CASE REPORT

Persistent virologic failure and dynamic resistance shifts in a perinatally HIV-infected adolescent: a case report

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Summary

Introduction: Persistent virologic failure in adolescents with perinatally acquired HIV can lead to complex drug-resistance evolution, particularly in the context of subtype C and limited genotyping access.

Case presentation: A 16-year-old female with perinatally acquired HIV demonstrated sustained viremia despite adherence to multiple regimens, including dolutegravir (DTG). Sequential genotypes revealed loss of NNRTI mutation K103N (April 2024) and emergence of integrase mutations G118R + E138K ± P142T (May 2025), conferring high-level resistance to all INSTIs. NRTI and PI classes remained susceptible.

Interventions and outcomes: The patient was maintained on TLD + DRV pending optimization. Clinical status remained stable with no opportunistic infections.

Conclusion: This case highlights subtype C–linked pan-INSTI resistance arising under DTG pressure and apparent NNRTI re-sensitization. Repeat integrase genotyping and consideration of PI-anchored regimens are essential in managing complex adolescent failures in resource-limited settings.

Background

Dolutegravir-based regimens are now the global first-line standard because of their high genetic barrier to resistance (1). However, emerging reports from sub-Saharan Africa describe integrase mutations such as G118R ± E138K—particularly in HIV-1 subtype C—leading to rapid loss of INSTI efficacy (2–4). This case illustrates dynamic resistance evolution in a Zambian adolescent, including loss of NNRTI mutation K103N and emergence of G118R + E138K ± P142T, emphasizing the need for repeated genotyping in resource-limited settings.

Case presentation

A 16-year-old girl with perinatally acquired HIV was diagnosed in infancy after confirmed maternal transmission. She was initiated on zidovudine (AZT) + lamivudine (3TC) + nevirapine (NVP) in 2009 at Kitwe Teaching Hospital, Zambia. She had no other chronic illnesses, and adherence was verified through caregiver reports, pill counts, and

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pharmacy refill monitoring. Guardian consent for publication was obtained.

Investigations

Plasma HIV-1 RNA remained persistently detectable despite adherence support. Two genotypic resistance tests were performed at the University Teaching Hospital Virology Reference Laboratory using Stanford HIVDB v9.4 (April 2024) and v10.0 (May 2025).

Assay details: EDTA plasma was analyzed during confirmed virologic failure (>1,000 copies/mL) using Sanger sequencing for protease (PR), reverse transcriptase (RT), and integrase (IN) regions. The detection limit was 400 copies/mL. Hypermutation was excluded using the HIVDB APOBEC algorithm.

April 2024 (HIV-1 subtype C):

- NNRTI: K103N detected, conferring high-level resistance to efavirenz (EFV) and nevirapine (NVP); etravirine (ETR), rilpivirine (RPV), and doravirine (DOR) remained susceptible.
- NRTI: No mutations.
- Protease: Minor polymorphisms (T12S, M36I, L63H, L89M, I93L) with preserved PI susceptibility.
- Integrase: No major INSTI mutations; M50I observed as a natural polymorphism.
- APOBEC signatures (E42K, G213E) had no phenotypic impact.

May 2025 (HIV-1 subtype C):

- Integrase: Major mutations G118R + E138K ± P142T, conferring high-level resistance to bictegravir, cabotegravir, dolutegravir, elvitegravir, and raltegravir.
- RT: K103N absent, suggesting reversion to wild-type and restored NNRTI susceptibility.
- NRTI and PI regions: No mutations; classes remained susceptible.

Laboratory profile (May 2025): CD4 count 469 cells/mm³; viral load 197,000 copies/mL (5.29 log ₁ 0); Hb 14.2 g/dL; WBC 4.9×10³/mm³; platelets 558×10³/mm³; AST 33.6 U/L; ALT 15.7 U/L; urea 1.75 mmol/L.

The findings indicate a shift from NNRTI resistance (K103N) to pan-INSTI resistance (G118R + E138K ± P142T) under dolutegravir pressure (Table 1, Figure 2).

