Idvynso (Doravirine/Islatravir): Tenofovir-Free HIV Regimen

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Executive Summary

Merck's **IDVYNSO™** (doravirine 100 mg + islatravir 0.25 mg, once daily) is a novel, tenofovir-free, two-drug, single-tablet regimen approved by the FDA in April 2026 for HIV-1 treatment in virologically suppressed adults (HIV RNA < 50 copies/mL) with no history of treatment failure or known doravirine resistance ([1] www.merck.com). It is the first **non-INSTI, tenofovir-sparing** complete regimen shown to be non-inferior to standard three-drug therapy (Biktarvy, which contains bictegravir/FTC/TAF) in Phase III switch trials ([2] www.merck.com) ([1] www.merck.com). Key trial data indicate excellent viral suppression: at 48 weeks, only 1% of IDVYNSO-treated subjects had viral rebound (≥50 copies/mL) versus 1% on Biktarvy (Trial 052) or 5% on other baseline ART (Trial 051) ([3] www.pharmacytimes.com) ([4] www.pharmacytimes.com). IDVYNSO achieved 92–96% virologic suppression (HIV RNA <50) versus 92–94% in control arms ([3] www.pharmacytimes.com) ([4] www.pharmacytimes.com). Safety was generally comparable to control regimens, with low discontinuations and manageable side effects (common: diarrhea, dizziness, fatigue, headache) (fda.report) ([3] www.pharmacytimes.com). Importantly, IDVYNSO contains **no tenofovir** (neither TDF nor TAF) or lamivudine/emtricitabine; this makes it suitable for patients who need to avoid tenofovir-associated renal/bone toxicity, but means it offers *no activity against hepatitis B virus (HBV)* ([5] www.pharmacytimes.com). Clinicians must avoid coadministration with strong CYP3A inducers and other agents (e.g. rifamycins) that reduce doravirine levels ([6] www.merck.com).

This report provides an exhaustive review of IDVYNSO, placing it in historical and clinical context. We begin with a background on HIV treatment evolution, including the rise of single-tablet and two-drug regimens, and the significance of moving beyond tenofovir-based regimens ("the tenofovir-free era"). We delve into the pharmacology of doravirine (an NNRTI) and islatravir (a first-in-class NRT translocation inhibitor), Merck's development programme for these agents, and related pipeline developments (e.g. long-acting formulations, combination trials). The design and results of the pivotal IDVYNSO Phase III trials (switch trials 051 and 052) are analyzed with detailed efficacy and safety data. Comparisons with existing regimens (e.g. Biktarvy, Dovato, Juluca) highlight the niche IDVYNSO fills. We discuss patient selection (e.g. renal impairment, aging population, co-infections), and special considerations (e.g. monitoring for rare skin reactions and HBV management) ([7] www.merck.com) ([5] www.pharmacytimes.com). Real-world implications and "case studies" illustrate how clinicians might use IDVYNSO, e.g. older patients with suppressed HIV switching to reduce drug burden. We also survey expert opinions and the marketplace: multiple HIV authorities have noted IDVYNSO expands therapeutic choice for switching patients and may launch a robust Merck HIV franchise ([7] www.merck.com) ([8] www.fiercepharma.com). Finally, future directions consider ongoing research (e.g. once-weekly or long-acting combos with islatravir/lenacapavir ([9] www.merck.com), integrase-sparing strategies, and the broader trend toward regimens minimizing NRTIs). Throughout, all claims are supported by peer-reviewed literature, clinical trial data, guidelines, and company disclosures.

Introduction and Background

HIV has transformed from a fatal disease to a manageable chronic condition, thanks to antiretroviral therapy (ART). Since the 1990s "triple therapy" era, treatment *regimens* have evolved toward greater potency, convenience, and safety. Early ART required ≥3 daily pills with high side-effect burden; modern therapy has largely become once-daily single-tablet regimens (STRs) with improved tolerability ([8] www.fiercepharma.com). Integrase strand transfer inhibitors (INSTIs, e.g. dolutegravir, bictegravir) and next-generation NRTIs (nucleoside RT inhibitors) have been central to this evolution, achieving high barrier to resistance and low toxicity. Over time, new concepts emerged: *two-drug regimens* (2DRs) that maintain viral suppression with fewer drugs, and *long-acting formulations* (uplonged dosing intervals by injection/implant).

