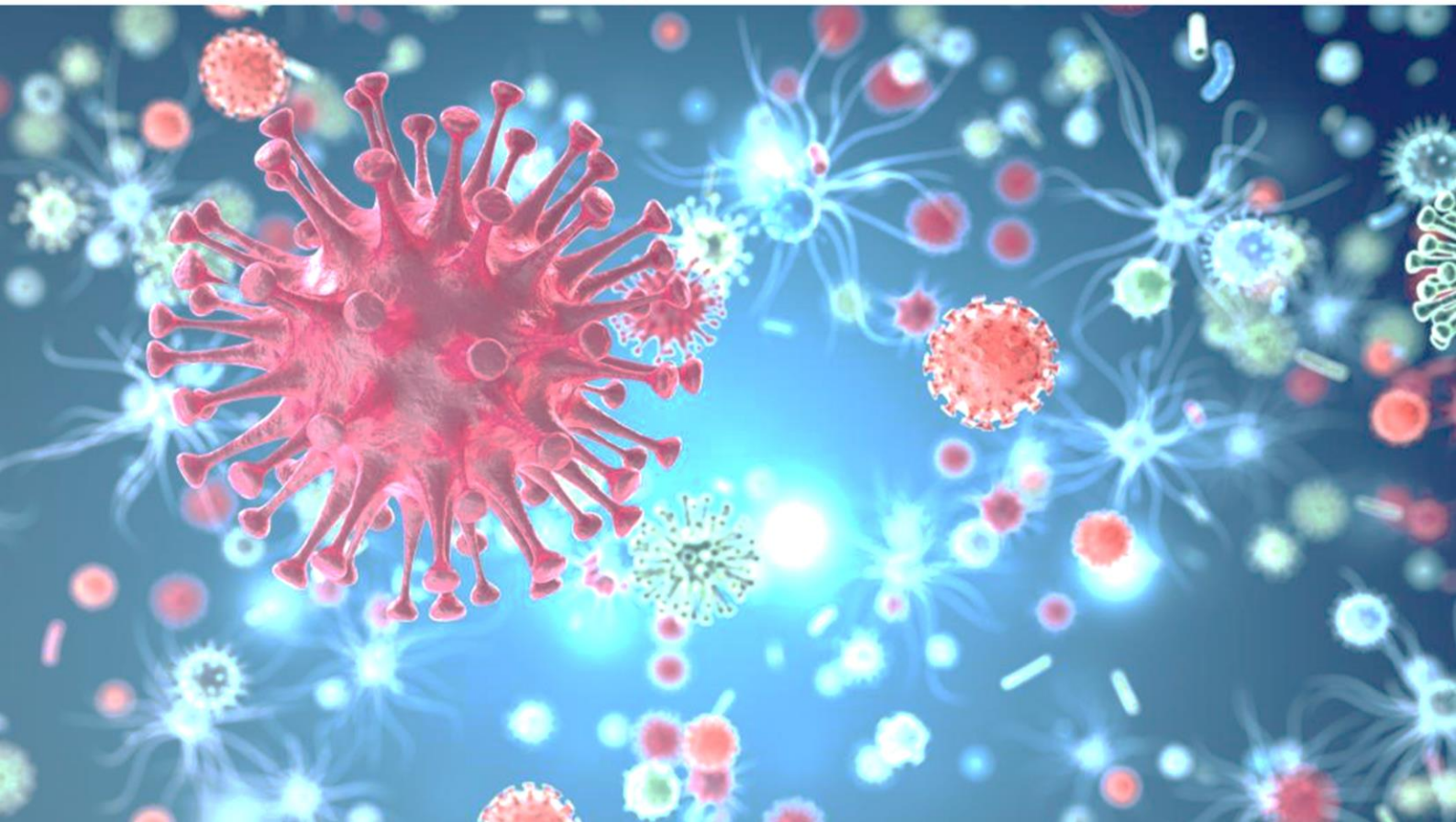
# UNDERSTANDING THE PLACE OF FDC OF DOLUTEGRAVIR, TENOFOVIR DISOPROXIL FUMARATE, LAMIVUDINE FDC TABLETS IN HIV-1 TREATMENT



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# Background and Objective of the Survey

The Fixed-Dose Combination (FDC) of dolutegravir (DTG), tenofovir disoproxil fumarate (TDF), and lamivudine (3TC) tablets holds a significant place in the treatment of HIV-1 infection due to its efficacy, safety profile, and convenience.

Dolutegravir is an integrase strand transfer inhibitor (INSTI) that effectively suppresses HIV replication by blocking the integration of viral DNA into the host cell genome. Tenofovir disoproxil fumarate and lamivudine are nucleoside reverse transcriptase inhibitors (NRTIs) that inhibit the reverse transcriptase enzyme, thereby preventing viral replication and reducing the viral load in the body.