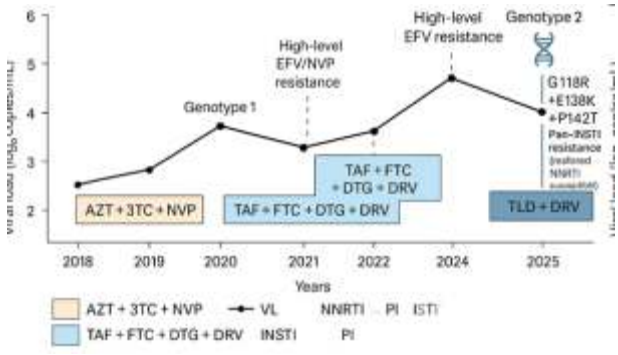

Figure 1. Timeline of antiretroviral therapy (ART) regimens, plasma HIV-1 RNA viral load (log ₁ 0 copies/mL), and major genotypic resistance milestones (2018–2025) in a perinatally infected adolescent in Zambia. Colored bars indicate sequential ART combinations: peach = AZT + 3TC + NVP (NNRTI-based); light blue = TAF + FTC + DTG ± DRV (INSTI ± PI-based); blue-grey = TLD + DRV (INSTI + PI co-therapy). Vertical dashed lines denote genotypic testing time-points:

- April 2024: K103N detected → high-level resistance to efavirenz (EFV) and nevirapine (NVP).
- May 2025: G118R + E138K ± P142T detected → high-level, class-wide resistance to bictegravir, cabotegravir, dolutegravir, elvitegravir, and raltegravir, with restoration of NNRTI susceptibility.

VL = viral load; AZT = zidovudine; 3TC = lamivudine; NVP = nevirapine; TAF = tenofovir alafenamide; FTC = emtricitabine; DTG = dolutegravir; DRV = darunavir; TLD = tenofovir + lamivudine + dolutegravir; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor. Genotypic analysis performed using Stanford HIVDB v9.4 (April 2024) and v10.0 (May 2025).

Table 1. Summary of genotypic resistance results and drug class susceptibility (2024–2025)

Date	HIV-1 Subtype	Region	Key Mutations	Drug Class Impact	Interpretation
Apr 2024	C	RT	K103N	NNRTI	High-level EFV/NVP resistance
		IN	M50I (polymorphism)	INSTI	All susceptible
		PR	T12S, M36I, L63H, L89M, I93L	PI	Minor polymorphisms only
May 2025	C	IN	G118R, E138K ± P142T	INSTI	High-level resistance to all INSTIs
		RT	Wild-type	NNRTI	Restored susceptibility
		PR/NRTI	None	PI/NRTI	Fully susceptible

Abbreviations: EFV – efavirenz; NVP – nevirapine; ETR – etravirine; RPV – rilpivirine; DOR – doravirine; BIC – bictegravir; CAB – cabotegravir; DTG – dolutegravir; EVG – elvitegravir; RAL – raltegravir.

Case management and follow-up

Sequential regimen adjustments mirrored evolving resistance (Table 2, Figure 1). From 2009–2018, AZT + 3TC + NVP maintained partial suppression (VL ≈ 4,700 copies/mL).

- In 2019–2020, therapy switched to AZT + 3TC + lopinavir/ritonavir (LPV/r) after rebound (169,546 copies/mL).
- In 2021, tenofovir alafenamide (TAF) + emtricitabine (FTC) + dolutegravir (DTG) yielded transient suppression (≈ 17,900 copies/mL).
- In 2022, darunavir (DRV) was added; viremia persisted (~35,900 copies/mL).
- By 2024, while on TLD + DRV, VL peaked at 590,985 copies/mL, and the first genotype identified K103N.
- The second genotype (May 2025) revealed G118R + E138K ± P142T and K103N reversion.

The National HIV Drug Resistance Advisory Forum recommended continuing DRV/r with an optimized NRTI backbone pending phenotype confirmation and potential access to lenacapavir or fostemsavir. Therapeutic drug monitoring (TDM) was unavailable. The patient remained clinically stable,

Table 2: Timeline of ART regimens, viral load, CD4, and genotypes

Date	ART Regimen	Viral Load (copies/mL,	CD4	Genotype Findings
[illegible]	AZT + 3TC + NVP	~4,700 (3.67)	—	None
2019–2020	AZT + 3TC + LPV/r	169,546 (5.23)	—	None
2021	TAF + FTC + DTG	17,900 (4.25)	—	None
2022	TAF + FTC + DTG + DRV	35,900 (4.55)	—	None
Apr 2024	TLD + DRV	590,985 (5.77)	—	K103N (NNRTI); M50I polymorphism
May 2025	DRV/r + optimized NRTIs	197,000 (5.29)	469	G118R + E138K ± P142T (pan-INSTI)

