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Long-Term Virologic Outcomes of Dolutegravir-Based Regimens in Treatment-Naïve Adults

Fortin L^{1*}, Bouchard V² and Morin M³

¹Department of Applied Sciences, Dakar Center for Clinical Infectious Disease, Canada Scopus Author ID: 57677580610 Email: laurent.fortin@dakar.edu
ORCID: <https://orcid.org/5669-3964-7711-0843>

²Department of Translational Medicine, Dakar Center for Clinical Infectious Disease, Switzerland Scopus Author ID: 57164569286 Email: vincent.bouchard@dakar.edu
ORCID: <https://orcid.org/8592-3286-4749-2650>

³Department of Applied Sciences, Montreal Institute of AIDS Clinical Medicine, Switzerland Scopus Author ID: 57222205610 Email: manon.morin@montreal.edu
ORCID: <https://orcid.org/4063-8694-9391-1603>

***Correspondence to:** Laurent Fortin, Department of Applied Sciences, Dakar Center for Clinical Infectious Disease, Canada Scopus Author ID: 57677580610 Email: laurent.fortin@dakar.edu

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Abstract

Dolutegravir-based regimens have become the dominant first-line antiretroviral therapy worldwide, but the evidence supporting that shift is spread across more than a decade of independently conducted trials and cohorts. This article synthesizes the literature on long-term virologic outcomes of dolutegravir-based regimens in treatment-naïve adults, tracing the pharmacological basis for dolutegravir's high genetic barrier to resistance through the pivotal phase 3 trials (SINGLE, SPRING-2, and FLAMINGO) that established its superiority or non-inferiority against efavirenz-, raltegravir-, and darunavir-based comparators, the ADVANCE and NAMSAL trials that extended this evidence to high-burden, resource-limited settings, and the GEMINI trials demonstrating that a simplified two-drug dolutegravir-lamivudine regimen preserves virologic durability through 96 weeks. We give particular attention to the resistance and cohort literature specific to integrase-inhibitor-naïve, first-line initiation, which finds treatment-emergent resistance to be rare even among the minority of dolutegravir recipients who experience virologic failure, and to the special-population evidence on pregnancy safety, weight and metabolic change, and tuberculosis coinfection that has shaped how dolutegravir is used in practice. Read together, the evidence supports dolutegravir-based first-line therapy as virologically durable and resistance-resilient in treatment-naïve adults, while leaving the mechanism and long-term clinical significance of dolutegravir-associated weight gain, and the operating characteristics of its resistance barrier under routine programmatic monitoring, as open areas for continued research.

Keywords: dolutegravir; integrase strand transfer inhibitor; treatment-naïve HIV; antiretroviral therapy durability; HIV drug resistance

1. Introduction

Dolutegravir has, in the space of roughly a decade, gone from an experimental second-generation integrase strand transfer inhibitor to the backbone of first-line antiretroviral therapy for the large majority of the roughly 40 million people living with HIV worldwide. That trajectory was not inevitable. When dolutegravir entered phase 3 development, the treatment-naïve space was already crowded with efavirenz-based regimens that had anchored global first-line therapy for over a decade, protease-inhibitor-boosted regimens favored for their high genetic barrier to resistance, and a first-generation integrase inhibitor, raltegravir, that had demonstrated excellent tolerability but required twice-daily dosing and had a comparatively low barrier to resistance. Dolutegravir's proposition was that a once-daily, low-milligram, boost-free integrase inhibitor could match or exceed the virologic potency of these established options while adding a genetic barrier to resistance that raltegravir and first-generation agents lacked. A succession of large randomized trials run over the following several years tested that proposition directly, in treatment-naïve adults, against every major class of comparator regimen then in use.

This article synthesizes what that trial program, and the substantial body of post-marketing and real-world cohort literature that followed it, has established about the long-term virologic outcomes of dolutegravir-based regimens specifically in treatment-naïve adults. We are not reporting new data; we are pulling together evidence that has accumulated across more than a decade of randomized comparisons, resistance surveillance, and implementation research, much of it conducted in the high-burden settings of sub-Saharan Africa where dolutegravir's public-health impact has been greatest. Five threads run through the literature and organize the discussion that follows: the pharmacological and structural basis for dolutegravir's high genetic barrier to resistance; the pivotal randomized trials that established virologic non-inferiority and, in several cases, superiority against first-line comparators; the two-drug dolutegravir-lamivudine regimen that has since become a preferred simplification strategy; the resistance and durability data specific to integrase-inhibitor-naïve, first-line initiation, which turns out to be a meaningfully different question from resistance after second-line switching; and the special-population evidence, on pregnancy, weight change, and tuberculosis coinfection,

that has shaped how dolutegravir is actually used in the populations who take it.

