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Bictegravir-Based Single-Tablet Regimens in Treatment-Naive Adults: Virologic Outcomes and Tolerability

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ABSTRACT

Human immunodeficiency virus (HIV) infection remained a substantial global health challenge, with approximately 39 million people living with HIV worldwide as of 2022. The advent of integrase strand transfer inhibitors (INSTIs) has transformed antiretroviral therapy (ART), offering enhanced virologic suppression with favorable tolerability profiles. Bictegravir (BIC), a second-generation unboosted INSTI, had emerged as a cornerstone of contemporary single-tablet regimens (STRs) for treatment-naive adults. This narrative review critically examined the virologic efficacy, metabolic tolerability, and safety profile of bictegravir-based STRs in antiretroviral-naive patients. A comprehensive literature search was conducted using PubMed, Embase, and Web of Science databases from January 2017 to November 2024, focusing on randomized controlled trials, observational cohorts, and mechanistic studies evaluating bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF). Evidence from pivotal phase III trials demonstrated that BIC-based STRs achieve virologic suppression rates exceeding 92% at 48 weeks, with sustained efficacy through 144 weeks and beyond. Compared with dolutegravir-based and boosted INSTI regimens, bictegravir exhibited non-inferior virologic outcomes while demonstrating superior weight neutrality, minimal drug-drug interactions due to its unboosted formulation, and a high genetic barrier to resistance. The favorable pharmacokinetic profile, characterized by high plasma protein binding and minimal renal elimination, contributes to once-daily dosing convenience and reduced metabolic perturbations. Bictegravir-based STRs represented a highly effective, well-tolerated first-line option for treatment-naive adults, combining potent virologic suppression with metabolic safety and simplified administration that enhances long-term adherence and clinical outcomes.

Keywords: Bictegravir, Integrase strand transfer inhibitors, Single-tablet regimen, Antiretroviral therapy, Treatment-naive HIV.

INTRODUCTION

The evolution of antiretroviral therapy (ART) over the past four decades has transformed human immunodeficiency virus (HIV) infection from an invariably fatal disease into a manageable chronic condition [1–3]. As of 2023, an estimated 38 million individuals globally are living with HIV [4], with 29.8 million accessing ART [5, 6]. Despite significant therapeutic advances, challenges persist in optimizing treatment regimens that balance maximal virologic efficacy with long-term tolerability, minimal drug interactions, and simplified dosing to support adherence. The integrase strand transfer inhibitor (INSTI) class has emerged as the preferred anchor agent in contemporary first-line regimens, displacing protease inhibitors and non-nucleoside reverse transcriptase inhibitors due to superior virologic potency, rapid viral load decline, and generally favorable safety profiles.

Bictegravir (BIC), a second-generation unboosted INSTI approved by regulatory agencies in 2018, represents a significant advancement in HIV pharmacotherapy [7, 8]. Chemically, bictegravir is a tricyclic carbamoyl pyridone derivative with distinct structural features that confer enhanced binding affinity to the HIV-1 integrase enzyme and a high genetic barrier to resistance [9, 10]. Formulated as a single-tablet regimen (STR) in combination with emtricitabine and tenofovir alafenamide (B/F/TAF), bictegravir offers the convenience of once-daily administration without the requirement for pharmacokinetic boosting, thereby minimizing potential drug-drug interactions [11].

Early clinical development programs demonstrated robust virologic suppression rates exceeding 90% in treatment-naive populations, with accumulating evidence suggesting advantages in weight neutrality and metabolic parameters compared to other contemporary INSTIs. The objective of this review is to critically synthesize current evidence on the virologic efficacy, tolerability profile, resistance characteristics, and clinical positioning of bictegravir-based single-tablet regimens in antiretroviral-naive adults.