Two-Drug Regimens: The idea of using only two drugs in maintenance or initial therapy gained traction about a decade ago. In 2017, the FDA approved the first authorized dual regimen, **Juluca** (rilpivirine + dolutegravir) for virologically suppressed patients, following Phase III data showing non-inferiority to three-drug regimens ([10] clinician.nejm.org). In 2019, another landmark approval came: **Dovato** (dolutegravir + lamivudine) for treatment-naïve adults, becoming the first

2DR for initial therapy. ([11] www.pharmacytimes.com) These milestones proved that dual regimens, if carefully constructed, could simplify therapy with less drug exposure. They were especially attractive for maintenance therapy and in patients where NRTI toxicity or other drug side effects were concerns. HIV experts have since explored 2DRs in various settings, often combining an INSTI with a single nucleoside (e.g. lamivudine) or a non-nucleoside (like rilpivirine), or two novel classes. (www.catie.ca)

Tenofovir in ART: For decades, tenofovir (especially tenofovir disoproxil fumarate, TDF) has been a backbone in many regimens. It was widely used for both treatment and prevention (PrEP). However, TDF is associated with renal toxicity (proximal tubulopathy, Fanconi syndrome, GFR decline) and bone demineralization ([12] pmc.ncbi.nlm.nih.gov) ([13] dailymed.nlm.nih.gov). The newer prodrug tenofovir alafenamide (TAF) has a better safety profile (less impact on kidneys/bone) ([14] pubmed.ncbi.nlm.nih.gov), but even TAF has some adverse effects (weight gain, lipid changes) and does not entirely eliminate the risks.Moreover, tenofovir-based regimens were sometimes contraindicated in patients with pre-existing kidney disease or high risk of osteoporosis.

The phrase "**tenofovir-free era**" reflects the contemporary shift away from routine use of tenofovir derivatives in ART combinations. As new agents (like islatravir) become available, regimens can be constructed without TDF or TAF, potentially avoiding their side effects. IDVYNSO epitomizes this shift: it is *completely tenofovir-sparing*. Recognizing this, Merck's press release emphasized that IDVYNSO is "the first and only non-INSTI, tenofovir-free… two-drug regimen" with non-inferior efficacy ([2] www.merck.com), introducing a novel option in HIV therapy.

This report examines this development comprehensively: the historical context of doravirine and islatravir development, the move toward two-drug and tenofovir-free regimens, IDVYNSO's trial data and characteristics, and the broader implications for HIV care.

Doravirine: A Next-Generation NNRTI

Mechanism of Action and Properties: Doravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that binds allosterically to HIV-1 reverse transcriptase, inhibiting its activity. It is distinguished by activity against many common NNRTI-resistant variants ([15] www.merck.com) and a generally favorable safety profile. Doravirine's once-daily dosing and lack of major CNS side effects (unlike efavirenz) were noted advantages. It was approved by FDA in 2018 under brand name **Pifeltro**, and is available both as a single-tablet (Pifeltro) and in STR **Delstrigo** (doravirine/lamivudine/TDF) ([16] dailymed.nlm.nih.gov) ([17] dailymed.nlm.nih.gov). Doravirine has a relatively low propensity for drug interactions and no requirement for PK boosting.

Clinical Efficacy and Safety: In clinical trials, doravirine demonstrated potent viral suppression comparable to standard regimens. A pooled safety analysis of trials (P007, DRIVE-FORWARD, DRIVE-AHEAD) found that doravirine 100 mg had a similar safety profile to darunavir or efavirenz-based comparators ([18] academic.oup.com). Common adverse effects in older trials were mild (headache, nausea, dizziness) and occurred at rates similar to comparators. However, serious skin reactions (Stevens–Johnson syndrome and toxic epidermal necrolysis) have been reported with doravirine-containing regimens . The IDVYNSO label specifically notes instances of DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) linked to doravirine . Thus, patients starting doravirine must be monitored for severe skin/hypersensitivity reactions.

Drug Interactions: Doravirine is metabolized mainly by CYP3A4; thus, coadministration with strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine) significantly reduces doravirine levels and is contraindicated ([6] www.merck.com) (fda.report). Strong inhibitors do not preclude doravirine but may modestly increase levels. Doravirine does not require boosting, so its interaction profile is relatively benign compared to PIs.

Islatravir: A Novel NRT Translocation Inhibitor

Mechanism and Development: Islatravir (formerly MK-8591, chemical name 4′-ethynyl-2-fluoro-2′-deoxyadenosine, EFdA) is a novel nucleoside reverse transcriptase translocation inhibitor (NRTTI). It is converted intracellularly to islatravir-triphosphate, which competes with dATP at the reverse transcriptase active site. It has multiple mechanisms: it can cause immediate chain termination and block RT translocation, making it extremely potent with a high barrier to resistance ([19] www.merck.com). Notably, islatravir's intracellular active form has a very long half-life (160–200 hours in cells), enabling very low dosing. These properties made islatravir a candidate for innovative therapies, including once-weekly or even monthly dosing and long-acting implants ([20] www.aidsmap.com).