It is worth being explicit about what this synthesis does and does not claim. The virologic efficacy case for dolutegravir in treatment-naïve adults is, by the standards of HIV therapeutics research, unusually well established: it rests on more than half a dozen large, independently conducted, randomized phase 3 trials with consistent findings across sub-Saharan African, European, and North American populations, followed by multi-year extension studies and large observational cohorts. What is less settled, and what the later sections of this article deal with directly, is the long-term metabolic and weight-related safety profile of dolutegravir-based regimens, the magnitude and clinical significance of an early pregnancy safety signal that has since been substantially, though not completely, resolved by additional surveillance, and the durability of dolutegravir's resistance barrier under the specific adherence and monitoring conditions of programmatic, rather than trial, settings. Reading the efficacy and the safety-and-durability literatures together, rather than treating them as separate stories, is the point of what follows.

2. Mechanism and Pharmacological Rationale for Dolutegravir as First-Line Therapy

Dolutegravir belongs to the integrase strand transfer inhibitor (INSTI) class, which blocks the strand transfer step of HIV-1 integration by chelating the two magnesium ions coordinated within the integrase active site, displacing the viral DNA 3' end from the active site and preventing its insertion into host chromosomal DNA. Structural and functional work by Hare and colleagues characterized dolutegravir's specific binding mode within this shared mechanistic framework, showing that it achieves a markedly slower dissociation rate from the integrase-DNA complex than the first-generation INSTIs raltegravir and elvitegravir, with a prolonged intasome-binding half-life that the authors linked directly to dolutegravir's higher genetic barrier to resistance and its retained activity against several integrase mutations that confer resistance to earlier agents in the class [1]. Later cryo-electron microscopy work by Passos and colleagues resolved the structural basis for this slow dissociation directly, visualizing how dolutegravir engages the integrase active site within the intasome — the higher-order nucleoprotein complex

formed by integrase bound to viral DNA ends — in a way that is comparatively tolerant of active-site mutations that would otherwise displace less tightly bound inhibitors [2]. Together, this structural literature gives a mechanistic account of an observation that would otherwise be purely empirical: that dolutegravir's resistance barrier in integrase-inhibitor-naïve individuals has, across an unusually large body of clinical trial and cohort data, turned out to be very high in practice, a point the later sections of this article return to with the actual clinical numbers.

Pharmacologically, dolutegravir's favorable properties extend beyond the integrase-binding kinetics. It is metabolized primarily via UGT1A1-mediated glucuronidation with a minor CYP3A4 contribution, has a plasma half-life of approximately 14 hours that supports once-daily, unboosted dosing, and does not require a pharmacokinetic booster (ritonavir or cobicistat) of the kind that protease-inhibitor-based and elvitegravir-based regimens depend on. The absence of a boosting requirement removes an entire category of drug-drug interactions that complicate boosted regimens, though dolutegravir's dependence on polyvalent-cation chelation for its integrase-binding activity does create a well-characterized interaction with mineral supplements (calcium, iron, and antacids) that must be dosed apart from dolutegravir to avoid absorption loss, and its interaction with rifampicin, a potent UGT1A1 and CYP3A4 inducer used in first-line tuberculosis treatment, has specific dosing implications that the tuberculosis-coinfection section below addresses directly. These pharmacological characteristics — once-daily unboosted dosing, a compact 50 mg tablet amenable to fixed-dose combination, and a side-effect profile without the lipid and gastrointestinal burden associated with older boosted protease-inhibitor regimens — were, alongside the resistance-barrier data, central to why dolutegravir was positioned for first-line, treatment-naïve use rather than reserved as a later-line option the way raltegravir largely had been.

