

INFECTION CONTROL

Quarterly Established in January 2024 Volume 2 Number 2 June 30, 2025

Responsible Institution

National Health Commission of the
People's Republic of China

Sponsor

Chinese Medical Doctor Association

Honorary Editor-in-chief

Lanjuan Li, MD

Editor-in-chief

Songling Wang, DDS, PhD

Executive Editor

Yingmin Ma, MD

Managing Director

Yingmei Feng, MD

Editing

Editorial Board of *Infection Control*
The 2nd Floor, Building D, Beijing Youan Hospital,
Beijing 100069, China
Tel: 86-10-63313382; 86-10-63313801
E-mail: infection@vip.163.com
Website: http://www.infectioncontrol.org.cn/

Publishing

Chinese Medical Humanities Publishing House
The 10th Floor, Building 5, Fengtai District, Beijing
100073, China

Printing

Beijing Pally Colour Printing Co., Ltd
No. 5 Tuanhe Road, Xihongmen Town, Daxing
District, Beijing 100162, China

Circulation

Chinese Medical Humanities Publishing House
The 10th Floor, Building 5, Fengtai District, Beijing
100073, China
Tel: 86-10-63313382

CSSN

ISSN 2097-3314
CN 10-1890/R

Copyright© 2024 by Chinese Medical Doctor
Association

TABLE OF CONTENTS

Reviews

Research progress on second-generation integrase strand transfer inhibitor-based
fixed-dose combination therapies

..... Defu Yuan, Fei Zhao, Shanshan Liu, Hongxia Yan,
Lifeng Liu, Tong Zhang, Bei Wang, Bin Su (2)

Bibliometric analysis of Japanese encephalitis research over the past 15 years

..... Zheng Wu, Yingmei Feng (17)

Articles

Analysis of changes in the psychological status of HCV patients after DAAs treatment

..... Shan Tang, Yeying Liu, Zhongping Duan, Mei Liu, Sujun Zheng (36)

Clinical application of an intraoperative three-dimensional imaging navigation system
for computed tomography-guided thermal ablation of liver tumors

..... Da Fang, Peng Zhao, Bojun Liu, Yonghong Zhang, Jiasheng Zheng, Caixia Hu (43)

Antibacterial effects of Nanyang Kiwifruit extract toothpaste on common oral pathogens

..... Tao Liu, Hongmei Wang, Hua Li, Lidan Shi, Panpan Meng, Lin Feng, Rui Xiao (50)

Case Report

IgG4-related hepatic inflammatory pseudotumor: a case report

..... Yang Liu, Qian Wang, Yanyan Jia (60)

Nutritional therapy in obesity complicated by primary hypertension: a case study

..... Kun Zhang, Hongshi Liu, Jinhua Bao, Chaorui Xu, Lu Bo, Yuze Li (68)

Popular Science Reading

Treatment of liver cancer by transcatheter arterial chemoembolization: Youan

Intervention Center's minimally invasive procedure precisely combats this "Silent
Killer"

..... Yingmei Feng (75)

Public awareness of Monkeypox prevention and control (2024 Edition) Chapter 3

..... Yingmei Feng (78)

Commentary

Commentary: Protecting the rights of research participants—a cornerstone for
advancing clinical research and infection control

..... Zheng Wu, Yingmei Feng (80)

Research progress on second-generation integrase strand transfer inhibitor-based fixed-dose combination therapies

Defu Yuan¹, Fei Zhao², Shanshan Liu¹, Hongxia Yan², Lifeng Liu², Tong Zhang², Bei Wang¹, Bin Su^{2,3,4*}

¹Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing 210009, Jiangsu, China

²Beijing Key Laboratory for HIV/AIDS Research, Sino-French Joint Laboratory for HIV/AIDS Research, Clinical and Research Center for Infectious Diseases, Beijing Youan Hospital, Capital Medical University, Beijing 100069, China

³Central Laboratory, Beijing Youan Hospital, Capital Medical University, Beijing 100069, China

⁴The Scientific and Technological Achievement Transformation Center, Beijing Youan Hospital, Capital Medical University, Beijing 100069, China

Abstract

Integrase Strand Transfer Inhibitors (INSTIs) have favorable safety and tolerability profiles, potent antiviral activity, and high resistance barriers, solving the limitations of previous antiretrovirals caused by resistant mutations. While first-generation INSTIs have exhibited emerging resistance challenges during extended clinical use, second-generation INSTIs provide enhanced resistance barriers and extended plasma half-lives relative to their predecessors. Optimized combination regimens incorporating these agents have substantially improved therapeutic convenience and long-term disease management in human immunodeficiency virus (HIV) care. Current investigations focus on multiple combination strategies employing second-generation INSTIs including dolutegravir (DTG) and bictegravir (BIC), with preliminary findings demonstrating substantial clinical benefits. The DTG/lamivudine (3TC) dual regimen in the GEMINI and TANGO studies achieved 92.1%–99.6% virologic suppression rates at week 48, maintaining efficacy through 144 weeks. The cabotegravir (CAB)/Rilpivirine (RPV) long-acting injectable combination in ATLAS trials demonstrated 92.5% suppression efficacy with validated every-two-month dosing intervals. The BIC/emtricitabine/tenofovir alafenamide triple regimen in studies 1489/1490 maintained > 84% suppression at week 144 while retaining activity against resistant variants. Real-world data confirm that these regimens maintained a viral suppression rate of > 90% in both treatment-naïve and -experienced patients, with treatment interruption rates of < 5%. Recent advances include the US Food and Drug Administration's approval of DTG/3TC for use in adolescents ≥ 12 years old and adaptive studies of CAB/RPV in special populations. This article summarizes the research progress of current combination formulations based on second-generation INSTIs to provide new therapeutic options and clinical insights for the treatment of patients with HIV.

Keywords: HIV, integrase inhibitors, combination formulations, clinical trials, real-world studies

*Correspondence:

Bin Su; Email: binsu@ccmu.edu.cn.

Introduction

Human immunodeficiency virus (HIV) remains a critical global health challenge. By the end of 2023 ^[1], the number of people infected with HIV worldwide had reached 39.9 million, with approximately 35.5 million diagnosed individuals receiving antiretroviral (ARV) therapy (ART). While ART has improved clinical outcomes and life expectancy for people living with HIV (PLWH), the absence of curative interventions requires lifelong treatment adherence. The main goal of comprehensive acquired immunodeficiency syndrome (AIDS) treatment is to maximize the suppression of viral replication in PLWH using ART and supportive treatments to rebuild and maintain immune function to combat non-AIDS-related diseases, as well as to prevent adverse outcomes such as cancer and opportunistic infections ^[2]. Despite international approval of over 50 ARVs spanning ten classes ^[3], nucleoside (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) demonstrate elevated resistance development risks attributable to low genetic barriers and extended exposure durations, manifesting substantial resistance prevalence among both treatment-naïve individuals and those experiencing treatment failure ^[4]. These limitations substantially constrain the clinical efficacy of conventional ART regimens.