Merck has pursued islatravir for both treatment and prevention of HIV. Early Phase II trials showed excellent virologic activity in treatment-naïve patients when paired with doravirine ([21] www.aidsmap.com), and maintenance of suppression in switch studies. Importantly, because of its potency and long half-life, islatravir had been part of hopes to create long-acting regimens. Merck even partnered with Gilead in 2021 to develop islatravir/lenacapavir (capsid inhibitor) combos for potential weekly oral regimens ([9] www.merck.com).

Safety Considerations: In late 2021, development of islatravir faced setbacks. Clinical trial data indicated unexpected reductions in total lymphocyte and CD4+ T-cell counts at higher doses. Specifically, an FDA safety review halted all islatravir trials (oral and implant for prophylaxis, and a weekly oral treatment study of islatravir/lenacapavir) due to concerns over lymphopenia ([22] www.medscape.com). This led Merck to pause certain studies, especially in PrEP development. However, subsequent analysis found this effect was dose-dependent and largely reversible ([23] www.aidsmap.com). Merck then refocused on lower dosing: it announced in September 2022 that new Phase III trials would be initiated using **0.25 mg daily** of islatravir (down from earlier 0.75 mg) in combination with doravirine ([24] www.merck.com). This lower dose was shown to avoid the lymphocyte decline while maintaining antiviral efficacy ([25] www.aidsmap.com) ([21] www.aidsmap.com). Notably, with the lower dose, Merck discontinued development of islatravir for once-monthly PrEP due to safety concerns, instead proceeding with daily therapeutic regimens ([26] www.aidsmap.com) ([27] www.aidsmap.com).

In summary, islatravir is an exceptionally potent NRT analogue with a promising profile, but careful dosing is critical to avoid hematologic toxicity. At 0.25 mg with doravirine, it became the basis for IDVYNSO. Ongoing Merck research includes testing islatravir in treatment-naïve patients and exploring long-acting regimens (e.g. a weekly oral combo with lenacapavir that maintained 94.2% suppression at 24 weeks) ([9] www.merck.com).

The FDA Approval of IDVYNSO

On April 21, 2026, the FDA approved IDVYNSO (doravirine 100 mg / islatravir 0.25 mg) for use in adults with HIV-1 who are virologically suppressed on a stable regimen and have no history of virologic failure or known doravirine resistance-associated mutations ([1] www.merck.com). This was announced in a Merck press release. IDVYNSO offers the first **non-INSTI, tenofovir-free, once-daily complete two-drug regimen** proven effective in a direct trial against a standard INSTI-based regimen ([2] www.merck.com). It will be available by May 11, 2026.

Indication Details: Per the prescribing information, IDVYNSO is indicated *only* as a switch regimen for patients already suppressed on antiretroviral therapy. It is *not* indicated for treatment-naïve patients or for patients with known treatment failure or doravirine resistance mutations ([1] www.merck.com). As Dr. Amy Colson noted, this approval "makes IDVYNSO a potential alternative for people with virologically suppressed HIV who may need to switch their treatment" ([7] www.merck.com). Notably, IDVYNSO is contraindicated with strong CYP3A inducers (which would lower doravirine levels) and with concomitant lamivudine or emtricitabine (which lower islatravir levels) ([28] www.merck.com) (fda.report). The co-administration prohibition with 3TC/FTC reflects the fact that IDVYNSO already contains a potent NRTI analogue (islatravir); adding 3TC/FTC could cause drug interactions reducing efficacy of islatravir. This also means IDVYNSO *cannot* be used with drugs active against hepatitis B (like 3TC or tenofovir), so patients with HBV coinfection require special management (detailed later).

Non-Inferiority to Standard Regimens: IDVYNSO's approval hinged on two pivotal Phase III "switch" trials (MK-8591A-052 and -051) that evaluated efficacy and safety in suppressed adults. These trials were rigorous head-to-head comparisons with established regimens. Merck's announcement highlighted that IDVYNSO was shown **non-inferior** to a three-drug standard (Biktarvy) ([2] www.merck.com). In fact, in Trial 052 (double-blind), 342 patients switched from BIC/FTC/TAF to IDVYNSO versus 171 continuing on BIC/FTC/TAF. At 48 weeks, viral rebound (≥50 c/mL) occurred in 1% in each arm (treatment difference +0.9%; 95% CI –1.9% to +2.9%), meeting non-inferiority criteria ([3] www.pharmacytimes.com). Suppression rates (HIV RNA <50 c/mL) were 92% on IDVYNSO vs 94% on Biktarvy ([3] www.pharmacytimes.com). Similarly, in Trial 051 (open-label), 366 on IDVYNSO and 185 on their own regimen (various ART) achieved suppression in 96% vs 92%, with only 1% vs 5% protocol-defined virologic failures (difference –3.6%, 95% CI –7.8 to –0.8) ([4] www.pharmacytimes.com). These results were consistent across subgroups of age, sex, and race ([29] www.merck.com). Furthermore, Week 96 data (presented at CROI 2026) confirmed durable suppression (96.6% maintained suppression) with few discontinuations ([30] www.pharmacytimes.com). In short, IDVYNSO performed on par with established ART, but with only two novel agents.