3. Establishing Efficacy: The Pivotal Phase 3 Trials in Treatment-Naïve Adults

SINGLE, SPRING-2, and FLAMINGO: Head-to-Head Superiority Trials

The clinical case for dolutegravir in treatment-naïve adults was built through a series of large, randomized,

comparator-controlled phase 3 trials run in close succession between roughly 2011 and 2014, each testing dolutegravir against a different first-line standard of the era. The SINGLE trial randomized treatment-naïve adults to dolutegravir plus fixed-dose abacavir-lamivudine versus fixed-dose efavirenz-tenofovir-emtricitabine (then the World Health Organization's preferred first-line regimen in high-income settings) and found that, at week 48, 88% of participants on the dolutegravir arm achieved HIV-1 RNA below 50 copies/mL compared with 81% on the efavirenz arm, a difference that met the trial's pre-specified criteria for statistical superiority rather than mere non-inferiority [3]. That superiority margin was driven substantially by fewer discontinuations for adverse events on the dolutegravir arm — efavirenz's central nervous system side effects (vivid dreams, dizziness, and mood disturbance) were, and remain, a well-documented driver of early discontinuation — rather than by a difference in on-treatment virologic response among participants who stayed on therapy, an important distinction that later resistance analyses of this trial and its successors returned to repeatedly. Extended follow-up of the SINGLE cohort through week 96 and week 144 confirmed that the initial superiority signal was durable rather than a short-term artifact of differential early discontinuation, with dolutegravir maintaining higher rates of virologic suppression through three years of follow-up and, notably, zero treatment-emergent integrase resistance mutations detected among participants who experienced protocol-defined virologic failure on the dolutegravir arm across the full 144-week observation period [4].

Table 1: Virologic suppression rates (HIV-1 RNA <50 copies/mL) reported in the pivotal randomized phase 3 trials of dolutegravir-based first-line therapy in treatment-naïve adults, by trial, comparator regimen, and timepoint of the reported result [3,5,7,10,14,15].

Trial	DTG-based arm(s)	Comparator	Timepoint	Suppression, DTG vs comparator
SINGLE [3]	DTG + abacavir/lamivudine	Efavirenz/TDF/FTC	Week 48	88% vs 81%
SPRING-2 [5]	DTG + investigator-selected NRTIs	Raltegravir	Week 48	88% vs 85%
FLAMINGO [7]	DTG + investigator-selected NRTIs	Darunavir/ritonavir	Week 48	90% vs 83%
ADVANCE [10]	DTG + TDF/FTC; DTG + TAF/FTC	Efavirenz/TDF/FTC	Week 48	85% and 84% vs 79%

Trial	DTG-based arm(s)	Comparator	Timepoint	Suppression, DTG vs comparator
NAMSAL [14]	DTG + TDF/3TC	Efavirenz 400 mg/TDF/3TC	Week 96	73.9% vs 72.3%
GEMINI-1/-2 (pooled) [15]	DTG + lamivudine (2-drug)	DTG + TDF/FTC (3-drug)	Week 48	91% vs 93%

SPRING-2 tested dolutegravir against raltegravir, the first-generation integrase inhibitor, in a double-blind, non-inferiority design — a direct within-class comparison rather than a comparison against a different drug class. At week 48, 88% of dolutegravir-treated participants and 85% of raltegravir-treated participants achieved HIV-1 RNA below 50 copies/mL, meeting the trial's non-inferiority criterion with a treatment difference small enough (2.5 percentage points, adjusted for baseline viral load and background nucleoside backbone) that the trial did not claim superiority, unlike SINGLE [5]. What distinguished SPRING-2 from a simple non-inferiority confirmation was its 96-week extension, which found that the small numerical advantage for dolutegravir was maintained through two years and, again, that no dolutegravir-treated, integrase-inhibitor-naïve participant developed a treatment-emergent integrase resistance mutation at virologic failure, in contrast to a small number of raltegravir-treated participants who did — the first head-to-head demonstration within a randomized trial that dolutegravir's higher genetic barrier translated into a measurably different resistance outcome under real trial conditions rather than remaining a purely structural or in vitro property [6].

FLAMINGO completed this initial trio by testing dolutegravir against ritonavir-boosted darunavir, historically the protease-inhibitor-based regimen with the strongest genetic barrier to resistance and, for that reason, often reserved for patients where resistance risk was a particular concern. In this open-label design, 90% of dolutegravir-treated participants achieved viral suppression at week 48 compared with 83% on darunavir-ritonavir, a statistically significant superiority margin of 7.1 percentage points, again driven substantially by differential discontinuation (more participants stopped darunavir-ritonavir for gastrointestinal adverse events) alongside a smaller contribution from differential virologic response among participants with higher baseline viral loads [7]. The 96-week extension of FLAMINGO confirmed durability

of this advantage and, notably, reported that dolutegravir's virologic superiority over boosted darunavir was most pronounced in the subgroup of participants presenting with baseline viral loads above 100,000 copies/mL, a clinically important subgroup because high baseline viral load has historically been associated with a higher risk of virologic failure across most antiretroviral classes [8]. A contemporaneous systematic review and meta-analysis pooling SINGLE, SPRING-2, FLAMINGO, and several smaller comparator trials confirmed, across the pooled trial population, that dolutegravir-based regimens achieved higher rates of virologic suppression and lower rates of treatment discontinuation than the comparator regimens tested across this first wave of phase 3 evidence, providing an aggregate statistical confirmation of what each individual trial had shown separately [9].