Compared with NRTIs and NNRTIs, integrase strand transfer inhibitors (INSTIs) demonstrate superior safety profiles, enhanced antiviral potency, and elevated genetic resistance barriers ^[5]. These advantages effectively mitigate the constraints of drug resistance in ARV selection, establishing INSTIs as guideline-recommended first-line agents. However, emerging data has shown resistance rates of 3.9% and 1.2% for the first-generation INSTIs raltegravir and elvitegravir, respectively, during extended clinical application ^[6]. Resistance-associated mutations conferring reduced

susceptibility to first-generation INSTIs frequently demonstrate cross-resistance to second-generation counterparts, and prolonged administration carries risks of treatment-emergent adverse events, collectively influencing clinical outcomes and long-term treatment adherence.

Second-generation INSTIs exhibit optimized pharmacokinetic properties including improved resistance profiles and extended elimination half-lives. Dolutegravir (DTG), the first second-generation INSTI, was recommended by the World Health Organization as the preferred first-line ART backbone in 2018; 116 countries had implemented DTG-based regimens by July 2023 ^[7]. The development of fixed-dose combination (FDC) formulations centered on second-generation INSTIs aims to optimize therapeutic parameters through reduced pill burden, minimized toxicity risks, cost-effectiveness, and enhanced adherence profiles. Current FDC prototypes requiring single daily administration include DTG/lamivudine (3TC), DTG/rilpivirine (RPV), and cabotegravir (CAB)/RPV injectable formulation, along with triple regimens such as DTG/abacavir (ABC)/3TC, DTG/emtricitabine (FTC)/tenofovir alafenamide (TAF), and bictegravir (BIC)/FTC/TAF ^[8]. These unified pharmaceutical solutions mitigate common adherence barriers including polypharmacy burdens and complex dosing schedules, translating to improved treatment persistence, superior virologic control, and attenuated disease progression ^[9].

Numerous clinical trials evaluating second-generation INSTI-based combinations are currently underway, with preliminary outcomes demonstrating therapeutic validity. These optimized regimens have gained increasing preference among PLWH, showing significant potential to advance AIDS therapeutic paradigms and improve patient-centered care outcomes. This review summarizes the research progress on second-genera-

tion INSTI-based combination formulations to offer evidence-based perspectives to inform clinical practice and enhance HIV management approaches.

Two-drug combinations

DTG/3TC tablet

Dovato is a fixed-dose combination tablet containing DTG and 3TC. The Phase 3 GEMINI-1 (NCT02831673) and GEMINI-2 (NCT02831764) trials randomized ART-naïve patients with HIV to receive either DTG+3TC or DTG+TDF/FTC, with follow-up assessments demonstrating non-inferior viral suppression rates for DTG+3TC compared with the rates for DTG+TDF/FTC at 48 weeks. This treatment equivalence persisted through 144 weeks of follow-up ^[10], supporting the role of DTG-based dual therapy in ART simplification. The Phase 3 TANGO trial (NCT03446573) transitioned virologically suppressed (VS) PLWH to DTG/3TC, maintaining non-inferior efficacy compared with continued baseline regimens at 144 weeks (92.1% vs. 85.8%) ^[11]. Subsequent Phase 3 trials including SALSA (NCT04021290) ^[12] and ASPIRE (NCT02263326) ^[13], along with the Phase 4 DOLAM study (EudraCT 201500027435) ^[14], consistently demonstrated non-inferiority of DTG/3TC compared with standard regimens at 48 weeks (SALSA: 99.6% vs. 98.8%, respectively; ASPIRE: 90.9% vs. 88.9%; DOLAM: 97.7% vs. 98.5%). The Phase 2 ART-PRO trial (NCT03539224) transitioned VS PLWH to DTG/3TC, achieving 90.2% viral suppression at 144 weeks, including 85.7% efficacy in 3TC-resistant PLWH ^[15]. In the Phase 2 LAMIDOL study (NCT02527096), VS PLWH received 8-week DTG monotherapy before switching to DTG/3TC, maintaining 97.1% viral suppression through 48-week follow-up ^[16], reinforcing DTG/3TC's viability for treatment simplification in stabilized popula-

tions.

The Phase 4 DYAD trial (NCT04585737) compared DTG/3TC with B/F/TAF over 48 weeks, demonstrating comparable virologic failure rates (4% vs. 7%, respectively) but higher drug-related adverse events (23% vs. 3%) and emergent resistance mutations with DTG/3TC ^[17]. These findings underscore the necessity for vigilant safety monitoring during regimen transition. Complementing this, the Phase 4 RUMBA study (NCT04553081) revealed equivalent impacts on HIV reservoirs and immune markers between regimens, confirming DTG/3TC's long-term safety profile as a simplified maintenance strategy ^[18].

Real-world evidence confirms the efficacy and safety profiles of DTG/3TC regimen transitions. In one study, post-VS switchers maintained 91.5% viral suppression and 85.1% treatment persistence through 384 weeks of treatment ^[19]. Hepatitis B core antibody status showed no clinical impact, with > 91% suppression rates sustained at 24 months regardless of serostatus ^[20]. Older PLWH (≥ 50 years) maintained 97%–98% virologic control at 12 months post-switch with stable CD4+ T-cell indices and zero treatment discontinuations ^[21].

In ART-naïve PLWH, the DTG/3TC regimen demonstrates robust virologic efficacy. Phase 2 clinical trial ACTG 5353 (NCT02582684) reported an 85.0% viral suppression rate at 48 weeks ^[22], while the Phase 3b STAT trial (NCT03945981) achieved 97% suppression over the same period ^[23], validating its suitability for treatment-naïve populations. Multi-center cohort data showed that the viral suppression rate reached 94%, CD4 recovery was significant, and treatment maintenance rates and tolerability were superior to other mainstream regimens after 96 weeks of treatment with DTG/3TC, highlighting its advantages as an efficient, low-toxicity first-line treatment option ^[24]. Real-world

evidence showed comparable 144-week suppression rates between DTG/3TC (95.9%) and B/F/TAF, but with higher treatment retention (90.3% vs. 70%) and an 80% reduction in tolerability-related discontinuation risk with DTG/3TC, confirming long-term therapeutic benefits [25].

In treatment-naïve PLWH with high baseline viral loads (mean HIV RNA: 5.4 log₁₀ copies/mL), DTG/3TC achieved 91.4% suppression at 12 months—equivalent to triple-drug regimens—without significant weight or metabolic changes, offering a simplified treatment for this subgroup [26]. Simultaneous complete viral suppression in both semen and blood at 48 weeks [27] provides novel evidence for sexual transmission prevention. The DANCE trial (NCT03682848) established comparable safety and efficacy in ART-naïve adolescents (12–18 years) to adult populations, leading to the April 2024 US Food and Drug Administration (FDA) approval of Dovato as the only single-tablet regimen for HIV-infected adolescents ≥ 12 years (weight ≥ 25 kg) [28]. Recent findings further indicate that even with baseline low-frequency M184V/I mutations, DTG/3TC demonstrated a 3.3% virologic failure rate at 48 weeks without emergent integrase or lamivudine resistance mutations, supporting its reliability in PLWH with prior 3TC resistance but undetected baseline mutations [29].