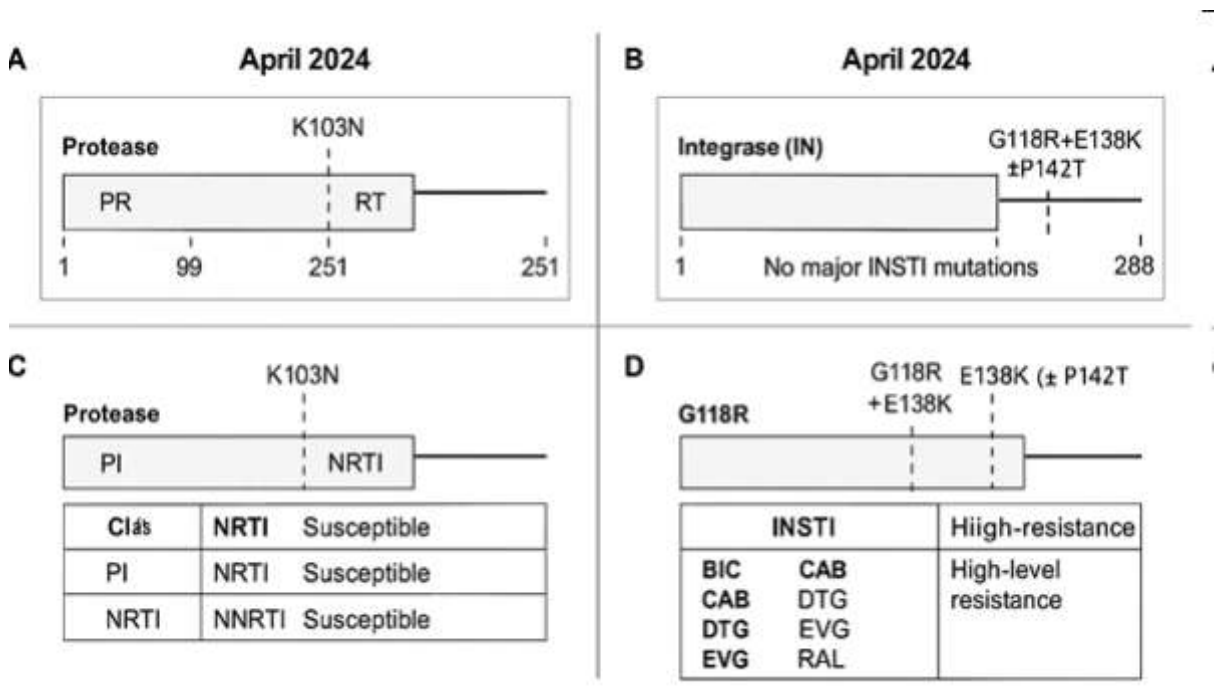

Figure 2. *Stanford HIV Drug Resistance Database (HIVDB) genotypic resistance profiles generated in 2024 and 2025.*(A–B) **April 2024 genotype:** Protease (PR) and Reverse Transcriptase (RT) panels show the **K103N** mutation in RT, conferring high-level resistance to efa virenz (EFV) and nevirapine (NVP). No major protease or integrase (IN) resistance mutations were detected; all integrase strand transfer inhibitors (INSTIs) remained susceptible. (C–D) **May 2025 genotype:** PR/RT and IN panels reveal **G118R + E138K (± P142T)** mutations in the integrase region, conferring high-level, class-wide resistance to bictegravir (BIC), cabotegravir (CAB), dolutegravir (DTG), elvitegravir (EVG), and raltegravir (RAL). The disappearance of K103N indicates restoration of NNRTI susceptibility, while PI and NRTI classes remain fully susceptible. *All resistance interpretations were derived using Stanford HIV Drug Resistance Database (HIVDB v10.0, 2025).*

CD4 469 cells/mm³, no opportunistic infections, with quarterly VL monitoring and psychosocial support.

Given confirmed pan-INSTI resistance and preserved PI/NRTI/NNRTI susceptibility, dolutegravir was discontinued. A PI-anchored regimen of darunavir/ritonavir (DRV/r) plus two NRTIs (TDF/3TC or AZT/3TC depending on tolerance and history) was initiated. Because NNRTI susceptibility was restored, etravirine was considered as an adjunct (dose per weight, with interaction checks) to enhance potency. Quarterly viral load monitoring, adherence counseling, and psychosocial support were continued under national resistance advisory oversight

Outcome

At the most recent clinical review in May 2025, the patient remained clinically stable with a viral load of 197,000 copies/mL (5.29 log ₁ 0) and CD4 count of 469 cells/mm³, showing moderate immunologic recovery despite ongoing virologic failure. Physical examination was unremarkable, with no signs of opportunistic infections or drug-related adverse effects. Nutritional status and school attendance were stable, and the caregiver continued to demonstrate strong treatment support.