Dolutegravir in High-Burden, Resource-Limited Settings: ADVANCE and NAMSAL

The SINGLE, SPRING-2, and FLAMINGO trial program was conducted predominantly in high-income settings, using efavirenz-tenofovir-emtricitabine, raltegravir, and boosted darunavir as comparators — none of which reflected the actual first-line landscape in the sub-Saharan African settings where the majority of people living with HIV reside and where efavirenz at standard 600 mg dosing, not the comparators used in the earlier trials, remained the entrenched first-line standard. Two trials, ADVANCE and NAMSAL, were designed specifically to close this evidence gap, and their results were instrumental in the World Health Organization's 2019 decision to recommend dolutegravir-based regimens as the preferred first-line option globally, including in low- and middle-income settings.

ADVANCE, conducted in South Africa, randomized treatment-naïve adults three ways: dolutegravir plus emtricitabine and tenofovir alafenamide (the newer tenofovir prodrug), dolutegravir plus emtricitabine and tenofovir disoproxil fumarate (the older, more widely available tenofovir prodrug), or efavirenz plus emtricitabine and tenofovir disoproxil fumarate, the standard first-line regimen across most of the region at the time. At week 48, viral suppression below 50 copies/mL was achieved by 85% of participants on dolutegravir plus tenofovir disoproxil fumarate, 84% on dolutegravir plus tenofovir alafenamide, and 79% on the

efavirenz-based comparator, confirming both dolutegravir's non-inferiority (and numerically higher response) relative to efavirenz in this specific population and the near-equivalence of the two tenofovir prodrugs when paired with dolutegravir [10]. The 96-week extension of ADVANCE confirmed durability of these suppression rates and became, alongside NAMSAL, one of the two trials most responsible for the weight-gain signal discussed in the special-populations section below, since ADVANCE's three-arm design allowed the field to separate the metabolic contribution of dolutegravir from that of tenofovir alafenamide for the first time in a single randomized comparison [11]. Implementation research following the ADVANCE trial period has extended this evidence into routine public-sector care: a large retrospective cohort analysis of dolutegravir-based first-line antiretroviral therapy roll-out in South Africa found that real-world virologic outcomes among people starting dolutegravir-based first-line therapy in routine clinical programs were broadly consistent with the suppression rates reported in the pivotal trials, an important confirmation that trial-level efficacy translated into programmatic effectiveness at national implementation scale rather than eroding under the adherence and retention pressures of routine care [12].

NAMSAL, conducted in Cameroon, took a different comparator approach: rather than testing dolutegravir against standard-dose (600 mg) efavirenz, it compared dolutegravir against a reduced 400 mg dose of efavirenz, itself an active area of first-line optimization research at the time because lower-dose efavirenz had shown comparable efficacy with an improved side-effect profile relative to the standard 600 mg dose. At week 96, 73.9% of participants on dolutegravir and 72.3% on low-dose efavirenz achieved HIV-1 RNA below 50 copies/mL, a result the trial interpreted as confirming non-inferiority between the two approaches, though the suppression rates in both arms were notably lower than the roughly 85–90% seen in SINGLE, SPRING-2, FLAMINGO, and ADVANCE — a difference the NAMSAL investigators attributed substantially to a high proportion of participants presenting with very high baseline viral loads (above 100,000, and in many cases above 500,000, copies/mL), a population in which virologic response to any first-line regimen, including dolutegravir, is measurably harder to achieve within a fixed follow-up window [13]. Extended follow-up of NAMSAL through

week 192 (nearly four years) found that this initial non-inferiority result held over the longer term, with durability of both regimens' virologic response, low rates of confirmed virologic failure with treatment-emergent resistance in the dolutegravir arm specifically, and continued documentation of the weight-gain differential between the two regimens that the trial's earlier reports had also flagged [14]. Read together, ADVANCE and NAMSAL close what had been a genuine evidence gap: they demonstrate that dolutegravir's efficacy advantage over efavirenz-based first-line therapy, established initially in largely European and North American trial populations, generalizes to the sub-Saharan African populations, viral subtypes, and baseline disease severity profiles that make up the majority of the global first-line antiretroviral therapy population.