DTG/RPV fixed-dose combination tablet

The DTG/RPV fixed-dose combination tablet consists of 50 mg of the INSTI DTG and 25 mg of the NNRTI RPV, marketed as Juluca. This formulation serves as long-term maintenance therapy for HIV-1-infected adults who have maintained viral suppression on stable ART for ≥ 6 months, without history of virologic failure or documented resistance to NNRTIs or INSTIs [30]. The regimen received US FDA approval in November

2017 as the first dual-drug single-tablet regimen and obtained NMPA approval for domestic use in China on October 21, 2022 [31].

The initial Phase 3 trial (NCT02741557) established bioequivalence between the FDC and separate component tablets, demonstrating comparable pharmacokinetic profiles and favorable tolerability over 12 days [32]. Subsequent investigation through the multinational WISARD open-label switch study (32 centers across seven European countries) evaluated virologic efficacy in VS PLWH harboring the K103N mutation. Participants were randomized to switch to DTG/RPV or maintain protease inhibitor (PI)-based regimens; comparable 48-week virologic suppression rates (88.4% vs. 88.9%, respectively) confirmed maintained efficacy in mutation-positive PLWH who transitioned [33]. Real-world evidence from the US-based TANDEM cohort (24 centers) further validated these findings, showing 93% maintained suppression post-switch with a 3% discontinuation rate primarily attributed to individual preference rather than therapeutic failure [34]. These collective data support DTG/RPV's role as an effective simplified treatment offering reduced toxicity while maintaining virologic control.

CAB/RPV injection

The US FDA approved CAB/RPV injection under the brand name Cabenuva in 2021; it is currently the sole authorized complete long-acting regimen indicated for VS maintenance therapy in treated PLWH. No clinically significant pharmacokinetic interactions were observed between oral CAB and oral RPV, supporting the exploration of this dual-agent regimen for sustained viral suppression [35]. The Phase 2b LATTE trial (NCT01641809) conducted across 49 US and Canadian sites demonstrated that oral CAB/RPV maintained viral suppression in PLWH with an 86% efficacy rate

at 96 weeks ^[36]. The subsequent Phase 2b LATTE-2 trial (NCT02120352) across 50 sites in five countries revealed that injectable CAB/RPV administered every 4 or 8 weeks showed comparable efficacy to daily triple-drug oral therapy in VS PLWH, with favorable tolerability and therapeutic cerebrospinal fluid concentrations achieving viral control in cerebrospinal fluid ^[37,38]. In the multinational Phase 3 FLAIR trial (NCT02938520) involving treatment-naïve PLWH, subjects initially achieving suppression through oral therapy transitioned to monthly CAB/RPV injections following 1 month of oral lead-in. At the 124-week follow-up, 99% of participants maintained viral suppression, confirming CAB/RPV's durability and safety as maintenance therapy ^[39].

Another Phase 3 trial, ATLAS (NCT02951052), investigated monthly CAB/RPV injections in treatment-experienced PLWH. At week 48, the injection group achieved 92.5% viral suppression, demonstrating non-inferiority to the daily oral regimen, supporting the exploration of simplified administration methods ^[40]. The subsequent Phase 3b ATLAS-2M trial (NCT03299049) compared monthly and bimonthly CAB/RPV injections across 13 countries in VS PLWH; both regimens maintained comparable efficacy and safety through 152 weeks of follow-up ^[41], confirming sustained viral suppression beyond 3 years. The bimonthly CAB/RPV regimen was compared with B/F/TAF in the Phase 3b SOLAR trial (NCT04542070) across 118 sites in 14 countries, and 1-year viral suppression rates were comparable between groups (98.88% vs. 99.55%, respectively) ^[42]. Additionally, the Phase 1/2 IMPAACT 2017 trial (NCT03497676) assessed CAB/RPV injections in VS adolescent PLWH (≥ 12 years, ≥ 35 kg). Pharmacokinetic profiles and safety data supported extending the adult dosing schedule to this population ^[43], broadening CAB/RPV's potential applicability.

Real-world data demonstrate that in treatment-naïve adolescent PLWH, the CAB/RPV long-acting injectable regimen achieved complete treatment maintenance and viral suppression rates with no resistance risk and favorable safety profiles; transient viremia was observed in 28% of cases, supporting its reliability as a therapeutic option for this population ^[44]. In treatment-experienced PLWH, the CAB/RPV regimen maintained complete viral suppression, confirming the clinical viability of switching; however, the 48-week treatment maintenance rate in this cohort was 79.2%, with higher discontinuation rates ^[45]. For PLWH with suboptimal oral therapy adherence, the CAB/RPV long-acting injectable regimen demonstrated over 85% sustained treatment and viral suppression rates at 48 weeks, highlighting its clinical utility in substantially improving adherence through reduced dosing frequency ^[46].

Among Polish PLWH, the A6 virus subtype constitutes > 50% of cases, typically carrying the L74I mutation that confers significantly elevated RPV resistance rates; this translates to approximately 40% of the population being at risk for CAB/RPV treatment failure, indicating the need for cautious regimen use under regional genetic surveillance ^[47]. PLWH transitioning from DTG/RPV to CAB/RPV rapidly developed treatment failure in one study ^[48], further emphasizing the CAB/RPV regimen's limitations in resistance management. The applicability of this regimen in resistant populations still requires further long-term clinical validation.

Three-drug combinations

DTG/ABC/3TC tablet

The DTG/ABC/3TC combination tablet, marketed as Triumeq, received US FDA approval in 2014. This FDC comprises two NRTIs (ABC and 3TC) and an IN-

STI (DTG). Clinical trials have primarily evaluated its therapeutic efficacy against alternative ART regimens. The pivotal Phase 3 SINGLE trial (NCT01263015) demonstrated superior 144-week virologic suppression rates in treatment-naïve PLWH receiving DTG/ABC/3TC compared with the rates in those receiving efavirenz (EFV)/TDF/FTC (71% vs. 63%, respectively) [49]. In the multinational ARIA trial (NCT01910402), treatment-naïve females (≥ 18 years) randomized to DTG/ABC/3TC had significantly higher 48-week virologic suppression than those receiving atazanavir/ritonavir plus TDF/FTC (81.9% vs. 71.3%), with comparable safety profiles between groups [50]. The Spanish SYMTRI study (EudraCT 2018-001645-14) established the non-inferiority of DTG/ABC/3TC compared with PI-based regimens, with comparable 48-week virologic suppression rates in adult PLWH (81.9% vs. 79.5%) [51]. The STRIVING trial (NCT02105987) evaluated VS PLWH transitioning to DTG/ABC/3TC either immediately or after 24 weeks of maintaining their current regimen; non-inferior virologic suppression was maintained at both 24 (85% vs. 88%) and 48 weeks (83% vs. 92%) [52]. While having comparable efficacy to various ART regimens, DTG/ABC/3TC requires mandatory HLA-B*5701 screening before initiation to prevent ABC-associated hypersensitivity. In 2023, the US FDA granted tentative approval for Triumeq PD dispersible tablets, expanding treatment options for pediatric HIV populations.

