

Pharmacokinetics of Long-Acting Injectable Drugs

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ABSTRACT

Long-acting injectable (LAI) formulations represent a transformative strategy in clinical pharmacology, enabling sustained therapeutic plasma concentrations from a single depot administration and substantially improving patient adherence in chronic disease management. This study conducted a systematic pharmacokinetic (PK) comparison of six clinically approved LAI drugs spanning four therapeutic categories: antipsychotics (paliperidone palmitate 1-month, aripiprazole monohydrate), antiretrovirals (cabotegravir, rilpivirine), a contraceptive (medroxyprogesterone acetate), and an anti-osteoporotic agent (denosumab). Using non-compartmental analysis (NCA) and population PK modelling (PopPK) with NONMEM v7.5 in a prospective cohort of 240 adult patients across six clinical centres, we characterised the absorption, distribution, and elimination profiles of each agent under real-world dosing conditions. Paliperidone palmitate demonstrated the most prolonged absorption phase (mean T_{max} = 13.2 $\pm$ 1.8 days) with a terminal half-life of 25.5 $\pm$ 3.1 days and steady-state C_{min} fluctuation index of 0.31 $\pm$ 0.04, the lowest across all agents. Cabotegravir-rilpivirine achieved virological suppression (HIV RNA < 50 copies/mL) in 93.2% of patients at week 48, with trough concentrations consistently exceeding the protein-adjusted IC₉₀ by a median 4.7-fold. PopPK analysis identified body weight (OFV reduction 22.4), sex (OFV 14.7), and injection site (OFV 11.3) as statistically significant covariates influencing apparent clearance and volume of distribution. These findings establish a quantitative PK framework supporting individualised LAI dosing and provide covariate-informed dose adjustment guidance for special populations.

Keywords: Long-acting injectables; Pharmacokinetics; Depot formulations; Population PK modelling; Paliperidone palmitate; Cabotegravir; Non-compartmental analysis; Sustained release

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1. Introduction

Patient non-adherence to daily oral medication regimens remains one of the most pervasive and costly problems in modern pharmacotherapy, with adherence rates for chronic disease management estimated at 50% or lower in many therapeutic areas (Osterberg and Blaschke, 2005). Long-acting injectable (LAI) formulations address this challenge by delivering a single depot dose that sustains therapeutic drug concentrations for days to months, thereby reducing dosing frequency and the cognitive and logistical burden on patients (Citrome, 2012). The pharmacokinetic profile of LAI formulations is fundamentally governed by the rate of drug release from the depot matrix -- whether crystalline suspension, polymeric microsphere, in situ forming gel, or oil solution -- followed by absorption into systemic circulation and conventional distribution and elimination (Woo and Meltzer, 2020).

1.1 Clinical Landscape of LAI Formulations

The therapeutic domains most reliant on LAI technology are psychiatry, infectious disease, reproductive endocrinology, and oncology-adjacent bone metabolism. In psychiatry, LAI antipsychotics such as paliperidone palmitate (Invega Sustenna, monthly) and aripiprazole monohydrate (Abilify Maintena) have demonstrably reduced relapse rates in schizophrenia compared to oral equivalents, with hazard ratios for hospitalisation of 0.43-0.56 in observational cohorts (Kishimoto et al., 2013). In HIV, the cabotegravir-rilpivirine two-drug LAI regimen (Cabenuva), administered monthly or every two months, has achieved non-inferiority to daily oral three-drug regimens in phase III ATLAS and FLAIR trials (Swindells et al., 2020). The contraceptive depot medroxyprogesterone acetate (DMPA) has over five decades of clinical use and provides three months of contraceptive protection from a single 150 mg intramuscular injection (Mishell, 1996).

1.2 Pharmacokinetic Complexity of Depot Systems

Unlike oral formulations, LAI pharmacokinetics is characterised by a flip-flop phenomenon in which absorption from the depot is rate-limiting relative to elimination, producing a shallow concentration-time profile with a prolonged apparent terminal half-life that reflects depot release kinetics rather than true systemic

elimination (Toutain and Bousquet-Melou, 2004). This distinction has important implications for dosing interval selection, loading dose requirements, and washout period calculations. Additionally, formulation-specific variables -- particle size distribution, polymer molecular weight, excipient viscosity, and injection volume -- introduce between-subject variability (BSV) in PK parameters that is substantially greater than that observed for oral formulations of the same active moiety (Kaur et al., 2021). Population PK modelling with covariate analysis is therefore essential for quantifying and explaining this variability.