4. Two-Drug Simplification: The GEMINI Trials and Long-Term Durability

A separate but related line of trial evidence asked a more specific question: given dolutegravir's high potency and resistance barrier, could a two-drug regimen — dolutegravir paired with a single nucleoside reverse transcriptase inhibitor rather than the conventional two-NRTI backbone — achieve comparable virologic outcomes while reducing long-term cumulative drug exposure. The GEMINI-1 and GEMINI-2 trials, two identically designed, double-blind, non-inferiority studies conducted in parallel, randomized treatment-naïve adults with baseline viral loads up to 500,000 copies/mL to dolutegravir plus lamivudine (the two-drug regimen) versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine (the standard three-drug regimen). At week 48, pooled across both studies, 91% of participants on the two-drug regimen and 93% on the three-drug regimen achieved HIV-1 RNA below 50 copies/mL, an adjusted treatment difference of –1.7 percentage points that comfortably met the trials' pre-specified non-inferiority margin [15]. This was a clinically consequential result: it established, for the first time in adequately powered, randomized, treatment-naïve trials, that dropping an entire drug class from first-line therapy did not come at a meaningful virologic cost, provided the two remaining agents (dolutegravir and lamivudine) each carried sufficient individual potency and resistance barrier to compensate for the lost backbone redundancy.

The 96-week extension of GEMINI-1 and GEMINI-2

confirmed that this non-inferiority result was durable rather than a short-term finding vulnerable to late failures once the initial treatment-naïve viral load had been suppressed for an extended period: virologic response rates remained closely matched between the two- and three-drug arms through two years of follow-up, and the trials' virologic-failure and resistance analyses found low, closely matched rates of confirmed virologic failure between arms, with treatment-emergent resistance remaining rare in both [16]. The durability finding matters specifically for the "long-term virologic outcomes" question this article is organized around, because a two-drug regimen's principal theoretical vulnerability — a smaller number of active drugs providing less redundancy against the emergence of resistance to any single agent — is precisely the failure mode that 96-week resistance surveillance was designed to detect, and did not find at meaningfully different rates from the three-drug comparator arm. The GEMINI program's results underpin the subsequent regulatory approval and clinical uptake of dolutegravir-lamivudine as a fixed-dose, single-tablet, two-drug first-line option, now used at meaningful scale as an alternative to three-drug dolutegravir-based regimens in treatment-naïve adults without evidence of hepatitis B coinfection (for whom the lamivudine-only NRTI backbone would be inadequate) or very high baseline viral load approaching the upper bound tested in the pivotal trials.

5. Genetic Barrier to Resistance and Long-Term Virologic Durability

The resistance-barrier claim that runs through every trial discussed above — that treatment-emergent integrase resistance in integrase-inhibitor-naïve, dolutegravir-treated participants is rare to the point of being difficult to observe even in trials with hundreds of participants followed for two to four years — is worth examining directly rather than accepting as a background assumption, because it is the single most consequential long-term virologic outcome this article addresses. A structured surveillance framework for integrase resistance, developed by Tzou and colleagues to standardize how transmitted and treatment-emergent INSTI resistance mutations are defined and reported across cohorts and surveillance programs, has become the reference classification used by most of the resistance literature synthesized in this section, and its adoption has itself improved the comparability of

resistance findings across the disparate trial and cohort datasets that make up this evidence base [17].

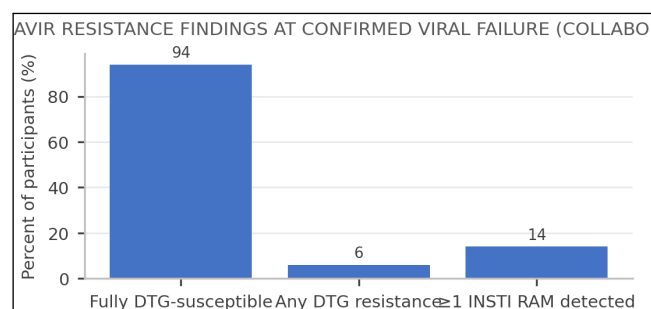


Figure 1: Dolutegravir susceptibility and integrase resistance-associated mutation (RAM) prevalence among people with confirmed virologic failure on dolutegravir-based antiretroviral therapy in a multi-country collaborative cohort analysis -- most failures remained fully susceptible to dolutegravir on phenotypic testing, underscoring the drug's high genetic barrier to resistance even among the minority of dolutegravir recipients who experience virologic failure [19].