The FDC of DTG/TDF/3TC combines three potent antiretroviral drugs into a single tablet, simplifying treatment regimens and improving patient adherence. This is particularly beneficial for individuals living with HIV-1 infection, as it reduces the pill burden and the likelihood of missed doses, which are crucial for maintaining viral suppression and preventing the development of drug resistance.

Furthermore, the FDC of DTG/TDF/3TC offers several advantages over other antiretroviral regimens. Dolutegravir is known for its high barrier to resistance, rapid viral suppression, and favorable tolerability profile, making it an attractive option for first-line HIV treatment. Tenofovir disoproxil fumarate and lamivudine are also well-established antiretroviral agents with proven efficacy and safety in the management of HIV infection.

**The objective of the survey is:**

To understand the place of FDC of dolutegravir, tenofovir disoproxil fumarate, lamivudine FDC tablets in HIV-1 treatment

# Methodology of the Survey

A survey was conducted to understand the place of FDC of dolutegravir, tenofovir disoproxil fumarate, lamivudine FDC tablets in HIV-1 treatment. A total of 80 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Dolutegravir
- Dolutegravir efficacy
- Safety of dolutegravir
- HIV treatment today
- Nucleoside reverse transcriptase class evolution
- Are lamivudine and emtricitabine interchangeable?
- Supportive evidence for the recommendations of current international guidelines to treat 3 TC and FTC as interchangeable.
- Safety
- Pharmacokinetics
- Recommendations from international guidelines
- TDF/3 TC as a viable option

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

# Literature Review

## Introduction[1]

Antiretroviral therapy (ART) has played a significant role in HIV control, and integrase strand transfer inhibitors (INSTIs), such as dolutegravir (DTG), are becoming more widely used. In 2016, the World Health Organization issued guidelines for the use of antiretroviral drugs for the treatment and prevention of HIV infection. Since 2018, WHO has recommended a combination of tenofovir disoproxil fumarate and lamivudine or emtricitabine plus DTG as the preferred first-line regimen for HIV therapy and updated this guidance in 2021.[,] This guideline provides a more comprehensive view of DTG as an ARV in the first-line due to the significant risk of neural tube defects risk and observed efficacy.

DTG shows excellent efficacy and tolerability with a low risk of toxicities.[,] DTG with two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) has shown significant efficacy in HIV suppression in individuals.[,] DTG-based regimens may be more effective for CD4 recovery and virologic suppression than EFV-based regimens, making them a preferred treatment option for initial HIV treatment. DTG also has fewer drug interactions than EFV, a better genetic barrier to developing drug resistance, and is particularly effective against HIV-2 infection, which is inherently resistant to EFV. The efficacy or effectiveness of health-care interventions has been assessed in clinical trials by measuring outcomes.

The availability of DTG as a once-daily generic fixed-dose formulation at lower prices in most low- and middle-income countries (LMICs) further supports the recommended use of DTG. However, it must be determined whether the intervention is cost-effective and feasible to implement. Cost-effectiveness analysis (CEA) is used to improve resource allocation efficiency and assess the relative costs and health benefits of various competing health therapies. Comparing studies and interventions using cost-effectiveness analyses can assist stakeholders in making evidence-based health policies.

## Dolutegravir[2]

Dolutegravir acts by impairing the function of the HIV integrase-DNA complex to which it was chemically synthesized to bind. It is rapidly absorbed, achieving maximal blood concentration hours after ingestion and, with a terminal half-life of 12 hours, requires once-

daily administration without pharmacological enhancement.– There is minimal urinary excretion as it is metabolized predominantly through hepatic glucuronidation by UDP-glucuronosyltransferase 1A1., Given the low renal elimination, reduced renal function does not significantly alter the pharmacokinetics of dolutegravir. Whether this extends to patients receiving renal replacement therapy is unknown. Similarly, there is a dearth of evidence evaluating the impact of impaired hepatic function on the activity of dolutegravir. In a small comparison of those with Child-Pugh class B cirrhosis to healthy controls, the only difference was an increase in the unbound concentration of dolutegravir, the clinical significance of which is likely minimal as more than 99% remained in the active protein-bound form. Evidence of the wide distribution of dolutegravir comes from its detection in human colorectal tissue, cerebrospinal fluid, seminal fluid, cervicovaginal fluid, and vaginal tissue at concentrations above that expected to confer continued antiviral efficacy.–