1. METHODS

A comprehensive narrative review was conducted to evaluate the efficacy and safety of bictegravir-based STRs in treatment-naive adults living with HIV. Literature searches were performed in PubMed/Medline, Embase, and Web of Science databases from January 2017 through November 2024. Search terms included combinations of "bictegravir," "B/F/TAF," "BIC/FTC/TAF," "integrase inhibitor," "treatment-naive," "antiretroviral therapy," "virologic suppression," "HIV," and "single-tablet regimen." Inclusion criteria encompassed randomized controlled trials (RCTs), prospective and retrospective cohort studies, pharmacokinetic analyses, and resistance studies involving treatment-naive adults initiating bictegravir-containing regimens. Priority was given to phase III clinical trials with robust sample sizes and long-term follow-up data. Exclusion criteria included case reports, conference abstracts without subsequent peer-reviewed publication, and studies exclusively in treatment-experienced populations unless directly relevant to resistance pathways. Additional references were identified through manual screening of bibliographies from key articles and systematic reviews. Evidence synthesis focused on comparative efficacy outcomes (virologic suppression rates, time to suppression), safety and tolerability (adverse events, weight changes, metabolic parameters), resistance development, and pharmacokinetic-pharmacodynamic relationships.

2. MOLECULAR PHARMACOLOGY AND MECHANISM OF ACTION

3.1 Integrase Enzyme Structure and HIV Replication Cycle

The HIV-1 integrase enzyme is a 288-amino acid protein essential for viral replication, catalyzing the insertion of reverse-transcribed viral DNA into the host chromosome [12]. This process occurs through three sequential biochemical steps: 3'-processing, in which integrase removes a dinucleotide from each 3' end of the viral DNA; strand transfer, wherein the processed viral DNA ends are covalently joined to host chromosomal DNA; and gap repair, mediated by host cellular machinery. INSTIs selectively inhibit the strand transfer step by binding to the integrase enzyme complexed with viral DNA at the pre-integration complex, preventing the formation of stable integration intermediates [13, 14]. This mechanism of action offers several theoretical advantages: the target is viral-specific with no human homologue, inhibition occurs early in the replication cycle before proviral integration, and the catalytic site exhibits structural conservation across HIV-1 subtypes.

3.2 Bictegravir Structure-Activity Relationships

Bictegravir possesses a tricyclic carbamoyl pyridone core structure that differs substantially from first-generation INSTIs such as raltegravir and elvitegravir, and second-generation agents including dolutegravir [15]. Critical structural features include a bridgehead nitrogen and a difluoromethyl substituent that enhance binding interactions within the integrase active site through optimized coordination with magnesium cofactors and increased van der Waals contacts with conserved catalytic residues. Biochemical assays demonstrate that bictegravir exhibits a 50% inhibitory concentration (IC_{50}) against wild-type HIV-1 integrase of approximately 7.5 nM in cell-based assays, with protein-binding adjusted IC_{90} values of 162 nM, comparable to dolutegravir [16]. The slow dissociation kinetics from the integrase-DNA complex (dissociative half-life >10 hours) contribute to prolonged intracellular antiviral activity, supporting once-daily dosing. Furthermore, the molecular architecture of bictegravir maintains potent activity against viruses harboring common integrase resistance mutations, including Q148 and N155 pathway substitutions that confer high-level resistance to earlier INSTIs.

3.3 Pharmacokinetic Profile

Bictegravir demonstrates favorable pharmacokinetic properties characterized by rapid oral absorption (time to maximum concentration approximately 2 hours), high plasma protein binding (>99%, predominantly to albumin and alpha-1 acid glycoprotein), and moderate volume of distribution. The predominant route of elimination is hepatic metabolism via CYP3A and uridine diphosphate glucuronosyltransferase (UGT) 1A1-mediated glucuronidation, with minimal renal excretion (<1% unchanged in urine) [17]. The terminal elimination half-life approximates 17 hours, providing pharmacokinetic support for once-daily administration. Critically, bictegravir does not require pharmacokinetic boosting with ritonavir or cobicistat, distinguishing it from elvitegravir and eliminating the associated risks of drug-drug interactions mediated by potent CYP3A inhibition. Bictegravir is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters but does not inhibit or induce major cytochrome P450 isoenzymes, UGT enzymes, or drug transporters at clinically relevant concentrations, thereby minimizing the potential for pharmacokinetic interactions with commonly co-administered medications.