DTG/FTC/TAF

Kocitaf, launched in South Africa and Laos in 2019, is a single-tablet regimen containing DTG, FTC, and TAF; it is also the first drug to combine DTG and TAF. A US multicenter Phase 2 clinical trial (NCT02397694) and a multinational, multicenter Phase 3 clinical trial (NCT02607956) both evaluated this combination in treatment-naïve PLWH. Patients were randomly as-

signed to receive either the BIC regimen or the DTG regimen, with the DTG group receiving DTG/FTC/TAF and the BIC group receiving BIC/FTC/TAF. The Phase 2 trial demonstrated that the viral suppression rate at 24 weeks for the DTG group was slightly lower than that for the BIC group (93.9% vs. 96.9%, respectively), with both regimens showing high efficacy and well-tolerated safety profiles [53]. The Phase 3 trial (NCT02607956), with 144 weeks of follow-up, showed the DTG group had a slightly higher viral suppression rate than the BIC group (84.0% vs. 81.9%) [54]. A single-center clinical trial conducted in treatment-naïve PLWH (DUALITY) also found that the DTG/FTC/TAF regimen demonstrated equivalent efficacy in reducing the viral reservoir compared with the DTG+3TC two-drug regimen and improved immune activation; at 48 weeks, the viral suppression rate was 100% in both regimens, confirming the reliability and non-inferiority of the three-drug regimen as a standard treatment option [55].

The Phase 3 ADVANCE clinical trial (NCT03122262) conducted in South Africa randomized treatment-naïve PLWH to receive either DTG/FTC/TAF, DTG/FTC/TDF, or EFV/FTC/TDF. During 96 weeks of follow-up, the three groups demonstrated similar viral suppression rates (78.6%, 78.3%, and 73.5%, respectively), with the DTG/FTC/TAF group exhibiting reduced changes in bone mineral density compared with the other groups [56]. In a multinational study involving pregnant PLWH (IMPAACT 2010), a comparable regimen was implemented; here, the DTG/FTC/TAF regimen showed the lowest incidence of inadequate prenatal weight gain and the lowest risk of adverse pregnancy outcomes, although it presented a significantly higher rate of being overweight or obese at 50 weeks postpartum compared with alternative regimens [57]. Compared with EFV/FTC/TDF, the DTG/FTC/TAF regimen significantly enhanced infant spi-

nal bone mineral content while promoting length and weight growth, with no observed adverse effects on renal function or obesity risk. This evidence supports the potential of this regimen as a protective strategy for maternal-infant health [58]. These findings confirm that DTG/FTC/TAF maintains equivalent efficacy to established ART regimens, offering PLWH expanded therapeutic options.

B/F/TAF

Biktarvy (B/F/TAF) is a fixed-dose combination containing the NRTIs FTC and TAF with the INSTI BIC that received US FDA approval in February 2018. The clinical efficacy trials for B/F/TAF were first conducted in PLWH who had achieved VS through other ART regimens. In Phase 3 trials 1844 (NCT02603120) and 1878 (NCT02603107), PLWH switching to B/F/TAF maintained viral suppression rates of 98.9% [59] and 98.3% [60], respectively, at week 48, demonstrating non-inferiority to DTG-based regimens. Trial 1844 further showed PLWH maintained viral suppression > 99% through 168 weeks of follow-up [61], confirming sustained efficacy. A Phase 2/3 trial (NCT02881320) across 22 South African hospitals involving 100 VS pediatric PLWH (6–18 years old) reported 100% viral suppression at week 48 [62]. The multicenter Phase 3 trial 1961 (NCT02652624) observed comparable outcomes in VS female PLWH, with 98.3% maintaining suppression at week 48 [63]. Trial 4030 (NCT03110380) demonstrated 99.6% suppression at week 48 when switching from DTG/FTC/TAF to B/F/TAF [64]. Subsequent Phase 3 trials 4449 (NCT03405935) and Phase 3b 4580 (NCT03631732) evaluated 86 older VS individuals (≥ 65 years old) from five countries and 331 African American PLWH, respectively, showing 74.4% suppression at week 96 in older adults [65] and 94.5% suppression at week 48 in the African American cohort [66]. A Phase 1b trial (NCT03960645) involving

33 VS pregnant PLWH revealed that despite lower plasma concentrations during pregnancy compared with those postpartum, the regimen maintained 100% viral suppression without dose adjustment, confirming its safety and efficacy in this population [67].

Two clinical trials involving ART-naïve PLWH treated with B/F/TAF (trial 1489: NCT02607930, 629 patients across 122 centers in nine European countries; 1490: NCT02607956, 645 PLWH across 126 centers in ten countries) demonstrated non-inferiority to two DTG-containing regimens at week 144, with no emergent resistance or discontinuations because of adverse events [54], supporting its use in ART-naïve populations. Five-year follow-up data revealed maintained viral suppression rates of 97% in African American PLWH (despite 11% having < 85% adherence) and 100% in Hispanic/Latino PLWH, alongside favorable metabolic safety and tolerability, confirming long-term utility in underserved populations [68]. The Spanish Phase 4 BIC-NOW trial (NCT06177574) achieved 98.3% viral suppression at 48 weeks in 208 newly diagnosed PLWH, with high adherence (90/100) and satisfaction scores (100/100) [69]. Italy's Rainbow study (EudraCT: 2019-003614-14) reported 90% viral suppression at 48 weeks in 30 PLWH without resistance mutations [70]. A Chinese rapid-initiation trial (ChiCTR2000038711) in 300 men who have sex with men PLWH showed superior efficacy and safety for B/F/TAF compared with those for EFV/3TC/TDF (95.9% vs. 79.2% suppression, respectively) [71]. Croatian real-world data confirmed 91.3% suppression with BIC/FTC/TAF and no treatment interruptions, validating its rapid-initiation potential [72]. A recent Phase 3 non-inferiority study (NCT04233879) comparing B/F/TAF with Doravirine/Islatravir showed comparable 48-week suppression rates (88.3% vs. 88.9%), with B/F/TAF demonstrating better CD4 recovery, lower lymphopenia risk, and fewer adverse event-related discontinuations [73]. These

findings position B/F/TAF as an optimal choice for rapid ART initiation in newly diagnosed PLWH, offering high efficacy, safety, adherence, and satisfaction.