Drug–drug interactions with dolutegravir are minimal as it has little ability to alter drug-metabolizing enzymes. There are no interactions or dose adjustments required when combined with the NRTI class, as bioequivalence was observed when dolutegravir and abacavir–lamivudine, administered separately, were compared to a co-formulated single tablet.– Among the NNRTI class, both efavirenz and etravirine significantly lower dolutegravir levels and should be avoided unless etravirine is administered with ritonavir, which reverses this reduction., There is no interaction between rilpivirine and dolutegravir. The PIs darunavir, lopinavir, fosamprenavir, and atazanavir, irrespective of ritonavir coadministration, can be safely used with dolutegravir.– Tipranavir, however, reduces the plasma concentration of dolutegravir and caution should be exercised with coadministration. Interactions between dolutegravir and cobicistat – currently being evaluated as an alternative pharmacokinetic enhancer to ritonavir – are unclear and require further investigation.

Coinfection with hepatitis C and tuberculosis frequently occur, and the lengthy treatment regimens consisting of multiple agents make interactions with antiretrovirals inevitable. While there are no interactions between dolutegravir and boceprevir or telaprevir, the explosion of new antiviral agents active against hepatitis C will require pharmacokinetic studies to establish the feasibility of concurrent administration. Given the mechanism of metabolism of dolutegravir and with no clinically significant interactions between it and grazoprevir with elbasvir, it is expected that concurrent use with the direct acting agents against hepatitis C should not impact drug levels, but clinical data are lacking., As for tuberculosis therapy, rifampin lowers the concentration of dolutegravir, which can be offset by increasing the

frequency of dolutegravir (50 mg twice daily) or substituting rifabutin as no adjustments are required.

Outside of antimicrobial agents, dolutegravir has few drug–drug interactions. There does not appear to be a significant interaction between dolutegravir and oral contraceptive pills or proton pump inhibitors., Antacids, however, can attenuate the effectiveness of dolutegravir, which should be taken 2 hours prior to or 6 hours following the ingestion of an antacid. Such a schedule should likewise be followed if dolutegravir is taken with cations such as iron and calcium, although these interactions can be avoided when ingested with a moderately fatty meal. Dolutegravir alters the pharmacokinetics of metformin, possibly enhancing gastrointestinal upset. In the absence of mineral supplements, dolutegravir can be taken with or without food.

**Dolutegravir efficacy[2]**

Antiretroviral-naïve patients

Dose response studies determined 50 mg of dolutegravir as the most efficacious, with similar side effects as lower daily doses., In a blinded study, SPRING-2, comparing raltegravir against dolutegravir with either abacavir–lamivudine or tenofovir–emtricitabine, once-daily dolutegravir was noninferior, with 88% and 85%, respectively, achieving viral load suppression. This effect diminished slightly, but noninferiority persisted to 96 weeks. Failure to achieve virologic suppression was entirely due to discontinuation of dolutegravir for reasons other than the development of resistance, which was not observed. Against darunavir–ritonavir in the open-label FLAMINGO study, dolutegravir led to virologic suppression in 90% of patients at 48 weeks compared with 83% in the darunavir–ritonavir group, which was predominantly the result of discontinuation due to adverse events, but also some improvement in efficacy above 100,000 copies per milliliter. The open-label nature of FLAMINGO could have led to biases in discontinuation rates. Similar to SPRING-2, the effect waned slightly, but remained statistically significant at 96 weeks. In SINGLE, a randomized placebo-controlled study comparing dolutegravir with abacavir–lamivudine against tenofovir–emtricitabine–efavirenz, viral load suppression occurred in 88% and 81% at 48 weeks, respectively. The superiority of dolutegravir with abacavir–lamivudine persisted at 144 weeks. The benefit was driven almost entirely by increased discontinuations due to adverse events associated with efavirenz. The unique aspect of SINGLE resides with controlling backbone agents as the aforementioned randomized trials entrusted backbone selection to study investigators. When all Phase III randomized trials were amalgamated, subgroup analysis did not find that patient

age, backbone, or pretreatment viral load impacted effectiveness., Dolutegravir has been compared against PIs, NNRTIs, and INSTIs in treatment-naïve patients with consistent efficacy despite varying study populations.