3. CLINICAL EFFICACY IN TREATMENT-NAIVE POPULATIONS

4.1 Pivotal Phase III Clinical Trials

The clinical efficacy of bictegravir-based STRs in treatment-naive adults has been established through two landmark phase III randomized, double-blind, active-controlled trials: Study 1489 and Study 1490 [18]. Study 1489 enrolled 629 antiretroviral-naive adults with screening HIV-1 RNA ≥500 copies/mL, randomizing participants 1:1 to receive once-daily B/F/TAF (bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg) or dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) [19]. At week 48, the primary endpoint of HIV-1 RNA <50 copies/mL was achieved in 92.4% of participants receiving B/F/TAF compared to 93.0% receiving DTG/ABC/3TC, meeting the pre-specified non-inferiority margin (adjusted treatment difference -0.6%, 95% confidence interval -4.5% to 3.3%). Study 1490 enrolled 645 treatment-naive participants, comparing B/F/TAF with boosted elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF). At week 48, virologic suppression rates were 92.4% for B/F/TAF versus 92.5% for E/C/F/TAF, again demonstrating non-inferiority. Importantly, both trials showed sustained efficacy through week 144, with virologic suppression maintained in 85-87% of participants in the B/F/TAF arm across studies, confirming durable antiviral activity.

4.2 Virologic Suppression Across Baseline Characteristics

Subgroup analyses from the pivotal trials reveal consistent virologic efficacy across diverse baseline characteristics, including high viral load (>100,000 copies/mL), low CD4+ T-cell counts (<200 cells/μL), sex, age, race/ethnicity, and HIV-1 subtype [20, 21]. Among participants with baseline viral loads exceeding 100,000 copies/mL, week 48 suppression rates for B/F/TAF were 88.9% (Study 1489) and 88.5% (Study 1490), comparable to active comparators. In individuals with baseline CD4+ counts <200 cells/μL—a population historically associated with delayed virologic response and higher rates of treatment failure—B/F/TAF achieved suppression rates of 90.3%, demonstrating robust efficacy even in advanced immunosuppression. The rapid kinetics of viral load decline with bictegravir-based therapy is noteworthy, with median time to HIV-1 RNA <50 copies/mL of approximately 12-16 weeks, comparable to other contemporary INSTI-based regimens and significantly faster than historical protease inhibitor-based therapies.

4.3 Real-World Evidence and Observational Cohorts

Beyond controlled trial settings, real-world observational studies corroborate the high effectiveness of bictegravir-based STRs. A multicenter European cohort study including 1,247 treatment-naive individuals initiating B/F/TAF reported 48-week virologic suppression rates of 91.7%, with low rates of virologic failure (1.8%) and treatment discontinuation due to adverse events (3.2%) [22, 23]. Similar findings emerged from the OPERA cohort in the United States, where 89.4% of treatment-naive participants achieved viral suppression by week 48 on B/F/TAF. These real-world data suggest that the efficacy observed in clinical trials translates effectively to diverse clinical practice settings with heterogeneous patient populations, including those with psychiatric comorbidities, substance use disorders, and complex medication regimens that were often excluded from registration trials.

4. SAFETY, TOLERABILITY, AND METABOLIC EFFECTS

5.1 Adverse Event Profile

The safety profile of bictegravir-based STRs is characterized by low rates of treatment-emergent adverse events leading to discontinuation. In the pooled analysis of Studies 1489 and 1490, drug-related adverse events occurred in 23% of B/F/TAF recipients, with discontinuations due to adverse events in only 1% of participants through 144 weeks [24, 25]. The most commonly reported adverse events were mild-to-moderate diarrhea (6%), nausea (5%), headache (5%), and upper respiratory tract infections (4%), with no discernible difference in frequency or severity compared to control arms. Importantly, the absence of pharmacokinetic boosting eliminates the gastrointestinal side effects and lipid perturbations commonly associated with cobicistat or ritonavir. Serious adverse events were infrequent and generally not attributable to study drugs, with no unexpected safety signals emerging during extended follow-up.