Henegar and colleagues' comprehensive review of treatment-emergent integrase resistance with dolutegravir-based regimens in real-world settings, synthesizing evidence across both clinical trials and observational cohorts, concluded that resistance-associated mutations conferring reduced dolutegravir susceptibility remained rare across both two-drug and three-drug dolutegravir regimens in real-world use, while noting that the great majority of documented cases of treatment-emergent dolutegravir resistance in the wider literature occurred in treatment-experienced individuals with prior exposure to other antiretroviral classes and, frequently, documented suboptimal adherence — a substantially different risk population from the integrase-inhibitor-naïve, first-line initiators who are the subject of this article [18]. This distinction between first-line, treatment-naïve initiation and later-line, treatment-experienced switching is one of the more important nuances the aggregate resistance literature makes clear: dolutegravir's resistance barrier, which the structural work described earlier grounds in its unusually slow dissociation from the integrase-DNA intasome complex, appears most robust precisely in the population — integrase-inhibitor-naïve adults starting first-line therapy — that this article is about, and comparatively more vulnerable in treatment-experienced populations carrying pre-existing nucleoside resistance mutations that reduce the effective potency of the NRTI backbone paired with dolutegravir.

A large collaborative cohort analysis pooling

drug-resistance testing data from people with confirmed virologic failure on dolutegravir-based antiretroviral therapy across multiple countries and cohorts provides the most granular quantitative picture available of what resistance looks like specifically among people whose treatment has already failed. Among participants in this collaborative analysis with confirmed virologic failure and resistance testing performed, 94% remained fully phenotypically susceptible to dolutegravir despite having failed dolutegravir-based therapy, with the remaining 6% distributed across potential low-level, low-level, intermediate, and high-level resistance categories; more broadly, 14% of participants with virologic failure carried at least one integrase inhibitor resistance-associated mutation of any kind, whether or not that mutation was sufficient to reduce dolutegravir susceptibility on phenotypic testing [19]. It is worth being precise about what this figure does and does not represent: it describes resistance prevalence among people who had already experienced virologic failure on dolutegravir-based therapy, the population in whom resistance would be expected to be concentrated, not the resistance rate among all dolutegravir initiators — the overwhelming majority of whom, consistent with the trial-level virologic suppression rates reported in the preceding sections, never experience virologic failure at all. Read against that denominator, a finding that even among the minority of people who do experience virologic failure on dolutegravir-based therapy, the large majority remain fully susceptible to the drug, is a striking confirmation of the resistance-barrier case built on the structural and trial-level evidence discussed earlier in this article, and it is the empirical anchor for Figure 1 below. The cohort analysis also identified that the great majority of its resistance-positive cases occurred among participants who had switched to dolutegravir from a prior, non-integrase-inhibitor regimen rather than having started dolutegravir as their initial first-line therapy, reinforcing the same first-line-versus-switch distinction that Henegar and colleagues' review had identified [18,19].

6. Special Populations: Pregnancy, Weight Gain, and Tuberculosis Coinfection

No synthesis of dolutegravir's long-term outcomes in treatment-naïve adults is complete without addressing the three areas of safety evidence that have most shaped clinical guidance and patient counseling since the drug's introduction: a pregnancy safety signal identified after

initial rollout, a weight-gain and metabolic effect observed consistently across the resource-limited-setting trials, and a specific pharmacokinetic interaction relevant to tuberculosis coinfection, which remains extremely common among people newly diagnosed with HIV in high-burden settings.

The pregnancy signal originated with the Tsepamo birth-outcomes surveillance study in Botswana, which in 2018 identified an excess of neural tube defects among infants born to women who had been taking dolutegravir at the time of conception, relative to women on other antiretroviral regimens at conception. The full published analysis by Zash and colleagues reported this excess prevalence with a magnitude — an increase from a baseline neural tube defect prevalence of roughly 0.1% to approximately 0.3–0.9% depending on the surveillance period examined — sufficient to prompt an immediate global regulatory and guideline response restricting dolutegravir use around the time of conception pending further data [20]. A subsequent surveillance update from the same Botswana program, incorporating additional births and refined case ascertainment, found that the excess signal, while still present, was smaller in the expanded dataset than the initial alarming estimate, and helped move the field from an initial blanket caution against dolutegravir in women of childbearing potential toward a more calibrated risk communication and shared-decision-making approach [21]. That more calibrated approach was subsequently reinforced by two major randomized trials designed specifically to generate prospective pregnancy safety and efficacy data: the IMPAACT 2010/VESTED trial, which randomized women starting antiretroviral therapy during pregnancy to dolutegravir-based versus efavirenz-based regimens and found favorable virologic and comparable-to-superior neonatal outcomes with dolutegravir-based therapy, without observing the neural tube defect signal in this prospectively enrolled, pregnancy-initiated population [22], and a subsequent United States-based trial directly comparing dolutegravir-based regimens against contemporary standard-of-care HIV regimens in pregnancy, which similarly did not identify an excess of neural tube defects and reported favorable virologic suppression with dolutegravir through delivery [23]. The net effect of this sequence — an initial alarming signal, followed by