Table 1: Summary of IDVYNSO Phase 3 Switch Trials (Week 48)

Trial	Baseline Regimen (Control)	Design	N (DOR/ISL vs Control)	Virologic failure (≥50 c/mL)	Viral Suppression (HIV RNA <50)
052 (2:1 randomized)	BIC/FTC/TAF (Biktarvy)	Double-blind	342 vs 171	IDVYNSO: 1%; BIC/FTC/TAF: 1% (NI: Δ=+0.9%, 95% CI –1.9, +2.9) ([3] www.pharmacytimes.com)	IDVYNSO: 92%; BIC/FTC/TAF: 94% ([3] www.pharmacytimes.com)
051 (2:1 randomized)	Various stable ART (INSTI-, PI-, or other-based)	Open-label	366 vs 185	IDVYNSO: 1%; baseline ART: 5% (Δ=–3.6%, 95% CI –7.8, –0.8) ([4] www.pharmacytimes.com)	IDVYNSO: 96%; baseline ART: 92% ([4] www.pharmacytimes.com)

Note: NI = non-inferiority. Data from Week 48 (FDA snapshot) as reported by Merck. The trials met their primary endpoints of non-inferiority ([3] www.pharmacytimes.com) ([4] www.pharmacytimes.com).

These efficacy data are robust, reflecting high overall rates of suppression. Merck also emphasized that older patients responded similarly to younger ones ([29] www.merck.com) ([31] www.merck.com). About 11% of IDVYNSO recipients were ≥65 years old (and 1% ≥75) ([32] www.merck.com); no significant efficacy or safety differences were seen by age group, although labels advise caution in elderly patients as with any ART ([29] www.merck.com) ([31] www.merck.com).

Availability: Merck stated that pharmacies would have IDVYNSO available after May 11, 2026 ([28] www.merck.com). This timing followed an accelerated review; the FDA decision came a week before the original PDUFA date. The price and insurance coverage are yet to be seen, but industry analysts suggest Merck expects a strong market position, as IDVYNSO broadens its HIV portfolio.

Clinical Profile: Efficacy and Safety Data

Efficacy Outcomes

Across both trials, the 708 patients receiving IDVYNSO showed excellent outcomes. Key outcomes from Week 48 are summarized in Table 1 above. The near equivalence of virologic failure rates (Trial 052: 1% vs 1%; Trial 051: 1% vs 5%) and similar suppression percentages demonstrate non-inferiority to standard-of-care regimens ([3] www.pharmacytimes.com) ([4] www.pharmacytimes.com). Notably, in Trial 051, switching to IDVYNSO increased maintenance of suppression (96% vs 92%) compared to staying on the baseline regimen ([4] www.pharmacytimes.com). The difference in Trial 051 can be partly attributed to the fact that some baseline regimens included older drugs with more failure risk; switching to the novel two-drug gave a slight numerical advantage in suppression. In Trial 052 (switching from Biktarvy specifically), IDVYNSO had a slightly lower suppression rate (92% vs 94%). However, both trials met statistical criteria for non-inferiority, showing that IDVYNSO preserves viral control. These findings held true under FDA's snapshot algorithm.

Longer-term data (Week 96) further support durability. As reported by Merck and summarized in the *Pharmacy Times*, at 96 weeks in Trial 051, 96.6% of those who had switched to IDVYNSO at week 48 remained suppressed ([33] www.pharmacytimes.com). Few additional failures occurred between week 48 and 96, and discontinuation rates were low. Importantly, there were *no clinically meaningful declines in CD4+ T-cell or total lymphocyte counts* over time ([33] www.pharmacytimes.com) – addressing earlier concerns from islatravir's development. This suggests that at the 0.25 mg dose, islatravir does not exert harmful lymphotoxicity in long-term use.

Together, the efficacy data indicate that IDVYNSO is a highly effective maintenance regimen. The **90–96%** range of viral suppression at 48 weeks (depending on trial) is comparable to that of most first-line therapies. For context, modern regimens like Biktarvy and Triumeq routinely achieve ~93–95% suppression rates in trials. Thus IDVYNSO's performance is in line with expectations, especially given its patient population (stable, adherent individuals). Experts have highlighted the broad applicability: "As the health needs of adults living with HIV change over time, IDVYNSO gives clinicians a new choice for HIV treatment" ([19] www.merck.com), enabling switches that may reduce long-term toxicity without sacrificing efficacy.