5.2 Weight Changes and Metabolic Parameters

Weight gain following ART initiation has emerged as a significant clinical concern, particularly with INSTI-based regimens and tenofovir alafenamide-containing formulations. However, comparative analyses suggest that bictegravir may have a more favorable weight profile than dolutegravir. In Study 1489, median weight gain from baseline to week 48 was 1.7 kg in the B/F/TAF arm compared to 2.2 kg in the DTG/ABC/3TC arm, though this difference did not achieve statistical significance in the overall population [26]. Notably, subgroup analyses revealed that weight gain was more pronounced among women and Black participants across all treatment arms, reflecting established demographic patterns in ART-associated weight changes. Post-hoc analyses adjusting for return-to-health effects (immune reconstitution and improved nutritional status) suggest that the incremental weight gain attributable specifically to antiretroviral agents is modest with bictegravir, typically 1-2 kg beyond that expected from HIV virologic control alone.

Metabolic laboratory parameters, including fasting lipid profiles and glucose homeostasis markers, remain generally stable or improve modestly with bictegravir-based therapy. Changes in total cholesterol, LDL-cholesterol, HDL-

cholesterol, and triglycerides from baseline to week 48 were minimal in both pivotal trials, with total cholesterol/HDL ratios remaining within normal ranges [27]. Importantly, no clinically significant alterations in fasting glucose, hemoglobin A1c, or insulin resistance indices were observed, distinguishing bictegravir from regimens containing boosted protease inhibitors or first-generation NNRTIs that frequently cause dyslipidemia and insulin resistance.

5.3 Neuropsychiatric Tolerability

Neuropsychiatric adverse events, including insomnia, depression, anxiety, and suicidal ideation, have been reported with various INSTIs, particularly efavirenz (an NNRTI) and, to a lesser extent, dolutegravir [28]. Bictegravir demonstrates a favorable neuropsychiatric profile, with low rates of treatment-emergent neuropsychiatric symptoms in clinical trials. In the pooled safety analysis, neuropsychiatric adverse events occurred in 6% of B/F/TAF recipients (versus 7% with DTG/ABC/3TC and 7% with E/C/F/TAF), with serious neuropsychiatric events rare (<1%). Post-marketing surveillance and patient-reported outcome measures have not identified substantive concerns regarding sleep disturbances or mood alterations with bictegravir, though vigilance remains warranted given the known vulnerability of people living with HIV to psychiatric comorbidities.

5.4 Renal and Bone Safety

Tenofovir alafenamide (TAF), the tenofovir prodrug included in B/F/TAF, exhibits improved renal and bone safety compared to its predecessor, tenofovir disoproxil fumarate (TDF), due to more efficient intracellular delivery and 90% lower circulating tenofovir concentrations [29]. In the bictegravir trials, changes in estimated glomerular filtration rate (eGFR) from baseline were minimal, with median decreases of 2-3 mL/min/1.73m² attributable primarily to tubular creatinine secretion inhibition by emtricitabine rather than true nephrotoxicity. Proteinuria and proximal tubular dysfunction (evidenced by urine beta-2 microglobulin or retinol-binding protein elevations) were uncommon. Similarly, bone mineral density (BMD) assessments via dual-energy X-ray absorptiometry (DXA) demonstrated significantly smaller declines in hip and spine BMD with B/F/TAF (-0.8% to -1.3%) compared to TDF-containing regimens (typically -2% to -3%), with low rates of osteoporotic fractures during follow-up.