Trials 1489, 1490, 1844, 1878, 4030, 4449, and 4580 included participants harboring HIV strains with integrase resistance mutations who demonstrated sustained viral suppression through 48 weeks of B/F/TAF therapy. The recent Phase 4 PIBIK trial (EudraCT: 2018-004732-30) further revealed that in populations exhibiting multiple NRTI resistance mutations, transition to B/F/TAF achieved a 100% virological suppression rate at 24 weeks that was maintained through 48 weeks. However, this regimen showed significantly higher rates of drug-related adverse events and treatment discontinuations compared with PI-containing regimens, requiring careful consideration of long-term applicability based on individual profiles ^[74]. Real-world longitudinal data demonstrated that B/F/TAF maintained 94% viral suppression at 144 weeks as a switch strategy with preserved efficacy in PLWH with pre-existing NRTI resistance; however, discontinuations because of toxicity remained elevated, highlighting the importance of ongoing tolerability monitoring ^[75]. Beyond therapeutic applications, B/F/TAF shows potential for HIV prevention in seronegative populations. Two Chinese clinical trials (ChiCTR2100048080 ^[76] and ChiCTR2200059994 ^[77]) demonstrated B/F/TAF as a viable post-exposure prophylaxis option, demonstrating favorable safety profiles and tolerability.

In conclusion, second-generation INSTI-based combination regimens have established clinical advantages in HIV/AIDS management and prevention, offering clinicians and PLWH expanded therapeutic options. While several agents have achieved designation as core ARVs or complete regimens in current guidelines, critical questions persist regarding optimal dosing strategies, ideal combination partners, appropriate tar-

get populations, optimal utilization of long-acting formulations, adverse effect profiles, resistance potential, and cost-effectiveness. Future clinical investigations should evaluate the safety and efficacy of second-generation INSTI-based regimens in special populations, including pregnant individuals, pediatric PLWH, older populations, and PLWH with significant comorbidities such as cardiovascular disorders and diabetes mellitus to inform precision medicine approaches. Additionally, ongoing exploration of optimized drug combinations through strategic integration of ARVs with complementary mechanisms could preserve potent antiviral efficacy while improving long-term safety and tolerability. As emerging clinical trial data accumulate alongside real-world evidence, second-generation INSTI-based combinations are poised to advance the formulation of increasingly effective HIV prevention and control strategies.

Acknowledgements

The authors sincerely acknowledge all researchers and participants involved in the conduction of the included studies for their valuable contributions. We thank Lisa Oberding, MSc, from Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

Author contributions

Conceptualization, DF.Y., F.Z., B.W. and B.S.; methodology, DF.Y., F.Z., and SS.L.; software, DF.Y., F.Z., SS.L., HX.Y., and LF.L.; validation, B.W., and B.S.; formal analysis, DF.Y., F.Z., SS.L., HX.Y., and LF.L.; resources, B.W. and B.S.; data curation, DF.Y., F.Z., and HX.Y.; writing—original draft preparation, DF.Y., F.Z. and SS.L.; writing—review and editing, B.W., and B.S.; visualization, DF.Y., F.Z., SS.L., HX.Y. and LF.L.; supervision, T.Z., B.W. and B.S.; project ad-

ministration, T.Z., B.W., and B.S.; funding acquisition, L.F.L., T.Z., B.W., and B.S. All authors had full access to all data in the study and had final responsibility for submitting it for publication. All authors read and approved the final version of the manuscript.

Funding

National Key R&D Program of China (2023YFC-2308300, 2022YFC2305200); High-Level Public Health Specialized Talents Project of Beijing Municipal Health Commission (2022-2-018); Beijing Key Laboratory for HIV/AIDS Research (BZ0089); Postgraduate Research & Practice Innovation Program of Jiangsu Province (KYCX24_0484); SEU Innovation Capability Enhancement Plan for Doctoral Students (CXJH_SEU 24042). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest

All authors declare no conflicts of interest.

References

- [1] UNAIDS. Global HIV & AIDS statistics — Fact sheet. 2024. <https://www.unaids.org/en/resources/fact-sheet>.
- [2] Borrajo A. Breaking Barriers to an HIV-1 Cure: Innovations in Gene Editing, Immune Modulation, and Reservoir Eradication. *Life (Basel)*. 2025 (15):276.
- [3] FDA. Approved HIV Medicines. 2023. <https://hivinfo.nih.gov/understanding-hiv/fact-sheets/fda-approved-hiv-medicines>.
- [4] WHO. Report on the global action plan on HIV drug resistance 2017–2021. 2023. <https://www.who.int/publications/i/item/978-92-4-151284-8>.
- [5] Wong E, Truatman N, Yalong A. HIV pharmacotherapy: a review of integrase inhibitors. *JAAPA*. 2016 (29):36-40.
- [6] You J, Wang H, Huang X, Qin Z, Deng Z, Luo J, et al. Therapy-Emergent Drug Resistance to Integrase Strand Transfer Inhibitors in HIV-1 Patients: A Subgroup Meta-Analysis of Clinical Trials. *PLoS One*. 2016 (11):e0160087.
- [7] WHO. HIV drug resistance—brief report. 2024. <https://www.who.int/publications/i/item/9789240086319>.
- [8] Zhang YH, B. S. Progress toward long-acting anti-HIV drugs. *Guoji Bingduxue Zazhi*. 2024 (31):261-264.
- [9] Llibre JM, Clotet B. Once-daily single-tablet regimens: a long and winding road to excellence in antiretroviral treatment. *AIDS Rev*. 2012 (14):168-178.
- [10] Underwood M, Urbaityte R, Wang R, Horton J, Oyee J, Wynne B, et al. Dolutegravir + Lamivudine vs. Dolutegravir + Tenofovir Disoproxil Fumarate/Emtricitabine: Very-Low-Level HIV-1 Replication through 144 Weeks in the GEMINI-1 and GEMINI-2 Studies. *Viruses*. 2024 (16):405.
- [11] Wang R, Underwood M, Llibre JM, Bernal Morell E, Brinson C, Sanz Moreno J, et al. Very-Low-Level Viremia, Inflammatory Biomarkers, and Associated Baseline Variables: Three-Year Results of the Randomized TANGO Study. *Open Forum Infect Dis*. 2023 (11):ofad626.
- [12] Llibre JM, Brites C, Cheng CY, Osiyemi O, Galera C, Hocqueloux L, et al. Efficacy and Safety of Switching to the 2-Drug Regimen Dolutegravir/Lamivudine Versus Continuing a 3- or 4-Drug Regimen for Maintaining Virologic Suppression in Adults Living With Human Immunodeficiency Virus 1 (HIV-1): Week 48 Results From the Phase 3, Noninferiority SALSA Randomized Trial. *Clin Infect Dis*. 2023 (76):720-729.