refined surveillance narrowing its magnitude, followed by prospective randomized trials not replicating a neural tube defect excess in pregnancy-initiated dolutegravir use specifically — has been a substantial, though not complete, resolution of the pregnancy safety question, and current guidance in most settings now supports dolutegravir as a preferred option in pregnancy and for women of childbearing potential, with continued surveillance rather than blanket restriction.

Weight gain has proven to be a more durable and less fully resolved safety finding. Across ADVANCE and NAMSAL specifically, participants randomized to dolutegravir-based regimens gained substantially more weight over 96 weeks than those randomized to efavirenz-based regimens, with the effect most pronounced among women and further amplified when dolutegravir was paired with tenofovir alafenamide rather than tenofovir disoproxil fumarate — a finding ADVANCE's three-arm design was specifically positioned to detect, since it isolated the tenofovir-prodrug contribution from the dolutegravir contribution within a single randomized comparison [11]. A review by Jemal synthesizing the accumulated weight-gain and metabolic-comorbidity literature across dolutegravir trials and cohorts found this weight-gain effect to be a consistent finding across studies and populations, associated with downstream increases in incident metabolic syndrome, new-onset diabetes, and hypertension in some but not all analyses, while noting that the underlying mechanism remains incompletely understood and that untangling dolutegravir's own contribution from that of efavirenz's appetite-suppressing and weight-reducing effect (efavirenz-treated participants in these same trials tended to lose or maintain weight, complicating simple attribution of the between-arm difference entirely to dolutegravir) remains an active methodological challenge in this literature [24]. What is not in dispute is the clinical relevance of this finding at population scale: given that dolutegravir-based first-line therapy is now used by tens of millions of people globally, even a modest per-person weight and metabolic effect translates into a substantial population-level burden of incident cardiometabolic disease, and this has become one of the most active areas of ongoing dolutegravir-related clinical and public-health research, distinct from, and in some ways now more prominent than, the virologic efficacy question this article's earlier

sections addressed.

Tuberculosis coinfection presents a narrower but clinically important pharmacokinetic challenge. Rifampicin, the cornerstone of first-line tuberculosis treatment, is a potent inducer of UGT1A1 and CYP3A4, the enzymes responsible for dolutegravir metabolism, and coadministration substantially reduces dolutegravir plasma exposure. The INSPIRING trial addressed this directly, testing dolutegravir dosed twice daily (rather than the standard once-daily dose) alongside rifampicin-based tuberculosis treatment in coinfecting adults, and found that this dose-adjustment strategy achieved virologic and tuberculosis treatment outcomes comparable to those seen with standard first-line regimens in tuberculosis-coinfecting populations, without the toxicity concerns that had historically limited concurrent protease-inhibitor and rifampicin use [25]. The subsequent RADIANT-TB trial tested an alternative approach — standard-dose (rather than doubled) dolutegravir alongside rifampicin — in a non-comparative design intended to determine whether the pharmacokinetic boost from twice-daily dosing was strictly necessary, and found that standard-dose dolutegravir achieved satisfactory virologic outcomes in most, though not all, participants during concurrent rifampicin-based tuberculosis treatment, a result that has kept twice-daily dosing as the more cautious and more widely recommended approach in current guidance while RADIANT-TB's findings continue to inform the ongoing debate about whether standard dosing is adequate for the subset of coinfecting patients who might tolerate it [26]. Given how common tuberculosis coinfection remains among people newly diagnosed with HIV in the highest-burden settings — precisely the settings where dolutegravir-based first-line therapy has scaled most rapidly — this dosing question is not a marginal pharmacological footnote but a frequently encountered clinical scenario that first-line prescribers in these settings manage routinely.