5. RESISTANCE PROFILE AND GENETIC BARRIER

6.1 Pre-Treatment Resistance and Baseline Mutations

The presence of baseline integrase resistance-associated mutations (RAMs) in treatment-naive populations is generally low (<5%), reflecting the limited historical use of INSTIs and the fitness cost associated with most integrase mutations. In Studies 1489 and 1490, baseline genotypic and phenotypic resistance testing identified INSTI RAMs in <1% of participants. Among individuals with detectable baseline polymorphisms (such as E157Q, a naturally occurring polymorphism with minimal impact on susceptibility), virologic outcomes with bictegravir remained comparable to those without such polymorphisms, underscoring the high genetic barrier and broad activity profile.

6.2 Virologic Failure and Treatment-Emergent Resistance

The incidence of virologic failure (defined as confirmed HIV-1 RNA ≥50 copies/mL after initial suppression or failure to achieve <50 copies/mL) on bictegravir-based STRs is exceptionally low. Through 144 weeks of follow-up in the pivotal trials, virologic failure occurred in <2% of participants receiving B/F/TAF, with no cases of treatment-emergent integrase resistance mutations detected among those who failed therapy. This absence of resistance emergence contrasts with earlier INSTIs such as raltegravir, where virologic failure frequently selected for Q148 and N155 pathway mutations [30, 31]. Mechanistic studies suggest that bictegravir's slow dissociation kinetics and enhanced binding affinity maintain antiviral activity even in the presence of single or dual integrase mutations, requiring the accumulation of multiple mutations to confer clinically significant resistance—a rare occurrence in adherent patients.

When treatment-emergent resistance has been documented with bictegravir in treatment-experienced populations or in vitro selection studies, the predominant pathways involve M50I or R263K mutations in integrase, often accompanied by reverse transcriptase mutations (M184V/I in the emtricitabine/lamivudine target) [32]. However, even viruses with M50I exhibit only modest reductions in bictegravir susceptibility (approximately 2-3 fold), typically insufficient to compromise virologic suppression at therapeutic drug concentrations. This robust genetic barrier is a critical advantage for long-term treatment success, particularly in settings where adherence monitoring is limited or viral load testing is infrequent.

6. DRUG INTERACTIONS AND SPECIAL POPULATIONS

7.1 Drug-Drug Interaction Profile

The absence of pharmacokinetic boosting is a distinguishing feature of bictegravir, substantially simplifying co-medication management. Unlike cobicistat- or ritonavir-boosted regimens, which potently inhibit CYP3A4 and multiple drug transporters, bictegravir exhibits minimal interaction potential with commonly prescribed medications [33]. Bictegravir plasma concentrations are not significantly altered by moderate CYP3A inducers or inhibitors at typical doses. However, co-administration with potent CYP3A and UGT1A1 inducers (rifampin, carbamazepine, phenytoin, St. John's wort) is contraindicated, as these agents substantially reduce bictegravir

exposure below therapeutic thresholds. Conversely, strong CYP3A inhibitors such as clarithromycin or ketoconazole do not necessitate dose adjustments due to bictegravir's wide therapeutic index.

Polyvalent cations (calcium, iron, magnesium, and aluminum) present in antacids, multivitamins, and mineral supplements can chelate bictegravir and reduce absorption [34, 35]. Administration recommendations include taking B/F/TAF at least 2 hours before or after such supplements when taken on an empty stomach, or simultaneously with food to mitigate the interaction. Importantly, bictegravir does not affect the pharmacokinetics of hormonal contraceptives, direct oral anticoagulants, statins, or most antihypertensives, facilitating management of common comorbidities in aging populations living with HIV.

7.2 Use in Special Populations

Bictegravir is approved for use in adults and children weighing ≥14 kg, with pediatric formulations available. Pharmacokinetic studies in adolescents (12-17 years) confirmed that bictegravir exposures achieved with weight-based dosing were comparable to those in adults, with similar safety and efficacy profiles [36]. However, data in pregnant individuals remains limited. Physiologic changes during pregnancy (increased plasma volume, enhanced hepatic metabolism, altered protein binding) may reduce bictegravir concentrations, though preliminary pharmacokinetic studies suggest that standard dosing maintains adequate exposure throughout gestation. The Antiretroviral Pregnancy Registry and ongoing prospective cohorts are monitoring pregnancy outcomes, with no signals of teratogenicity or adverse fetal effects detected to date, though sample sizes remain insufficient for definitive conclusions.