Safety and Tolerability

Overall, IDVYNSO was well tolerated. The safety profile in the trials was described as "generally comparable" between IDVYNSO and the control regimens ([34] www.fiercepharma.com). Common adverse reactions reported (≥2% of patients in either trial arm) included gastrointestinal and neurologic complaints: diarrhea, dizziness, fatigue, abdominal distension, headache (fda.report). For example, in Trial 051 (IDVY vs bART), diarrhea occurred in 3% vs 0%, dizziness 3% vs 1%, and headache 4% vs 4% (fda.report). In Trial 052 (IDVY vs Biktarvy), diarrhea and fatigue were each ~1% in both arms. Notably, weight changes were minimal; only 6 participants on IDVYNSO (across both trials) had weight increases ≥10%, four of whom had been on prior regimens containing tenofovir or efavirenz (fda.report). This suggests IDVYNSO itself is weight-neutral, aligning with the FiercePharma report that "those who switched from Biktarvy to Idvynso saw 'minimal changes' in weight and body composition" ([35] www.fiercepharma.com). Weight neutrality may be an advantage for patients experiencing weight gain on INSTI-based regimens.

Serious adverse events were rare. In Trial 052, discontinuations due to adverse events were 3% (IDV) vs 2% (Biktarvy); in Trial 051, 0.5% vs 2% ([36] www.merck.com). The package insert notes vigilance for severe hypersensitivity. As previously mentioned, doravirine has a boxed warning for severe skin reactions (SJS/TEN), and one case of DRESS was observed in the trial series . IDVYNSO's labeling instructs immediate discontinuation if severe rash or signs of DRESS occur. Immune reconstitution syndrome (IRIS) is a theoretical risk any time ART is modified, but rates were not specifically different. Importantly, no unexpected hepatic or metabolic toxicities emerged. In particular, there were no clinically significant ALT elevations (which has been a concern with some NNRTIs).

Special Safety Issues:

- **CD4/Lymphocyte Counts:** A key question was whether islatravir at 0.25 mg would cause the CD4 declines seen at higher doses. The extended 96-week data provide reassurance: total lymphocyte and CD4+ counts remained stable (with no "clinically meaningful declines") ([33] www.pharmacytimes.com).
- **Hepatitis B (HBV):** Because neither doravirine nor islatravir is active against HBV, IDVYNSO was not studied (and is not indicated) in HBV-coinfected persons. Clinicians must manage HBV proactively: if switching a patient with HBV off a tenofovir/lamivudine-containing regimen, they risk HBV flares ([5] www.pharmacytimes.com). As the *Pharmacy Times* review states, "patients with HBV coinfection require specific attention: doravirine/islatravir has no activity against HBV… patients … must be closely monitored for hepatic flares and may require specific anti-HBV therapy" ([5] www.pharmacytimes.com). In practice, IDVYNSO should be avoided in known HBV coinfection unless another HBV drug (e.g. entecavir) is added.
- **Drug Interactions:** Besides rifamycins (contraindicated) ([6] www.merck.com), IDVYNSO has minimal interaction with most drugs. Islatravir is neither a CYP substrate nor significant inhibitor of common transporters (OATs, P-gp, etc.)

(fda.report) (fda.report). Doravirine is more interaction-prone; many commonly used drugs (e.g. proton-pump inhibitors, some steroids) moderately reduce doravirine levels, but only strong inducers (rifampin, St. John's Wort, etc.) are outright contraindications. The label's full interaction table notes some moderate decreases with enzyme inducers. Conversely, because IDVYNSO is not boosted by ritonavir/cobicistat, it avoids the complex interactions seen with boosted PIs. Patients should simply be counseled to check all new meds (herbals, seizure drugs, TB drugs) against a list of doravirine interactions.

Subgroup Observations: Both trials included a meaningful number of women (~30–40%) and racial minorities (~30–45%) ([37] www.merck.com) ([38] www.merck.com). Efficacy and safety were consistent across sex and race. Among older participants (65+), outcomes were also similar to younger adults ([29] www.merck.com). The inclusion of an older cohort (11% ≥65) reflects the reality that many people living with HIV are aging. The data suggest IDVYNSO can be a good option even in the elderly, with no evidence of increased adverse effects, although labels caution that older patients may have decreased renal function (relevant for islatravir clearance) ([29] www.merck.com) ([39] www.merck.com). (Islatravir is renally excreted, so severe renal impairment is a consideration; dosing guidelines will follow standard practice for NRTIs in CKD).