7. Open Challenges

Several gaps recur across the literature synthesized here and are worth naming directly rather than leaving implicit. First, the weight-gain and metabolic-comorbidity signal remains mechanistically unresolved: the trial-level evidence that dolutegravir-based regimens are associated with more weight gain than efavirenz-based regimens is consistent

and robust, but the relative contribution of dolutegravir itself, the specific NRTI backbone it is paired with, and the weight-suppressing counter-effect of the efavirenz comparator arm, has not been cleanly separated by the existing randomized evidence, and longer-term cardiometabolic outcome data (rather than weight and lipid surrogates) remain comparatively sparse [24]. Second, the pregnancy safety question, while substantially reassured by IMPAACT 2010/VESTED and the subsequent United States trial, has not been definitively closed in the sense of ruling out a small residual risk, particularly for conception-period exposure specifically as opposed to pregnancy-initiated exposure, and the field continues to rely on ongoing birth-outcomes surveillance rather than a single conclusive trial to monitor this question [20,21,22].

Third, the resistance-barrier evidence synthesized in this article, while reassuring at the population level, is concentrated in trial populations and cohorts with comparatively close virologic monitoring; how well the same low resistance rates hold in programmatic settings with less frequent viral load testing and longer intervals between detecting virologic failure and switching therapy — the actual operating conditions across much of the high-burden, resource-limited settings where dolutegravir-based first-line therapy is now used at the largest scale — is addressed only partially by the available implementation cohort data, and continued resistance surveillance under real programmatic monitoring intervals, rather than trial-level monitoring frequency, remains a priority [12,19]. Fourth, the tuberculosis-coinfection dosing question is not fully settled: INSPIRING established twice-daily dosing as effective, and RADIANT-TB has begun to test whether standard dosing might suffice for at least some patients, but a definitive comparative trial powered to detect clinically meaningful differences in virologic outcome between the two dosing strategies, across the full range of tuberculosis-coinfected patients rather than a non-comparative pilot population, has not yet been conducted [25,26]. Finally, essentially all of the pivotal efficacy evidence synthesized here was generated in trial populations with close monitoring, high retention, and study-drug adherence support that differ systematically from routine care; the durability of dolutegravir's virologic and resistance advantages under the adherence and retention conditions of unselected, real-world first-line populations, while reassuringly consistent with

trial-level findings in the implementation cohorts available so far, deserves continued longitudinal follow-up as the population of people who started dolutegravir-based first-line therapy years ago continues to age on treatment.

8. Conclusion

The literature reviewed here supports a specific and, by the standards of antiretroviral therapeutics research, unusually well-corroborated claim: dolutegravir-based first-line regimens, whether combined with a standard two-NRTI backbone or simplified to the two-drug dolutegravir-lamivudine combination, achieve virologic suppression rates in treatment-naïve adults that consistently equal or exceed those of the efavirenz-based, raltegravir-based, and boosted-protease-inhibitor-based regimens they were designed to replace, across trial populations spanning high-income and high-burden, resource-limited settings, and that this virologic advantage is durable through at least two to four years of follow-up in the trials with adequately long extension data [4,6,8,11,14,16]. That durability rests substantially on a genetic barrier to resistance that structural studies trace to dolutegravir's unusually slow dissociation from the integrase-DNA intasome complex [1,2], and that clinical resistance surveillance, from the pivotal trials through large collaborative cohort analyses of confirmed virologic failure, has consistently found to translate into low rates of treatment-emergent resistance specifically among integrase-inhibitor-naïve, first-line initiators, the population this article has focused on [17,18,19].

That efficacy and resistance-barrier case is, at this point, not the most actively contested part of the dolutegravir literature; the weight-gain and metabolic signal, and the residual uncertainty around conception-period pregnancy safety, are. Making sense of dolutegravir's overall risk-benefit profile for a treatment-naïve individual starting therapy today requires holding the strength of the virologic evidence and the genuine, still-being-characterized weight and metabolic signal in view simultaneously, rather than treating either in isolation — precisely because the same trials (ADVANCE and NAMSAL, in particular) that generated the most consequential efficacy evidence for resource-limited settings are also the trials that generated the clearest weight-gain signal [10,11,13,24]. The consistency with which independent trial teams, across different

countries, comparator regimens, and patient populations, have converged on similar virologic efficacy and resistance-barrier findings is the strongest evidence available that dolutegravir's first-line role reflects a genuine and durable pharmacological advantage rather than an artifact of any single trial design, even as the metabolic and pregnancy-safety literatures continue to mature and warrant the kind of sustained, deployment-grounded surveillance this article's open-challenges section has outlined.

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Conflict of Interest

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 article did not involve human participants, animal subjects, or the collection or analysis of primary data, and therefore did not require ethical approval.

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