In individuals with renal impairment, dose adjustment is not required for creatinine clearance ≥30 mL/min, as bictegravir undergoes predominantly hepatic elimination. For severe renal impairment (CrCl <30 mL/min) or end-stage renal disease, B/F/TAF is not recommended due to tenofovir alafenamide accumulation concerns, though alternative tenofovir-sparing bictegravir regimens may be considered [37]. In hepatic impairment, bictegravir pharmacokinetics are not significantly altered in Child-Pugh Class A or B, and dose adjustment is unnecessary; data in severe hepatic impairment (Child-Pugh Class C) are lacking, warranting cautious use.

7. COMPARATIVE EFFECTIVENESS AND CLINICAL POSITIONING

8.1 Comparison with Other Second-Generation INSTIs

Direct comparison of bictegravir with dolutegravir, the most widely prescribed second-generation INSTI, reveals comparable virologic efficacy with potential advantages in tolerability. Both agents achieve >90% virologic suppression rates in treatment-naive populations with similarly high genetic barriers to resistance. Meta-analyses incorporating data from multiple head-to-head and network comparisons suggest no statistically significant difference in virologic outcomes, though bictegravir may be associated with less weight gain and fewer neuropsychiatric adverse events in certain subgroups [38]. The single-tablet formulation of B/F/TAF offers a dosing convenience advantage over dolutegravir-based regimens requiring separate tablets (e.g., DTG + 3TC or DTG + FTC/TAF), potentially enhancing adherence in busy clinical practices.

Cabotegravir, a long-acting injectable INSTI, represents an alternative approach for individuals desiring non-oral ART or those with adherence challenges to daily oral therapy [39, 40]. While cabotegravir (administered monthly or every-two-months intramuscularly with rilpivirine) demonstrates non-inferior efficacy to oral regimens, the requirement for clinic visits, injection-site reactions, and the long pharmacokinetic tail (with potential for resistance selection if viral rebound occurs after discontinuation) positions it as complementary rather than competitive with bictegravir-based STRs for most treatment-naive adults.

8.2 Cost-Effectiveness and Access Considerations

Economic evaluations from high-income settings suggest that bictegravir-based STRs are cost-effective compared to alternative first-line regimens when incorporating quality-adjusted life years (QALYs), treatment persistence, and management of adverse events [41]. The higher acquisition cost of B/F/TAF relative to generic dolutegravir-based regimens is offset in part by reduced monitoring requirements (no need for HLA-B*5701 screening as required for abacavir), fewer adverse event-related clinical visits, and superior long-term adherence associated with STR formulations. However, in resource-limited settings where generic DTG-based regimens dominate WHO-recommended first-line therapy at substantially lower costs, the role of bictegravir remains limited pending generic availability and price reductions [42].

8. FUTURE DIRECTIONS AND RESEARCH GAPS

9.1 Long-Acting and Extended-Release Formulations

While bictegravir's pharmacokinetic profile supports once-daily dosing, research into long-acting formulations (subcutaneous or intramuscular depot injections, implantable devices, or ultra-long-acting oral prodrugs) remains an area of active investigation. The success of cabotegravir long-acting injections has reinvigorated interest in developing injectable or implantable bictegravir formulations that could extend dosing intervals to monthly or longer, potentially improving adherence and reducing stigma associated with daily pill-taking [43, 44]. Preliminary preclinical studies of bictegravir nanocrystal suspensions demonstrate prolonged drug release, though translating these findings to clinically viable formulations faces substantial pharmaceutical and regulatory hurdles.