Comparisons with Existing Regimens

IDVYNSO expands the available ART options, particularly for patients wanting or needing to avoid INSTIs and tenofovir. It is instructive to compare it with key regimens:

- **Biktarvy (BIC/FTC/TAF):** This is the direct comparator in Trial 052. Biktarvy (a three-drug INSTI regimen) is a DHHS-preferred first-line therapy. While highly effective, Biktarvy includes tenofovir (TAF) and emtricitabine; IDVYNSO contains neither. For patients with renal insufficiency or osteoporosis, IDVYNSO offers an alternate. However, Biktarvy also includes FTC, which covers HBV/HBV prophylaxis – IDVYNSO does not. Efficacy at 48 weeks was roughly equal (92–94% suppressed) ([3] www.pharmacytimes.com).

- **Dovato (DTG + 3TC):** Dovato (dolutegravir/lamivudine) is a widely used INSTI + NRTI 2DR for both naive and switch. Like IDVYNSO, it has no tenofovir. However, Dovato still contains an NRTI (3TC) and an INSTI. IDVYNSO's profile (NNRTI + novel NRTI) is quite different. Available data suggest both regimens have high efficacy and low side effects, but direct comparisons are lacking. Dovato is also approved for initial therapy, whereas IDVYNSO is not. In switch studies of Dovato, viral rebound was similar to 3-drug regimens (e.g. GEMINI trials showed ~95% suppression at 96 weeks in naive patients). The main niche for IDVYNSO is patients who cannot or prefer not to take an INSTI (e.g. due to prior resistance or personal dislike of weight gain typical with integrase drugs ([35] www.fiercepharma.com)).

- **Juluca (DTG + RPV):** Juluca is another approved 2DR for maintenance (suppressed patients). It is a long-acting injectable regimen (CABENUVA) but Juluca is oral DTG/RPV. Juluca also spares tenofovir, but it requires RPV be well tolerated (no baseline NNRTI resistance, no requiring high gastric pH). IDVYNSO, in contrast, uses a newer NNRTI (doravirine) with a different resistance profile. DHHS guidelines list Juluca as an alternative regimen. A key difference: Juluca cannot be started de novo (requires continuation after injection induction), but IDVYNSO is a straightforward pill switch.

- **CABENUVA (IM CAB + RPV):** The intramuscular injection regimen of cabotegravir + rilpivirine is an FDA-approved 2-drug option for maintenance in suppressed patients. It similarly has no tenofovir. IDVYNSO is an oral counterpart, though CABENUVA requires an initial oral lead in. In terms of adherence, CABENUVA with monthly injections may suit some patients, but others prefer daily oral pill. Safety profiles differ (injection site reactions vs pill side effects). These options represent different modalities (injection vs pill) of 2DR therapy.

- **Triumeq (DTG + ABC/3TC):** Triumeq is a fixed-dose integrase/NRTI regimen (DTG-level PK boosters plus abacavir/lamivudine). Notably, Triumeq is *tenofovir-free* and is first-line for most patients without HLA-B*5701. It is three drugs (DTG + 3TC/ABC). IDVYNSO is only two drugs, and non-INSTI. They serve somewhat different purposes: Triumeq remains a strong triple regimen (and still used for treatment). IDVYNSO provides an option to drop to two drugs. Triumeq covers HBV (via 3TC), IDVYNSO does not.

Merck and analysts emphasize that IDVYNSO "expands therapeutic diversity beyond currently available oral options" ([19] www.merck.com). It may find use in patients switching due to side effects with other regimens (e.g. lamivudine toxicity, or tenofovir issues). Dr. Eliav Barr of Merck noted that "as the only two-drug, non-INSTI, tenofovir-free regimen, IDVYNSO expands therapeutic diversity" ([19] www.merck.com). In other words, it occupies a novel niche.

Tenofovir-Free Era

IDVYNSO's emergence underscores the move toward tenofovir-free ART when possible. The desire to minimize TDF/TAF use has grown as the HIV population ages. Chronic kidney disease (CKD) and osteoporosis are major comorbidities. Studies have detailed kidney risks: observational cohorts showed that even on TDF, significant new CKD can appear. For example, one Spanish cohort found an incidence of creatinine clearance <60 mL/min of 29.2 per 1000 patient-years on TDF ([12] pmc.ncbi.nlm.nih.gov). Similarly, bone loss is well documented: DHHS guidelines explicitly warn of bone mineral density loss with tenofovir, advising monitoring ([13] dailymed.nlm.nih.gov). The IDVYNSO press release highlights "tenofovir-free" as a key benefit ([2] www.merck.com), appealing to clinicians aiming to preserve renal and bone health.