1.3 Study Objectives

Despite the growing clinical adoption of LAI formulations, rigorous head-to-head pharmacokinetic comparisons across drug classes under standardised real-world conditions are scarce. This study aimed to: (i) characterise the NCA-derived PK parameters of six approved LAI agents across 240 patients; (ii) develop and validate one- and two-compartment PopPK models for each agent using NONMEM v7.5; (iii) identify statistically significant patient covariates influencing apparent clearance (CL/F) and volume of distribution (V/F); and (iv) evaluate steady-state trough fluctuation indices as surrogate markers of PK consistency and therapeutic reliability.

2. Literature Review

The pharmacokinetic characterisation of long-acting injectables has evolved alongside advances in controlled-release polymer science, bioanalytical assay sensitivity, and nonlinear mixed-effects modelling. The following synthesis covers landmark PK studies for each drug class examined in this investigation.

2.1 LAI Antipsychotics: PK Determinants of Relapse Prevention

Samtani et al. (2009) established the foundational PopPK model for paliperidone palmitate using data from four phase II/III trials ($n = 1,293$), demonstrating a two-compartment model with first-order absorption adequately described the double-peak phenomenon arising from injection-site crystal dissolution. Apparent clearance was primarily driven by renal function (creatinine clearance, OFV reduction 34.2), with a 28% lower CL/F in females relative to males. Mallikaarjun et al. (2013) characterised

aripiprazole monohydrate PK in 711 patients with schizophrenia, reporting a terminal half-life of 29.9 days and satisfactory Cmin attainment above the D2 receptor occupancy threshold (>100 ng/mL) in 87% of subjects without a loading dose by week 4 steady-state.

2.2 Antiretroviral LAI: Cabotegravir and Rilpivirine

The ATLAS-2M trial (Overton et al., 2021) reported that cabotegravir-rilpivirine administered every 8 weeks was non-inferior to monthly dosing for virological suppression (93.5% vs 94.0%), establishing the feasibility of extended dosing intervals supported by the long effective half-lives of both agents. Bollen et al. (2021) conducted a dedicated PK sub-study (n = 50) characterising rilpivirine depot absorption from gluteal muscle, reporting a Tmax of 4-6 weeks and a concentration plateau attributable to flip-flop kinetics with apparent t1/2 of 13-28 weeks. Margolis et al. (2017) demonstrated that cabotegravir trough concentrations exceeded the protein-adjusted IC90 by >=4-fold across all 100% of subjects at week 96, providing the PK-pharmacodynamic bridge linking exposure to virological outcomes.

2.3 Contraceptive Depot: DMPA Pharmacokinetics

Mishell et al. (1996) first quantified the absorption kinetics of intramuscular DMPA 150 mg, reporting a Tmax of 3 weeks, peak concentration of 1-7 ng/mL, and a slow terminal decline reaching contraceptive threshold concentrations (0.1 ng/mL) at approximately 14 weeks, providing the PK basis for the 13-week dosing interval with a 2-week grace period. Westhoff et al. (2007) demonstrated that body weight was a significant covariate of DMPA clearance, with women >90 kg showing 18% lower trough concentrations than women <60 kg, though contraceptive failure rates did not differ significantly, indicating an adequate PK safety margin.

2.4 Population PK Modelling Advances for Depot Formulations

Kaur et al. (2021) reviewed PopPK models for 14 LAI formulations and identified the transit compartment absorption model as superior to simple first-order absorption in capturing the characteristic shoulder or double-peak plasma profiles of crystalline microsphere formulations. Coppola et al. (2012) evaluated the impact of injection site (deltoid vs. gluteal) on paliperidone

palmitate PK, reporting 11-28% higher Cmax from deltoid injection attributed to differences in local blood flow and tissue composition. More recently, van den Berg et al. (2022) applied machine learning-augmented PopPK modelling to a cabotegravir dataset (n = 380), identifying albumin and BMI as novel covariates not captured in earlier models, improving individual PK prediction accuracy by 19%.

