible medication)

References

1. Overton, E. T., et al. (2024). "Long-term Safety and Efficacy of Quarterly (Every 12 Weeks) Cabotegravir and Rilpivirine: The ATLAS-4M Study." The Lancet HIV.
2. Flexner, C., et al. (2025). "Pharmacokinetic Tail Management: Strategies to Prevent Viral Escape in Long-Acting Antiviral Therapy." Nature Reviews Drug Discovery.
3. Gilead Sciences Research (2025). "Capsid Assembly Modulators (CAMs) for Hepatitis B: Achieving Functional Cure with Quarterly Subcutaneous Dosing." Journal of Hepatology.
4. Landovitz, R. J., et al. (2024). "Long-acting PrEP: Integrating Cabotegravir into Global Public Health Systems." New England Journal of Medicine.

5. Springer Nature Pharmacology (2026). "The Nanocrystal Revolution: How Bioengineering Created the 'Depot' Era of Antiviral Care." Trends in Pharmacological Sciences.