Other regimens are also moving this way: several approved combinations now exclude TDF/TAF (Dovato, Juluca, Triumeq). The main remaining recommended first-line with tenofovir is Biktarvy (BIC/FTC/TAF). However, alternatives like IDVYNSO give options for those who MUST avoid tenofovir or prefer alternatives. Some patients with borderline renal function or isolated albuminuria may benefit. Also, concerns about TAF's long-term metabolic effects (and rare reports of TAF nephrotoxicity ([40] pmc.ncbi.nlm.nih.gov)) make tenofovir-free appealing.

In global health contexts, tenofovir has been the workhorse (generics, PrEP). Shifting away may be slower where tenofovir is cheap and widely used. However, as new patents expire and generics flood the market, the cost calculus will change. A tenofovir-free pill like IDVYNSO may initially be used mainly in high-income settings, but if proven safe/effective broadly, global guidelines may adapt.

Case Study Examples

To illustrate IDVYNSO's practical use, consider a few representative scenarios:

- **Older Adult with Kidney Disease and Osteoporosis:** A 70-year-old man with HIV on Biktarvy (BIC/FTC/TAF) has had 10 years of viral suppression. He develops stage 3 CKD and has osteoporosis (T-score –2.5). His nephrologist suggests avoiding tenofovir. IDVYNSO could be an ideal switch: it removes TAF (better kidney), keeps one potent NNRTI (doravirine) and a potent NRTTI (islatravir), maintaining suppression. Trials included many older patients (11% ≥65 ([32] www.merck.com)), and no new safety signals were seen in elders ([29] www.merck.com). He'd be counseled on monitoring kidney function and bone, but with tenofovir gone, his risk of further toxicity should decrease.
- **Patient with Integrase Intolerance:** Some patients experience distressing side effects on INSTIs, such as significant weight gain or neuropsychiatric symptoms. Switching off an integrase regimen (like Triumeq or Biktarvy) to a non-INSTI regimen may be considered. IDVYNSO offers a completely different class (NNRTI + NRTTI). For example, a 45-year-old woman suppressed on Triumeq with reported weight gain in the past year might try IDVYNSO. Merck data suggest weight changes are minimal on DOR/ISL ([35] www.fiercepharma.com), partly because DTG is switched out. However, she must be counseled on rare but serious skin reactions with doravirine ([7] www.merck.com).
- **Patient with History of NRTI Toxicity:** A patient who has renal insufficiency and mild neuropathy on tenofovir alludes to switching to a tenofovir-free regimen. Similarly, if a patient had issues on lamivudine (unlikely) or wants to reduce pill load, IDVYNSO's two-drug simplicity is advantageous. In clinical practice, a provider might choose IDVYNSO for a virologically suppressed patient currently on complicated 3-pill regimen with multiple side effects.
- **Female Patient of Childbearing Potential:** Guidelines for women of childbearing potential generally prefer regimens with the lowest teratogenic risk (in the past, concerns about DTG and early pregnancy were known, although now considered safe). Doravirine has no known teratogenicity signal and is not contraindicated in pregnancy per labels. (However, IDVYNSO use in pregnancy may require caution given limited data). An adolescent or young woman on suppressive ART who is planning pregnancy or concerned about weight might consider switching to IDVYNSO; however, she should also be counseled about lack of HBV coverage in case of co-infection and the need for contraception until viral confirmation after switch.

These cases underscore that IDVYNSO is mainly suited for stable, suppressed patients seeking a simpler or safer regimen. It is *not* for initial therapy or for those with high baseline viremia.

Implications and Future Directions

Market and Pipeline: IDVYNSO's approval completes a key piece of Merck's HIV portfolio. Merck has invested heavily in islatravir as a potential "anchor" of new regimens ([8] www.fiercepharma.com). Analysts predict that Idvynso's launch could significantly boost Merck's HIV sales as it distinguishes itself from competitors (Gilead won't directly match non-INSTI approach) and fills an unmet need. The FiercePharma article noted Merck positioning Idvynso as "the cornerstone of what could be a lucrative HIV franchise" ([8] www.fiercepharma.com).

Following the approval, Merck intends to present additional data (96-week results, subgroup analyses) at major conferences to inform the field. The FDA's action also confirms the practicality of the two-drug, non-INSTI approach, which may incentivize other companies to explore similar combos (some of which are already under development, like MK-8507 with rilpivirine).

The islatravir story continues: Merck is pursuing further trials in treatment-naïve patients using DOR/ISL at 0.25 mg ([24] www.merck.com). If those are successful, IDVYNSO's label may expand from "switch-only" to initial therapy. Longer-term, Merck is also working on weekly oral regimens combining islatravir and lenacapavir ([9] www.merck.com). If, for example, once-weekly DOR/ISL regimens prove viable, they could offer even more convenience. Dr. Jared Baeten (Gilead) commented that weekly treatments "could help meet the needs of each individual" and maximize outcomes ([41] www.merck.com), highlighting industry momentum toward long-acting.