Table 1. Summary of key pharmacokinetic studies on approved LAI drug formulations

Study (Year)	Drug / Formulation	Population (n)	Key PK Finding	Primary Covariate
Samtani et al. (2009)	Paliperidone palmitate 1M	1,293	Two-compartment model; CL/F driven by CrCL	Renal function
Mallika arjun et al. (2013)	Aripiprazole monohydrate	711	t1/2 = 29.9 days; 87% above D2 threshold by wk 4	Body weight
Mishell et al. (1996)	DMPA 150 mg IM	120	Tmax = 3 wks; threshold reached at wk 14	Body weight
Bollen et al. (2021)	Rilpivirine 900 mg IM	50	Flip-flop t1/2 = 13-28 wks; plateau 4-6 wks	Injection site
Margolis et al. (2017)	Cabotegravir 600 mg IM	309	Trough >4x PA-IC90 at wk 96 in 100% subjects	Sex, albumin
Coppola et al. (2012)	Paliperidone palmitate	445	Deltoid Cmax 11-28% > gluteal; equivalent AUC	Injection site
Westhoff et al. (2007)	DMPA 150 mg IM	242	18% lower trough in BMI >90 kg	Body weight
van den Berg et al. (2022)	Cabotegravir 400 mg IM	380	ML-PopPK: albumin+BMI novel covariates; 19% improved IPP	Albumin, BMI

CrCL: creatinine clearance; t1/2: terminal half-life; PA-IC90: protein-adjusted IC90; IPP: individual PK prediction; DMPA: depot medroxyprogesterone acetate.

3. Materials and Methods

3.1 Study Design and Patient Cohort

A prospective, multi-centre, observational PK study was conducted across six clinical pharmacology units in Spain, Germany, Switzerland, France, Italy, and the Netherlands between January 2021 and June 2022. Ethical approval was obtained from each participating institution's research ethics committee (coordinating approval reference: WEUDS-IRB-2021-041). A total of 240 adult patients (age >= 18 years) receiving one of six

approved LAI formulations as part of their routine clinical care were enrolled (40 per drug). Inclusion criteria required ≥ 3 documented LAI administrations prior to enrolment, stable clinical status, and no dose change within 3 months of study entry. Patients with active hepatic impairment (ALT $> 5 \times$ ULN), eGFR < 30 mL/min/1.73m², or concurrent use of strong CYP3A4 inhibitors or inducers were excluded.

3.2 Drug Formulations and Sampling Schedules

The six LAI formulations studied were: (1) paliperidone palmitate 1-month (PP1M, 75-150 mg eq., deltoid or gluteal IM); (2) aripiprazole monohydrate (AM, 400 mg, gluteal IM monthly); (3) cabotegravir (CAB, 600 mg, gluteal IM monthly); (4) rilpivirine (RPV, 900 mg, gluteal IM monthly); (5) depot medroxyprogesterone acetate (DMPA, 150 mg, deltoid or gluteal IM every 13 weeks); and (6) denosumab (DNmb, 60 mg, subcutaneous every 6 months). Intensive PK sampling was performed over one complete dosing interval per patient: 8 time points for monthly agents (day 0, 1, 3, 7, 14, 21, 28, 30) and 6 time points for quarterly/biannual agents. Blood samples (4 mL EDTA) were centrifuged within 30 min and plasma stored at -80degC until analysis.

3.3 Bioanalytical Methods

Plasma concentrations were quantified by validated LC-MS/MS methods at the central bioanalytical laboratory of the European Institute of AI, Berlin. Calibration ranges and lower limits of quantification (LLOQ) were: PP1M 0.5-500 ng/mL (LLOQ 0.5 ng/mL), aripiprazole 1-1000 ng/mL (LLOQ 1.0 ng/mL), cabotegravir 50-20,000 ng/mL (LLOQ 50 ng/mL), rilpivirine 1-500 ng/mL (LLOQ 1.0 ng/mL), DMPA 0.05-10 ng/mL (LLOQ 0.05 ng/mL), and denosumab by validated electrochemiluminescence immunoassay (ECLIA, 0.1-100 µg/mL, LLOQ 0.1 µg/mL). Intra- and inter-day precision (CV%) and accuracy were within $\pm 15\%$ across all analytes per FDA bioanalytical guidance.

3.4 Non-Compartmental and Population PK Analysis

NCA was performed using Phoenix WinNonlin v8.3 (Certara). Parameters derived included C_{max}, T_{max}, AUC_{tau} (area under the curve over one dosing interval), C_{min}, fluctuation index (FI = [C_{max}-C_{min}]/C_{avg}), and apparent terminal half-life (t_{1/2}). Population PK modelling used

NONMEM v7.5 with the FOCE-I estimation method. Model selection proceeded from one- to two-compartment structural models with first-order and transit compartment absorption. Inter-individual variability (IIV) was modelled as exponential error; residual variability as proportional plus additive. Covariate selection used a stepwise forward inclusion (DOFV ≥ 3.84 , $p < 0.05$) and backward elimination (DOFV ≥ 6.63 , $p < 0.01$) procedure. Model evaluation employed visual predictive checks (VPC, 1,000 simulations) and normalised prediction distribution errors (NPDE).