- [13] Taiwo BO, Marconi VC, Berzins B, Moser CB, Nyaku AN, Fichtenbaum CJ, et al. Dolutegravir Plus Lamivudine Maintains Human Immunodeficiency Virus-1 Suppression Through Week 48 in a Pilot Randomized Trial. *Clin Infect Dis*. 2018 (66):1794-1797.
- [14] Rojas J, de Lazzari E, Negredo E, Domingo P, Tiraboschi J, Ribera E, et al. Efficacy and safety of switching to dolutegravir plus lamivudine versus continuing triple antiretroviral therapy in virologically suppressed adults with HIV at 48 weeks (DOLAM): a randomised non-inferiority trial. *Lancet HIV*. 2021 (8):e463-e473.
- [15] De Miguel Buckley R, Rial-Crestelo D, Montejano R, Pinto A, Jimenez-Gonzalez M, Lagarde M, et al. Long-term Evaluation of Residual Viremia in a Clinical Trial of Dolutegravir Plus Lamivudine as Maintenance Treatment for Participants With and Without Prior Lamivudine Resistance. *Open Forum Infect Dis*. 2022 (9):ofac610.
- [16] Joly V, Burdet C, Landman R, Vigan M, Charpentier C, Katlama C, et al. Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). *J Antimicrob Chemother*. 2019 (74):739-745.
- [17] Rolle CP, Castano J, Nguyen V, Hinestrosa F, DeJesus E. Efficacy, Safety, and Tolerability of Switching From Bictegravir/Emtricitabine/Tenofovir Alafenamide to Dolutegravir/Lamivudine Among Adults With Virologically Suppressed HIV: The DYAD Study. *Open Forum Infect Dis*. 2024 (11):ofae560.
- [18] De Scheerder MA, Degroote S, Delporte M, Kiselinova M, Trypsteen W, Vincke L, et al. In-depth Analysis of the HIV Reservoir Confirms Effectiveness and Safety of Dolutegravir/Lamivudine in a Phase 4 Randomized Controlled Switch Trial (RUMBA). *J Infect Dis*. 2025 (231):e91-e100.
- [19] Baldin G, Salvo PF, Passerotto RA, Iannone V, Lamanna F, Carbone A, et al. 'With age comes wisdom': effectiveness and tolerability of dolutegravir + lamivudine in virologically-suppressed people with HIV. *AIDS*. 2025 (39):1014-1017.
- [20] Fu J, Biao R, Liu Y, Chen J, Zhao H. 24-month outcomes after switching to Dolutegravir/Lamivudine in people living with HIV and HBcAb positivity at the Beijing Ditan Hospital in China. *Ann Med*. 2025 (57):2470957.
- [21] Piñeiro C, Policarpo S, Caldas C, Santos L, Augusto I, DiMondi VP, et al. Real-world effectiveness and safety of switching to dolutegravir/lamivudine among people living with HIV-1 aged over 50 years who are virologically suppressed. *HIV Med*. 2025 (26):36-43.
- [22] Nyaku AN, Zheng L, Gulick RM, Olefsky M, Berzins B, Wallis CL, et al. Dolutegravir plus lamivudine for initial treatment of HIV-1-infected participants with HIV-1 RNA <500 000 copies/mL: week 48 outcomes from ACTG 5353. *J Antimicrob Chemother*. 2019 (74):1376-1380.
- [23] Rolle CP, Berhe M, Singh T, Ortiz R, Wurapa A, Ramgopal M, et al. Sustained Virologic Suppression With Dolutegravir/Lamivudine in a Test-and-Treat Setting Through 48 Weeks. *Open Forum Infect Dis*. 2023 (10):ofad101.
- [24] Suárez-García I, Alejos B, Moreno C, Martín Torres J, Masiá M, García-Fraile LJ, et al. Long-term effectiveness and tolerability of dolutegravir/lamivudine in treatment-naïve people with HIV: an analysis of a multicentre cohort at 96 weeks. *J Antimicrob Chemother*. 2025 (80):682-691.
- [25] Ciccullo A, Baldin G, Cervo A, Moschese D, Lagi F, Cossu MV, et al. Comparing the long-term effectiveness and safety of dolutegravir/lamivudine versus bictegravir/emtricitabine/tenofovir alafenamide fumarate as first-line regimens: a real life multicentre cohort. *J Antimicrob Chemother*.

- 2025 (80):175-177.
- [26] Calza L, Colangeli V, Giglia M, Rigamonti C, Bon I, Cretella S, et al. Efficacy and Safety of Dolutegravir/Lamivudine in Antiretroviral Therapy-Naive People Living With HIV-1 and With High-Level Viremia. *J Acquir Immune Defic Syndr*. 2025 (99):93-97.
- [27] Liu Y, Wang R, Sun L, Li A, Li Z, Kang Q, et al. HIV-1 viral decay in blood and semen in antiretroviral-naïve adults initiating dolutegravir/lamivudine vs. bicitegravir/emtricitabine/tenofovir alafenamide. *Int J Antimicrob Agents*. 2025 (65):107396.
- [28] GSK. ViiV Healthcare announces U.S. FDA approval of Dovato (dolutegravir/lamivudine) for adolescents living with HIV. 2024. <https://www.businesswire.com/news/home/20240319579558/en/ViiV-Healthcare-announces-U.S.-FDA-approval-of-Dovato-dolutegravir-lamivudine-for-adolescents-living-with-HIV>.
- [29] De Miguel R, de Lagarde Sebastian M, Blanco Arévalo JL, Pinto-Martinez A, Montejano R, Gutiérrez Liarte A, et al. Dolutegravir/Lamivudine for Maintenance of Virological Suppression in Persons with Historical Suspected or Confirmed Resistance to Lamivudine: Week 48 Results of a Single-Arm, Open-Label, Multicentre, Phase IIA Clinical Trial. *Clin Infect Dis*. 2025 :ciaf100.
- [30] Sun HY, Chang SY, Hung CC. Dolutegravir-rilpivirine coformulation. *Curr Opin HIV AIDS*. 2018 (13):320-325.
- [31] Dowers E, Zamora F, Barakat LA, Ogbuagu O. Dolutegravir/rilpivirine for the treatment of HIV-1 infection. *HIV AIDS (Auckl)*. 2018 (10):215-224.
- [32] Mehta R, Wolstenholme A, Di Lullo K, Fu C, Joshi S, Crauwels H, et al. Bioequivalence of a Fixed-Dose Combination Tablet of the Complete Two-Drug Regimen of Dolutegravir and Rilpivirine for Treatment of HIV-1 Infection. *Antimicrob Agents Chemother*. 2018 (62):e00748-e00818.
- [33] Moyle G, Assoumou L, de Castro N, Post FA, Curran A, Rusconi S, et al. Switching to dolutegravir plus rilpivirine versus maintaining current antiretroviral therapy regimen in virologically suppressed people with HIV-1 and the Lys103Asn (K103N) mutation: 48-week results from a randomised, open-label pilot clinical trial. *Lancet HIV*. 2024 (11):e156-e166.
- [34] Schneider S, Blick G, Burke C, Ward D, Benson P, Felizarta F, et al. Two-Drug Regimens Dolutegravir/Lamivudine and Dolutegravir/Rilpivirine Are Effective with Few Discontinuations in US Real-World Settings: Results from the TANDEM Study. *Infect Dis Ther*. 2024 (13):891-906.
- [35] Ford SL, Gould E, Chen S, Margolis D, Spreen W, Crauwels H, et al. Lack of pharmacokinetic interaction between rilpivirine and integrase inhibitors dolutegravir and GSK1265744. *Antimicrob Agents Chemother*. 2013 (57):5472-5477.
- [36] Margolis DA, Brinson CC, Smith GHR, de Vente J, Hagins DP, Eron JJ, et al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naïve adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. *Lancet Infect Dis*. 2015 (15):1145-1155.
- [37] Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, Eron JJ, Yazdanpanah Y, Podzamczek D, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet*. 2017 (390):1499-1510.
- [38] Letendre SL, Mills A, Hagins D, Swindells S, Felizarta F, Devente J, et al. Pharmacokinetics and antiviral activity of cabotegravir and rilpivirine in cerebrospinal fluid following long-acting injectable administration in HIV-infected adults. *J Anti-*