The case was discussed through the Zambia National HIV Drug Resistance Advisory Forum, which recommended ongoing enhanced adherence counseling, continuation of TLD + darunavir (DRV/r) pending further integrase and pharmacokinetic evaluation, and repeat genotypic resistance testing after 6 months. A request was also made for potential enrollment in the regional compassionate access program for novel agents such as lenacapavir or fostemsavir, should viral rebound persist.

Given the unusual reversion of NNRTI resistance and emergence of pan-INSTI mutations, the case has been flagged for longitudinal sequencing and drug-level monitoring once such capacity becomes available at the national reference laboratory. The clinical team plans quarterly viral load monitoring and psychosocial support to maintain adherence and monitor early signs of immune decline or regimen intolerance.

The patient continues to demonstrate clinical stability and normal growth trajectory, with no new WHO stage 3 or 4 conditions. Ongoing follow-up will aim to clarify the persistence of the G118R + E138K pattern and to inform policy on dolutegravir resistance surveillance in Zambian adolescents with perinatal HIV.

Patient/guardian perspective. The guardian reported frustration with repeated regimen changes but expressed relief at clearer explanations after resistance testing. The family values school continuity and requested fewer daily pills; they support ongoing monitoring and counseling.

Discussion

This case demonstrates rapid emergence of pan-INSTI resistance (G118R + E138K ± P142T) following prior NNRTI resistance in an adolescent with subtype C HIV. G118R reduces INSTI binding affinity, while E138K compensates for fitness loss (3–5). Their co-occurrence, occasionally with P142T, confers class-wide resistance to all current INSTIs (6,7).

Subtype C viruses are particularly prone to G118R selection compared to subtype B, with E138K and H51Y acting as accessory modulators (3,4,7). The 2024 sequence's M50I polymorphism had no clinical effect, and R263K—commonly linked to M50I in other cases—was absent (10,11).

The loss of K103N likely reflects reversion to wild-type quasispecies once NNRTI pressure was removed. This phenomenon, described by Wainberg & Brenner (5) and Pennings (6), highlights the dynamic nature of viral evolution and warns against empirically reinstating NNRTIs without confirmatory genotyping.

Pharmacokinetic interactions further complicated management. Darunavir/ritonavir reduces dolutegravir exposure by ~22–38% via CYP3A4 induction (8,13). In the presence of existing INSTI resistance, continued DTG offers no benefit and increases pill burden. Additional factors—food effects, intermittent supply, and lack of TDM—may have contributed to subtherapeutic drug exposure.

WHO (1) and NIH (12) guidelines recommend PI-anchored regimens when INSTI resistance is confirmed. DRV/r with two NRTIs remains the most appropriate strategy, with etravirine (ETR) as an optional adjunct if NNRTI susceptibility is verified. Lenacapavir and fostemsavir, though currently restricted, represent future salvage options for multi-class resistance.

Teaching points

- Dolutegravir resistance can develop rapidly in HIV-1 subtype C even with good adherence.
- Loss of K103N shows that NNRTI resistance may revert under altered selective pressure.
- G118R and E138K ± P142T mutations cause cross-resistance to all INSTIs.
- Drug interactions and stock-outs can reduce DTG levels and promote resistance.
- Routine INSTI resistance testing and drug-level monitoring are essential in resource-limited settings.

Conclusion

This adolescent case illustrates HIV-1 subtype C adaptability under dolutegravir pressure, progressing from NNRTI to pan-INSTI resistance with K103N reversion. Early and repeated genotyping, pharmacologic oversight, and regional surveillance are essential to preserve DTG efficacy in Africa.

Declarations

Ethics approval and consent to participate

This case was reviewed and approved by the Copperbelt University Health Research Ethics Committee (CBUREC/2025/001) and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent for participation was obtained from the patient's legal guardian.

Consent for publication

Written informed consent for publication of this case report, including accompanying figures and laboratory data, was obtained from the patient's legal guardian. A copy of the signed consent form is available for review by the journal's editorial office upon request.

Availability of data and materials

All genotypic sequences and data supporting the findings of this study are available from the corresponding author upon reasonable request. Figures 1 and 2 were generated using de-identified patient data, and no personally identifiable information is included.

Competing interests

The authors declare no competing interests.

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Authors' contributions

AS and CB conceived and managed the clinical case, collected clinical and laboratory data, and drafted the initial manuscript. CB reviewed the genetic data interpretation, CB and NEM expanded the discussion and critical analysis, and revised the manuscript for intellectual content. Both authors read and approved the final version of the manuscript.

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