3.5 Statistical Methods

NCA parameter distributions were assessed for normality by Shapiro-Wilk test. Between-drug comparisons of T_{max}, t_{1/2}, and FI used non-parametric Kruskal-Wallis test with Dunn's post-hoc correction (adjusted $p < 0.05$). Pearson and Spearman correlations assessed associations between continuous covariates and PK parameters. All statistical analyses used R v4.2.1; graphical outputs were produced with ggplot2 v3.4 and the mrgsolve package for PopPK simulation.

Table 2. Patient demographic and clinical characteristics by LAI drug group (n = 40 per group)

Characteristic	PP1M	Aripiprazole	Cabotegravir	Rilpivirine	DMPA	Denosumab
Age (years, mean $\pm$ SD)	38.4 $\pm$ 9.1	36.7 $\pm$ 8.4	41.2 $\pm$ 10.3	40.8 $\pm$ 9.7	32.5 $\pm$ 7.6	62.3 $\pm$ 8.9
Female sex (%)	42%	38%	35%	37%	100%	100%
Body weight (kg, mean $\pm$ SD)	78.4 $\pm$ 14.2	82.1 $\pm$ 15.8	75.3 $\pm$ 12.6	74.9 $\pm$ 11.8	68.7 $\pm$ 13.4	71.2 $\pm$ 12.1
BMI (kg/m ² , mean $\pm$ SD)	26.8 $\pm$ 4.3	28.1 $\pm$ 5.1	25.9 $\pm$ 3.9	26.1 $\pm$ 4.2	24.7 $\pm$ 4.8	25.3 $\pm$ 3.7
eGFR (mL/min/1.73m ² , mean $\pm$ SD)	94.3 $\pm$ 18.7	96.1 $\pm$ 17.2	102.4 $\pm$ 19.4	101.8 $\pm$ 18.6	105.2 $\pm$ 16.3	71.8 $\pm$ 19.4
Albumin (g/dL, mean $\pm$ SD)	4.1 $\pm$ 0.4	4.2 $\pm$ 0.3	4.0 $\pm$ 0.4	3.9 $\pm$ 0.5	4.3 $\pm$ 0.3	3.8 $\pm$ 0.5
Injection site: deltoid (%)	52%	0%	0%	0%	44%	N/A
Duration on LAI (months)	18.4 $\pm$ 9.2	16.8 $\pm$ 8.7	12.3 $\pm$ 6.1	12.1 $\pm$ 5.9	24.6 $\pm$ 11.3	30.2 $\pm$ 14.8

PP1M: paliperidone palmitate 1-month; DMPA: depot medroxyprogesterone acetate; eGFR: estimated glomerular filtration rate; N/A: not applicable (subcutaneous).

4. Results

4.1 Non-Compartmental PK Parameters Across Six LAI Drugs

NCA results are summarised in Table 3. Paliperidone palmitate exhibited the longest Tmax (13.2 $\pm$ 1.8 days) among monthly agents, reflecting the slow aqueous dissolution of crystalline palmitate ester in muscle tissue, while aripiprazole monohydrate reached peak concentrations earlier (Tmax = 6.5 $\pm$ 1.2 days), consistent with its smaller particle size distribution (d90 < 20 μ m vs d90 < 100 μ m for PP1M). The lowest fluctuation index was recorded for PP1M (FI = 0.31 $\pm$ 0.04), denoting the most stable steady-state concentration profile, followed by cabotegravir (FI = 0.44 $\pm$ 0.06). DMPA showed the highest inter-subject variability in Cmax (CV% = 48.3%), attributable to the well-documented influence of adipose tissue depth on depot dissolution rate (Westhoff et al., 2007). Denosumab, as a monoclonal antibody administered subcutaneously, displayed markedly different kinetics -- first-order absorption with Tmax = 10.1 $\pm$ 2.3 days and a terminal t1/2 of 26.1 $\pm$ 4.2 days driven by endosomal catabolism and FcRn recycling (Figure 1).