9.2 Resistance Surveillance and Minority Variants

Although treatment-emergent resistance to bictegravir is rare, ongoing surveillance using next-generation sequencing to detect low-frequency resistance variants (<20% of the viral population) is critical. Minority integrase variants present at baseline, undetectable by standard Sanger sequencing, may theoretically impact treatment outcomes, though current evidence suggests minimal clinical impact on bictegravir efficacy [45, 46]. Expanded genotypic and phenotypic characterization of viruses from individuals experiencing virologic failure will elucidate resistance mechanisms and inform salvage therapy strategies.

9.3 Optimization in Special Populations

Further research is needed to optimize bictegravir use in underrepresented populations, including pregnant individuals across all trimesters, neonates and young children, and persons with advanced liver disease or significant comorbidities. Dedicated pharmacokinetic studies with intensive sampling, coupled with maternal-fetal safety monitoring, will establish evidence-based dosing recommendations and safety profiles. Additionally, investigations into potential drug interactions with emerging therapies (e.g., immune checkpoint inhibitors for HIV-associated malignancies, novel obesity pharmacotherapies) will ensure safe co-administration as treatment paradigms evolve [47, 48].

9.4 Two-Drug Regimens and Treatment Simplification

The concept of two-drug regimens (dual therapy) for HIV treatment, exemplified by dolutegravir/lamivudine, has gained traction as a strategy to reduce cumulative drug exposure, long-term toxicity, and cost while maintaining virologic efficacy [49, 50]. Bictegravir's potent antiviral activity and favorable resistance profile position it as a candidate anchor for dual regimens. Pilot studies evaluating bictegravir/emtricitabine (without tenofovir) or bictegravir/lamivudine combinations in virologically suppressed individuals have shown promising preliminary results, though adequately powered non-inferiority trials in treatment-naive populations are necessary to validate this approach.

9.5 Biomarkers of Treatment Response and Toxicity

Identifying biomarkers that predict virologic response, adherence patterns, or susceptibility to specific adverse events (e.g., excessive weight gain, neuropsychiatric symptoms) would enable precision medicine approaches. Pharmacogenomic studies examining polymorphisms in drug-metabolizing enzymes (CYP3A5, UGT1A1), transporters (ABCG2, ABCB1), or host immunogenetic factors (HLA alleles, cytokine gene variants) may reveal genetic determinants of bictegravir pharmacokinetics and tolerability [51–53]. Integration of multi-omics data (genomics, metabolomics, proteomics) could refine patient selection and personalize treatment strategies to optimize outcomes.

CONCLUSION

Bictegravir-based single-tablet regimens represent a significant advancement in first-line antiretroviral therapy for treatment-naive adults living with HIV. The synthesis of evidence from rigorous randomized controlled trials, real-world cohorts, and mechanistic investigations establishes bictegravir as a highly effective integrase inhibitor with virologic suppression rates consistently exceeding 90% at 48 weeks and sustained efficacy through extended follow-up. The favorable safety and tolerability profile, characterized by low rates of treatment discontinuation, minimal neuropsychiatric effects, relative weight neutrality compared to alternative INSTIs, and preserved renal and bone health, enhances the therapeutic value of bictegravir in contemporary clinical practice. The absence of pharmacokinetic boosting simplifies drug interaction management, broadening applicability across diverse patient populations with complex comorbidities and polypharmacy. The high genetic barrier to resistance, with virtually no documented treatment-emergent integrase mutations in treatment-naive individuals, provides confidence in long-term virologic durability even in settings with suboptimal adherence or limited virologic monitoring. While questions remain regarding optimal use in pregnancy, extreme renal or hepatic impairment, and potential roles in two-drug simplification strategies, the totality of current evidence supports bictegravir/emtricitabine/tenofovir alafenamide as a preferred first-line regimen. Ongoing surveillance for rare adverse events, resistance patterns, and long-term metabolic consequences will continue to refine clinical guidance and ensure that the benefits observed in controlled settings translate to improved health outcomes across the global HIV care continuum. Bictegravir/emtricitabine/tenofovir alafenamide should be considered a preferred first-line single-tablet regimen for antiretroviral-naive adults based on its superior virologic efficacy, favorable tolerability, high resistance barrier, and simplified drug interaction profile.

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