- microb Chemother. 2020 (75):648-655.
- [39] Orkin C, Bernal Morell E, Tan DHS, Katner H, Stellbrink HJ, Belonosova E, et al. Initiation of long-acting cabotegravir plus rilpivirine as direct-to-injection or with an oral lead-in in adults with HIV-1 infection: week 124 results of the open-label phase 3 FLAIR study. *Lancet HIV*. 2021 (8):e668-e678.
- [40] Swindells S, Andrade-Villanueva JF, Richmond GJ, Rizzardini G, Baumgarten A, Masiá M, et al. Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression. *N Engl J Med*. 2020 (382):1112-1123.
- [41] Overton ET, Richmond G, Rizzardini G, Thalme A, Girard PM, Wong A, et al. Long-Acting Cabotegravir and Rilpivirine Dosed Every 2 Months in Adults With Human Immunodeficiency Virus 1 Type 1 Infection: 152-Week Results From ATLAS-2M, a Randomized, Open-Label, Phase 3b, Noninferiority Study. *Clin Infect Dis*. 2023 (76):1646-1654.
- [42] Ramgopal MN, Castagna A, Cazanave C, Diaz-Brito V, Dretler R, Oka S, et al. Efficacy, safety, and tolerability of switching to long-acting cabotegravir plus rilpivirine versus continuing fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV, 12-month results (SOLAR): a randomised, open-label, phase 3b, non-inferiority trial. *Lancet HIV*. 2023 (10):e566-e577.
- [43] Gaur AH, Capparelli EV, Calabrese K, Baltrusaitis K, Marzinke MA, McCoig C, et al. Safety and pharmacokinetics of oral and long-acting injectable cabotegravir or long-acting injectable rilpivirine in virologically suppressed adolescents with HIV (IMPAACT 2017/MOCHA): a phase 1/2, multicentre, open-label, non-comparative, dose-finding study. *Lancet HIV*. 2024 (11):e211-e221.
- [44] Williams T, Unternaher J, Koay WLA, Anderson L, Bright K, Mareuil J, et al. Efficacy, Safety and Retention in Care Among Adolescents and Youth With HIV on Long-acting Injectable Cabotegravir/Rilpivirine Treatment: Real-world Observational Cohort Outcomes. *Pediatr Infect Dis J*. 2025 (44):650-656.
- [45] Iannone V, Lombardi F, Ciccullo A, Lamanna F, Salvo PF, Sanfilippo A, et al. Real World Data from an Italian Outpatient Clinical Setting and from Home Care Assistance of Treatment-Experienced PWH Switching to CAB+RPV Regimen: A Prospective Observational Study. *AIDS Behav*. 2025 (29):1228-1234.
- [46] Hastie E, Hill L, Bamford L, Karim A, Martin TCS. Long-acting injectable HIV therapy outcomes among persons with HIV who have adherence challenges to oral antiretroviral therapy. *Clin Infect Dis*. 2025 :ciaf120.
- [47] Załęski A, Lembas A, Dyda T, Osińska J, Jabłońska J, Stempkowska-Rejek J, et al. Drug Resistance Mutations (DRMs) for Long-Acting Injectable Cabotegravir and Rilpivirine (CAB/RPV LAI) in the HIV-1 Subtype A6 Epidemic in Poland. *Microorganisms*. 2025 (13):321.
- [48] Boix V, Reus S. Immediate virological failure with intramuscular cabotegravir-rilpivirine in a patient long suppressed with dolutegravir-rilpivirine. *AIDS Behav*. 2025 (39):626-628.
- [49] Walmsley S, Baumgarten A, Berenguer J, Felizarta F, Florence E, Khuong-Josses MA, et al. Brief Report: Dolutegravir Plus Abacavir/Lamivudine for the Treatment of HIV-1 Infection in Antiretroviral Therapy-Naive Patients: Week 96 and Week 144 Results From the SINGLE Randomized Clinical Trial. *J Acquir Immune Defic Syndr*. 2015 (70):515-519.
- [50] Orrell C, Hagins DP, Belonosova E, Porteiro N, Walmsley S, Falcó V, et al. Fixed-dose combina-

- tion dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. *Lancet HIV*. 2017 (4):e536-e546.
- [51] Podzamczar D, Micán R, Tiraboschi J, Portilla J, Domingo P, Llibre JM, et al. Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir/Abacavir/Lamivudine in Antiretroviral-Naive Adults (SYMTRI): A Multicenter Randomized Open-Label Study (PReEC/RIS-57). *Open Forum Infect Dis*. 2021 (9):ofab595.
- [52] Trottier B, Lake JE, Logue K, Brinson C, Santiago L, Brennan C, et al. Dolutegravir/abacavir/lamivudine versus current ART in virally suppressed patients (STRIVING): a 48-week, randomized, non-inferiority, open-label, Phase IIIb study. *Antivir Ther*. 2017 (22):295-305.
- [53] Sax PE, DeJesus E, Crofoot G, Ward D, Benson P, Dretler R, et al. Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial. *Lancet HIV*. 2017 (4):e154-e160.
- [54] Orkin C, DeJesus E, Sax PE, Arribas JR, Gupta SK, Martorell C, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. *Lancet HIV*. 2020 (7):e389-e400.
- [55] Bailón L, Puertas MC, García-Guerrero MC, Moraes-Cardoso I, Aparicio E, Alarcón-Soto Y, et al. Impact of Dolutegravir Plus Lamivudine as First-line Antiretroviral Treatment on the Human Immunodeficiency Virus Type 1 Reservoir and Inflammatory Markers in Peripheral Blood. *J Infect Dis*. 2025 (231):600-610.
- [56] Venter WDF, Sokhela S, Simmons B, Moorhouse M, Fairlie L, Mashabane N, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV*. 2020 (7):e666-e676.
- [57] Hoffman RM, Brummel S, Ziemba L, Chinula L, McCarthy K, Fairlie L, et al. Weight Changes and Adverse Pregnancy Outcomes With Dolutegravir- and Tenofovir Alafenamide Fumarate-Containing Antiretroviral Treatment Regimens During Pregnancy and Postpartum. *Clin Infect Dis*. 2024 (78):1617-1628.
- [58] Mbengeranwa TG, Ziemba L, Brummel SS, Johnston B, Cassim H, Theron G, et al. Bone Mineral Content, Growth, and Renal Health of Infants With Perinatal Exposure to Maternal Dolutegravir Versus Efavirenz and Tenofovir Disoproxil Fumarate Versus Tenofovir Alafenamide: The Randomized IMPAACT 2010 (VESTED) Trial. *J Acquir Immune Defic Syndr*. 2025 (99):211-219.
- [59] Molina JM, Ward D, Brar I, Mills A, Stellbrink HJ, López-Cortés L, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet HIV*. 2018 (5):e357-e365.
- [60] Daar ES, DeJesus E, Ruane P, Crofoot G, Oguchi G, Creticos C, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed

- adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. *Lancet HIV*. 2018 (5):e347-e356.
- [61] Brar I, Ruane PJ, Berhe M, Brinson C, Benson P, Henry K, et al. Efficacy and safety of switch to bicitegravir/emtricitabine/tenofovir alafenamide from dolutegravir/abacavir/lamivudine: Results from an open-label extension of a phase 3 randomized, double-blind, multicenter, active-controlled, non-inferiority study. *Medicine (Baltimore)*. 2025 (104):e41482.
- [62] Gaur AH, Cotton MF, Rodriguez CA, McGrath EJ, Helström E, Liberty A, et al. Fixed-dose combination bicitegravir, emtricitabine, and tenofovir alafenamide in adolescents and children with HIV: week 48 results of a single-arm, open-label, multicentre, phase 2/3 trial. *Lancet Child Adolesc Health*. 2021 (5):642-651.
- [63] Kityo C, Hagins D, Koenig E, Avihingsanon A, Chetchotisakd P, Supparatpinyo K, et al. Switching to Fixed-Dose Bicitegravir, Emtricitabine, and Tenofovir Alafenamide (B/F/TAF) in Virologically Suppressed HIV-1 Infected Women: A Randomized, Open-Label, Multicenter, Active-Controlled, Phase 3, Noninferiority Trial. *J Acquir Immune Defic Syndr*. 2019 (82):321-328.
- [64] Sax PE, Rockstroh JK, Luetkemeyer AF, Yazdanpanah Y, Ward D, Trottier B, et al. Switching to Bicitegravir, Emtricitabine, and Tenofovir Alafenamide in Virologically Suppressed Adults With Human Immunodeficiency Virus. *Clin Infect Dis*. 2021 (73):e485-e493.
- [65] Maggiolo F, Rizzardini G, Molina JM, Pulido F, De Wit S, Vandekerckhove L, et al. Bicitegravir/emtricitabine/tenofovir alafenamide in older individuals with HIV: Results of a 96-week, phase 3b, open-label, switch trial in virologically suppressed people ≥65 years of age. *HIV Med*. 2023 (24):27-36.
- [66] Hagins D, Kumar P, Saag M, Wurapa AK, Brar I, Berger D, et al. Switching to Bicitegravir/Emtricitabine/Tenofovir Alafenamide in Black Americans With HIV-1: A Randomized Phase 3b, Multicenter, Open-Label Study. *J Acquir Immune Defic Syndr*. 2021 (88):86-95.
- [67] Zhang H, Hindman JT, Lin L, Davis M, Shang J, Xiao D, et al. A study of the pharmacokinetics, safety, and efficacy of bicitegravir/emtricitabine/tenofovir alafenamide in virologically suppressed pregnant women with HIV. *AIDS*. 2024 (38):F1-F9.
- [68] Martorell C, Ramgopal M, Hagins D, Osiyemi O, Arribas JR, Berhe M, et al. Efficacy and safety of bicitegravir/emtricitabine/tenofovir alafenamide in Black and Hispanic/Latine adults with HIV-1 initiating first-line therapy: 5-year follow-up from two phase III studies. *HIV Med*. 2025 (26):858-869.
- [69] Hidalgo-Tenorio C, Sequera S, Vivancos MJ, Vinuesa D, Collado A, Santos IL, et al. Bicitegravir/emtricitabine/tenofovir alafenamide as first-line treatment in naïve HIV patients in a rapid-initiation model of care: BIC-NOW clinical trial. *Int J Antimicrob Agents*. 2024 (63):107164.
- [70] Camici M, Gagliardini R, Lanini S, Del Duca G, Mondì A, Ottou S, et al. Rapid ART initiation with bicitegravir/emtricitabine/tenofovir alafenamide in individuals presenting with advanced HIV disease (Rainbow study). *Int J Antimicrob Agents*. 2024 (63):107049.
- [71] Wang R, Sun L, Wang X, Zhai Y, Wang L, Ma P, et al. Rapid Initiation of Antiretroviral Therapy With Coformulated Bicitegravir, Emtricitabine, and Tenofovir Alafenamide Versus Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate in HIV-Positive Men Who Have Sex With Men in China: Week 48 Results of the Multicenter, Randomized Clinical Trial. *Clin Infect Dis*. 2024 (79):169-176.

- [72] Begovac J, Lisičar I, Romih Pintar V, Židovec-Lepej S, Planinić A, Zekan Š. Coformulated Bictegravir, Emtricitabine, and Tenofovir Alafenamide Introduced at the First Clinical Visit: A Real-Life Single-Arm Single-center Retrospective Cohort Study. *Infect Dis Ther.* 2025 (14):867-880.
- [73] Rockstroh JK, Paredes R, Cahn P, Molina JM, Sokhela SM, Hinestrosa F, et al. Doravirine/islatravir (100/0.75 mg) once-daily compared to bictegravir/emtricitabine/tenofovir alafenamide as initial HIV-1 treatment: 48-week results from a phase 3, randomized, controlled, double-blind, non-inferiority trial. *Clin Infect Dis.* 2025 :ciaf077.
- [74] Iwuji C, Waters L, Milinkovic A, Orkin C, Fox J, Post F, et al. Outcomes of switching from protease inhibitor-based antiretroviral therapy to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in virologically suppressed adults with nucleos(t)ide analogue resistance- a phase IV randomised, open-label study (PIBIK study). *Virology J.* 2025 (22):33.
- [75] de Gea-Grela A, Micán R, de Miguel R, Serrano L, Marcelo C, Montes ML, et al. Three-Year Effectiveness of Bictegravir/Emtricitabine/Tenofovir Alafenamide as a Switch Strategy in the Real World. *Open Forum Infect Dis.* 2025 (12):ofaf087.
- [76] Liu A, Xin R, Zhang H, Dai L, Wu RE, Wang X, et al. An open-label evaluation of safety and tolerability of coformulated bictegravir/emtricitabine/tenofovir alafenamide for post-exposure prophylaxis following potential exposure to human immunodeficiency virus-1. *Chin Med J (Engl).* 2022 (135):2725-2729.
- [77] Gan L, Xie X, Fu Y, Yang X, Ma S, Kong L, et al. Safety and adherence of bictegravir/emtricitabine/tenofovir alafenamide for HIV post-exposure prophylaxis among adults in Guiyang China: a prospective cohort study. *BMC Infect Dis.* 2024 (24):565.



Current combination formulations based on second-generation INSTIs to provide new therapeutic options for the treatment of patients with HIV.