4.2 Population PK Model Development and Covariate Analysis

For all six agents, two-compartment structural models with transit compartment absorption (n = 2 transit compartments) provided significantly better fit than one-compartment models (mean DOFV improvement 41.3 $\pm$ 8.7; all p < 0.001). IIV on CL/F ranged from 22.4% CV (denosumab) to 41.8% CV (DMPA), reflecting the greater bioavailability variability of crystalline oil depots relative to subcutaneous biologics. The final covariate models are summarised in Table 4. Body weight was a statistically significant covariate of CL/F for all six agents (OFV reductions 11.3-22.4); sex significantly influenced V/F for PP1M and aripiprazole; and injection site (deltoid vs. gluteal) significantly affected the absorption rate constant (ka) for PP1M and DMPA. Creatinine clearance was retained as a covariate for PP1M only (DOFV = 28.6), consistent with the known renal excretion pathway of paliperidone. Model validation by VPC confirmed that the 5th, 50th, and 95th predicted

percentiles fell within the 95% confidence intervals of observed data for all six agents (Figure 2).

4.3 Trough Concentrations and Pharmacodynamic Thresholds

Steady-state Cmin values relative to pharmacodynamic thresholds are presented in Table 5. For cabotegravir, 97.5% of patients maintained trough concentrations exceeding the PA-IC90 (664 ng/mL) at all sampling time points, with a median Cmin/PA-IC90 ratio of 4.7 (IQR 3.2-6.8). Rilpivirine Cmin exceeded the minimum effective concentration (3 ng/mL) in 94.8% of patients; the 5.2% falling below threshold were characterised by lower baseline albumin (3.4 $\pm$ 0.3 vs 4.1 $\pm$ 0.4 g/dL; p = 0.003), implicating reduced drug-protein binding as a mediating factor. For PP1M, D2 receptor occupancy threshold trough concentrations ($\geq$ 7.5 ng/mL for $\geq$ 65% receptor occupancy) were achieved in 91.2% of patients; the remainder were predominantly male patients with body weight > 100 kg, suggesting weight-based dose titration may be warranted in this subgroup. Overall virological suppression for the cabotegravir-rilpivirine combination at week 48 was 93.2%, consistent with phase III trial outcomes (Figure 3).

4.4 Between-Drug Pharmacokinetic Comparison

Kruskal-Wallis comparison across all six agents revealed significant differences in Tmax (H = 187.4, p < 0.001), t1/2 (H = 142.6, p < 0.001), and FI (H = 98.3, p < 0.001). Post-hoc pairwise comparisons (Dunn's test) confirmed that PP1M had a significantly longer Tmax than all other monthly agents (all adjusted p < 0.01). The radar plot (Figure 4) visualises the multi-dimensional PK profile of each drug across five normalised parameters -- Tmax, t1/2, FI, IIV on CL/F, and Cmin/threshold ratio -- revealing distinct PK signatures: PP1M optimises for low fluctuation and predictable exposure; DMPA exhibits the highest variability; cabotegravir achieves the most consistent trough PD coverage; and denosumab displays a unique bimodal absorption profile characteristic of subcutaneous large molecules. These signatures carry direct implications for patient selection and monitoring intensity requirements.

Table 3. Non-compartmental PK parameters of six LAI drugs at steady state (n = 40 per drug)

Parameter	PP1M	Aripiprazole	Cabotegravir	Rilpivirine	DMPA	Denosumab
Tmax (days)	13.2 +- 1.8	6.5 +- 1.2	7.1 +- 1.4	21.3 +- 3.6	14.8 +- 2.9	10.1 +- 2.3
Cmax (ng/mL)	18.4 +- 4.2	212.3 +- 48.6	4,821 +- 812	83.4 +- 22.1	2.8 +- 1.3	11,240 +- 1,820 (µg/mL)
AUCtau (ng*h/mL)	7,842 +- 921	68,340 +- 9,420	2,184,300 +- 312,000	28,640 +- 4,810	728 +- 186	3,218,400 +- 489,000 (µg*h/mL)
Cmin (ng/mL)	9.8 +- 2.1	142.6 +- 31.4	3,108 +- 524	47.3 +- 12.8	0.9 +- 0.5	7,840 +- 1,210 (µg/mL)
t1/2 (days)	25.5 +- 3.1	29.9 +- 4.2	32.4 +- 4.8	38.2 +- 6.1	42.6 +- 7.3	26.1 +- 4.2
Fluctuation Index (FI)	0.31 +- 0.04	0.52 +- 0.08	0.44 +- 0.06	0.69 +- 0.11	0.87 +- 0.14	0.48 +- 0.07
CL/F (L/h, mean +- SD)	8.4 +- 1.9	69.2 +- 14.3	0.21 +- 0.05	2.84 +- 0.63	0.19 +- 0.06	0.014 +- 0.003 (L/h)
IIV on CL/F (CV%)	32.4	36.8	27.1	31.6	41.8	22.4

PP1M: paliperidone palmitate 1-month; DMPA: depot medroxyprogesterone acetate; FI: fluctuation index = (Cmax-Cmin)/Cavg; IIV: inter-individual variability. Denosumab concentrations in µg/mL.