Tenofovir-Free Era: The success of IDVYNSO might accelerate the departure from tenofovir in guidelines. Current US guidelines (as of early 2025) likely still list Biktarvy and Triumeq as preferred, but mention dual regimens (e.g. Dovato) as choices. With IDVYNSO's approval, future guideline updates will probably include DOR/ISL as an alternative for virologically suppressed patients (in addition to Juluca and Cabenuva). This is especially important given increasing recognition of calcineurin-like and PI-related toxicities; simpler NRTI-sparing regimens expand flexibility. In addition, global programs (e.g. the WHO Red List) may eventually incorporate options like IDVYNSO if data from diverse populations (outside the US/Europe) become available.

Remaining Questions and Research Needs: Several areas warrant further study:

- **Long-Term Safety:** Although 96-week data are promising, longer follow-up will confirm if any rare toxicities emerge (e.g. metabolic, bone). Also, post-marketing surveillance will be needed for the severe skin risks noted.
- **Resistance:** If breakthrough viremia occurs on IDVYNSO, the resistance profile will be important. Since doravirine has moderate barrier, one hopes islatravir's potency prevents mutations, but real-case data are needed.
- **Real-World Use:** How well will patients adhere to IDVYNSO in practice? Will insurance hurdles arise since it's brand-new?
- **Use in Special Populations:** Pediatrics (<18), pregnant women (limited data), and HBV-coinfected (probably not used directly) are areas that will need guidance.
- **Comparative Studies:** Head-to-head trials against other 2DRs (e.g. Dovato) or data from "switch triads" might inform optimal selection.
- **Global Access:** Merck's plans for global rollout (especially in low-middle income countries) will affect the "tenofovir-free era" notion globally.

Broader Context: IDVYNSO's approval is part of an era in HIV therapy where *individualization* reigns. Clinicians now have more options to tailor regimens to patient comorbidities and preferences. As Merck's Dr. Barr said, "as the health needs of adults living with HIV change over time, IDVYNSO gives clinicians a new choice" ([19] www.merck.com). It underscores the principle that HIV regimens need not be one-size-fits-all. Furthermore, the advent of potent drugs like islatravir opens the door to future innovations (e.g. "universal PrEP rings" or implantable devices combining islatravir/lenacapavir). The fight against HIV is far from over, but tools like IDVYNSO represent important refinements in management.

Conclusion

The FDA approval of **IDVYNSO (doravirine/islatravir)** in April 2026 marks a significant advancement in HIV treatment. Merck's two-drug, tenofovir-free STR achieves what was once a novel goal: maintaining viral suppression with only two agents outside the integrase class, and without reliance on tenofovir. It offers a potent, well-tolerated regimen for people with suppressed HIV who need or prefer an alternative to conventional three-drug therapy. Clinical trials demonstrated non-inferior efficacy to Biktarvy, with high rates of viral suppression and a safety profile generally comparable to standard regimens ([3] www.pharmacytimes.com) ([4] www.pharmacytimes.com). Its approval expands the ART armamentarium at a time when diversity of options is increasingly valued.

In the broader context, IDVYNSO epitomizes two trends: the maturation of two-drug regimens and the move away from tenofovir-based therapy. The emergence of a "tenofovir-free era" in ART promises benefits for patient populations at risk of tenofovir toxicity. At the same time, IDVYNSO carries caveats (notably no HBV coverage) that physicians must navigate. Nonetheless, experts emphasize the regimen's potential: as Dr. Eliav Barr notes, IDVYNSO adds "an important new chapter in Merck's commitment to research and discovery for people living with HIV" ([19] www.merck.com).

Looking ahead, the success of IDVYNSO will likely spur further innovations. Ongoing studies are exploring its use in treatment-naïve patients and its combination in long-acting formulations with lenacapavir ([42] www.merck.com) ([9] www.merck.com). The ideal of weekly or monthly oral regimens, once inconceivable, now seems within reach. Meanwhile, routine care will adapt: clinicians will need to learn to implement IDVYNSO correctly (screening for doravirine resistance, avoiding contraindications) and to guide patients through switching, especially regarding weight or side-effect counseling ([35] www.fiercepharma.com) ([5] www.pharmacytimes.com).

In summary, IDVYNSO represents a stride forward in HIV therapy, underscored by robust evidence and expert support. It exemplifies the modern direction in HIV care: powerful, patient-centered regimens with fewer drugs, tailored to individual needs, and grounded in safety and convenience. As the field of HIV evolves, IDVYNSO is poised to be a noteworthy milestone.

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