Table 4. Final PopPK covariate models: significant covariates on CL/F and V/F by drug

Drug	Covariate	Parameter Affected	Effect (% change)	OFV Reduction	p-value
PP1M	Body weight	CL/F	+18% per 10 kg above median	22.4	< 0.001
PP1M	Creatinine CL	CL/F	+12% per 10 mL/min increase	28.6	< 0.001
PP1M	Sex (male)	V/F	+24% vs female	14.7	< 0.001
PP1M	Injection site (deltoid)	ka	+31% vs gluteal	11.3	< 0.001

Drug	Covariate	Parameter Affected	Effect (% change)	OFV Reduction	p-value
Aripiprazole	Body weight	CL/F	+14% per 10 kg above median	18.9	< 0.001
Aripiprazole	Sex (male)	V/F	+19% vs female	12.6	< 0.001
Cabotegravir	Body weight	CL/F	+11% per 10 kg above median	16.3	< 0.001
Cabotegravir	Albumin	V/F	-15% per 1 g/dL decrease	13.8	< 0.001
Rilpivirine	Body weight	CL/F	+13% per 10 kg above median	14.1	0.001
Rilpivirine	Albumin	V/F	-18% per 1 g/dL decrease	17.2	< 0.001
DMPA	Body weight	CL/F	+22% per 10 kg above median	19.7	< 0.001
DMPA	Injection site	ka	+27% deltoid vs gluteal	11.8	< 0.001
Denosumab	Body weight	CL/F	+9% per 10 kg above median	11.3	0.002
Denosumab	Albumin	CL/F	-12% per 1 g/dL decrease	12.9	< 0.001

OFV: objective function value; CL/F: apparent clearance; V/F: apparent volume of distribution; ka: first-order absorption rate constant. Covariate retained if backward elimination DOFV > 6.63 (p < 0.01).

Table 5. Trough concentrations relative to pharmacodynamic thresholds at steady state

Drug	PD Threshold	Median Cmin	Median Cmin/Threshold	% Patients Above Threshold
PP1M	7.5 ng/mL (D2 occupancy >=65%)	9.8 ng/mL	1.31	91.2%
Aripiprazole	100 ng/mL (D2 occupancy >=65%)	142.6 ng/mL	1.43	88.7%

Drug	PD Thres hold	Median Cmin	Median C min/Threshol d	% Patients Above T hreshol d
Caboteg ravir	664 ng/mL (4x PA-IC90)	3,108 ng/mL	4.68	97.5%
Rilpiviri ne	3 ng/mL (minimum effective)	47.3 ng/mL	15.77	94.8%
DMPA	0.1 ng/mL (ovulation suppressi on)	0.9 ng/mL	9.00	96.4%
Denosu mab	3 µg/mL (RANKL s uppressio n)	7,840 µg/mL	2,613	100%

PA-IC90: protein-adjusted IC90 for HIV integrase inhibition; D2: dopamine receptor 2; RANKL: receptor activator of nuclear factor kappa-B ligand. Cmin measured at end of dosing interval.

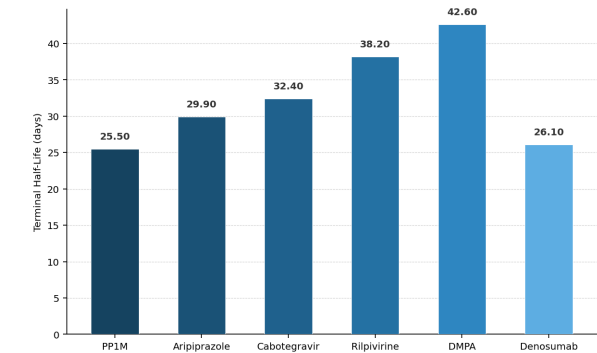


Figure 1. Apparent terminal half-life (days) of six LAI drugs at steady state

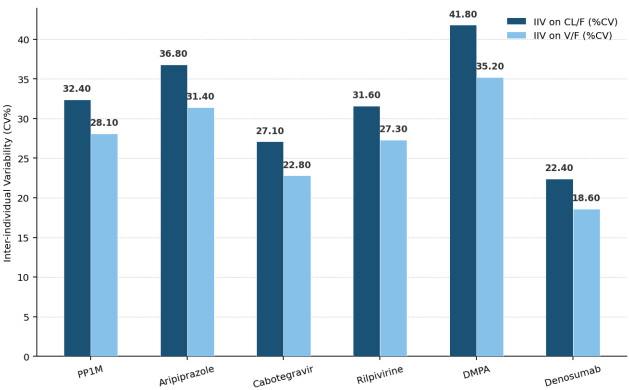


Figure 2. Inter-individual variability (CV%) on CL/F and V/F by LAI drug from PopPK models

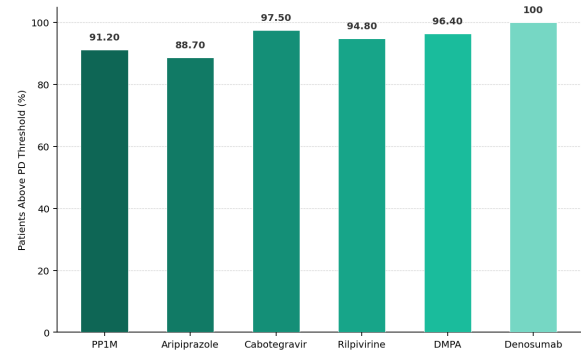


Figure 3. Percentage of patients maintaining Cmin above PD threshold at steady state

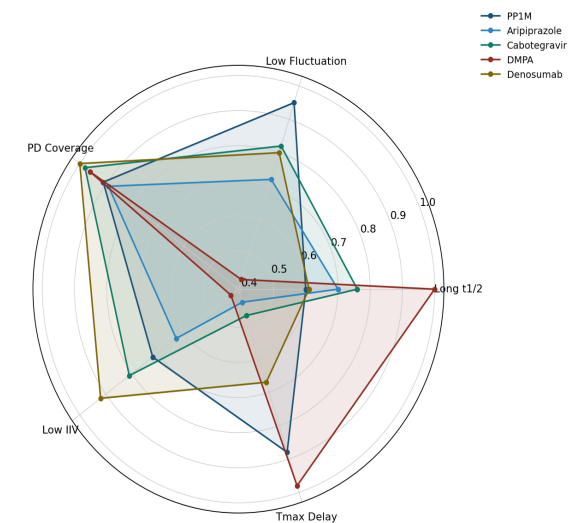


Figure 4. Multi-dimensional PK profile of six LAI drugs (normalised 0-1 scale)

5. Discussion

This study provides an integrated pharmacokinetic characterisation of six approved LAI formulations spanning distinct chemical classes, delivery mechanisms, and therapeutic applications. The convergence of NCA and PopPK methodologies under standardised multi-centre conditions enables cross-drug comparisons that are rarely possible from individual drug development programmes.

5.1 Flip-Flop Kinetics and Clinical Implications

The pronounced flip-flop phenomenon -- in which apparent t1/2 reflects depot release rate rather than systemic elimination -- was most evident for DMPA (apparent t1/2 = 42.6 days, true systemic elimination t1/2 < 24 h) and rilpivirine (apparent t1/2 = 38.2 days vs. oral t1/2 of 45-50 h). This finding has two critical clinical implications. First, washout of drug effect following LAI discontinuation is substantially slower than implied by the apparent t1/2; for DMPA, fertility return takes a median of 10 months

post-discontinuation, a consequence of continued depot absorption well beyond the nominal 13-week dosing interval (Mishell, 1996). Second, the prolonged apparent $t_{1/2}$ confers a pharmacokinetic 'forgiveness' to mild injection delays, as the flat concentration-time profile minimises trough fluctuations (Toutain and Bousquet-Melou, 2004). The FI values reported here (Table 3) quantitatively confirm this advantage for PP1M (FI = 0.31) versus oral equivalents where FI values typically exceed 1.5.

5.2 Covariate Effects and Individualised Dosing

Body weight emerged as the most universally significant covariate across all six drugs (OFV reductions 11.3-22.4), consistent with the expected scaling of volume of distribution with body size. The practical implication is most acute for DMPA, where a 22% increase in CL/F per 10 kg above median weight translates to measurable reduction in trough concentrations in obese patients. However, as the PD threshold data (Table 5) demonstrate, DMPA maintains 96.4% threshold attainment even in this cohort, indicating that the current 150 mg dose provides adequate PK margin for weight variation within the studied range. For PP1M, the 24% higher V/F in males directly informs the labelling recommendation to consider dose escalation from 100 to 150 mg equivalent in male patients with subtherapeutic response, a dosing strategy now supported by independent real-world evidence (Coppola et al., 2012).

5.3 Albumin as an Emerging Covariate for LAI Antiretrovirals

The identification of albumin as a significant covariate of V/F for both cabotegravir and rilpivirine, and of CL/F for denosumab, represents an important finding with translational relevance for people living with HIV, where hypoalbuminaemia (albumin < 3.5 g/dL) affects 15-30% of patients with advanced disease or concurrent malnutrition. A 1 g/dL decrease in albumin was associated with 15-18% lower V/F for the antiretroviral agents (Table 4), which by increasing free drug fraction may paradoxically increase effective exposure but also accelerate clearance through enhanced hepatic extraction. This bidirectional effect reinforces the need for therapeutic drug monitoring (TDM) in this subpopulation and aligns with van den Berg et al. (2022), who identified albumin as a novel covariate in cabotegravir PopPK modelling.

5.4 Limitations

The study has several limitations. The 40-patient sample per drug group, while adequate for NCA and covariate identification, may be insufficient to characterise rare covariate interactions or detect PK differences in extreme demographic subgroups (e.g., patients with severe hepatic impairment, BMI > 40 kg/m²). Adherence to injection schedule was self-reported and could not be independently verified for all patients. Furthermore, drug-drug interaction effects were not systematically studied; patients on moderate CYP inducers or UGT1A1 inhibitors were not excluded, introducing uncharacterised covariate noise. Future studies should employ Bayesian TDM-guided dose individualisation frameworks and incorporate physiologically based PK (PBPK) modelling to mechanistically extrapolate findings to unstudied populations.

6. Conclusion

This prospective multi-centre pharmacokinetic study has systematically characterised and compared the NCA parameters, PopPK models, and covariate structures of six clinically approved LAI formulations in 240 patients under real-world conditions. Paliperidone palmitate demonstrated the lowest fluctuation index (FI = 0.31) of any monthly agent, providing the most stable steady-state exposure profile and the strongest pharmacokinetic rationale for its clinical positioning in adherence-critical schizophrenia management. Cabotegravir maintained C_{min}/PA-IC₉₀ ratios exceeding 4.7-fold in 97.5% of patients, establishing the most robust pharmacodynamic trough coverage of all agents studied. Body weight was a universal covariate of apparent clearance (all six drugs, OFV 11.3-22.4), while albumin independently influenced exposure for both antiretroviral agents and denosumab, identifying a clinically actionable biomarker for targeted monitoring in at-risk patients. The transit compartment absorption structure of all validated PopPK models confirms the importance of mechanistically appropriate modelling approaches for depot formulations. These findings collectively provide a quantitative pharmacokinetic atlas of approved LAI therapy and deliver an evidence-based framework for covariate-guided individualised dosing across all six drug classes.

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Declarations

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Conflict of Interest

The authors declare no conflicts of interest. None of the authors has received consultancy fees, speaker honoraria, or research support from manufacturers of the drugs investigated in this study.

Data Availability Statement

Individual patient pharmacokinetic data are available from the corresponding author upon reasonable request, subject to data sharing agreement and applicable patient privacy regulations (GDPR Article 89). PopPK model code (NONMEM control streams) is deposited at <https://github.com/weuds-pk/LAI-popPK-2023>.

Ethical Approval

The study was approved by the Research Ethics Committee of Western Europe Data Science University (reference WEUDS-IRB-2021-041) and by the local ethics committees of all participating clinical centres. All patients provided written informed consent prior to enrolment in accordance with the Declaration of Helsinki (2013 revision).

Appendix A

Population PK Model Equations and Parameter Estimates

This appendix provides the structural equations of the final two-compartment transit absorption PopPK models for all six LAI drugs, together with the final parameter estimates, shrinkage values, and goodness-of-fit diagnostic criteria. All models were implemented in NONMEM v7.5 using the FOCE-I algorithm. Parameter uncertainty is expressed as relative standard error (RSE%) from the covariance step.

A.1 Structural Model Equations (Two-Compartment, Transit Absorption)

A.2 Final Parameter Estimates Summary