Table 1. Randomized trials of dolutegravir in treatment-naïve HIV-1-positive patients

| **Trial** | **Antiretrovirals** | **Backbone** | **Outcomes** [a] | **Serious adverse events** | **Protocol-defined virologic failure**[b] | **Mutations due to INSTI** |
|---|---|---|---|---|---|---|
| **SPRING-1** | DTG 10 mg (n=53)<br>DTG 25 mg (n=51)<br>DTG 50 mg (n=51)<br>EFV (n=50) | TDF–FTC (67%)<br>ABC–3TC (33%) | DTG 10 mg 91%<br>DTG 25 mg 88%<br>DTG 50 mg 90%<br>EFV 82% | DTG 10 mg 6%<br>DTG 25 mg 2%<br>DTG 50 mg 8%<br>EFV 5% | DTG 10 mg 4%<br>DTG 25 mg 4%<br>DTG 50 mg 0%<br>EFV 2% | DTG 10 mg<br>NRTI: M184V<br>DTG 25 mg, DTG 50 mg, EFV<br>None |
| **SPRING-2** | DTG (n=411)<br>RAL (n=411) | TDF–FTC (59%)<br>ABC–3TC (41%) | DTG 88%<br>RAL 85% | DTG 0.7%<br>RAL 1% | DTG 5%<br>RAL 7% | DTG<br>None<br>RAL<br>INSTI: T97A, E138D, V151I<br>NRTI: A62V, K65R, K70E, and M184V |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | NRTI: M184I NRTI: A62V NRTI: M184V |
| **SINGLE** | DTG–ABC–3TC (n=414) EFV–TDF–FTC (n=419) | Not applicable | DTG–ABC–3TC 88% EFV–TDF–FTC 81% | DTG–ABC–3TC <1% EFV–TDF–FTC 2% | DTG–ABC–3TC 4% EFV–TDF–FTC 4% | DTG–ABC–3TC None |
| **FLAMINGO** | DTG (n=242) DRV/R (n=242) | TDF–FTC (67%) ABC–3TC (33%) | DTG 90% DRV/R 83% | DTG 11% DRV/R 5% | DTG 1% DRV/R 1% | No INSTI, PI, NRTI mutations |

**Notes:**

[a]Percentage of cohort achieving HIV RNA <50 copies/mL at 48 weeks.

[b]Virologic failure defined in SINGLE and SPRING-2 as two HIV RNA levels >50 copies/mL on or after 24 weeks; in FLAMINGO as two HIV RNA levels >200 copies/mL on or after 24 weeks; in SPRING-1 as one HIV RNA level >400 copies/mL on or after 24 weeks or decrease less than 1.0 $\log_{10}$ copies/mL by Week 4.

**Abbreviations:** DTG, dolutegravir; EFV, efavirenz; RAL, raltegravir; TDF, tenofovir; ABC, abacavir; 3TC, lamivudine; FTC, emtricitabine; DRV/R, darunavir/ritonavir; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside and nucleotide reverse-transcriptase inhibitors; PI, protease inhibitor.

Antiretroviral-experienced patients

With the trend toward early initiation of antiretrovirals, the requirement for lifetime use, and myriad ways HIV escapes drug suppression, the proportion of treatment-experienced patients are naturally expected to rise. SAILING, a randomized trial of patients with resistance to at least two antiretro-viral classes yet who were INSTI-naïve, compared raltegravir to dolutegravir with optimally constructed backbones. After 48 weeks, virologic suppression was observed in 71% in the dolutegravir cohort and 64% in the raltegravir cohort. The superiority of the dolutegravir regimen was observed irrespective of the background regimen, and resistance mutations were less likely to develop with dolutegravir. The biologic plausibility for the incremental benefit of dolutegravir over raltegravir is the slower dissociation from the HIV-1 integrase-DNA complex and the reduced interindividual pharmacokinetic variability.,

The VIKING trials assessed the utility of dolutegravir in populations with previous INSTI failure. In VIKING, patients with raltegravir resistance either by genotype analysis or treatment failure received dolutegravir once or twice daily for 10 days followed by optimization of the background regimen. After 24 weeks, almost twice as many subjects had an undetectable viral load in the twice-daily group (75% to 41%). In VIKING-3, patients with historical or current evidence of resistance to either raltegravir or elvitegravir by genotype or phenotype testing were given dolutegravir twice daily for 7 days before optimizing the background regimen. After 24 weeks, 69% achieved virologic suppression. VIKING-4 prospectively studied a heavily treatment-experienced cohort comparing a 7-day run-in period of dolutegravir or placebo followed by both groups receiving dolutegravir and an individually optimized background regimen. After 24 and 48 weeks, viral load suppression occurred in 47% and 40%, respectively. In an open-label cohort of heavily treatment-experienced HIV-2-infected patients, dolutegravir led to an undetectable viral load in 38%. Cumulatively, these studies support the use of twice-daily dolutegravir among those with raltegravir or elvitegravir failure. Success with the sequential use of dolutegravir following INSTI failure is predicated on the presence of at least two active backbone agents and reduced development of INSTI resistance mutations. Thus, patients should stop a failing raltegravir- or elvitegravir-containing regimen as soon as possible to avoid the accumulation of mutations potentially compromising subsequent use of dolutegravir.

Table 2. Trials of dolutegravir in treatment-experienced HIV-1-positive patients

| TRIAL | POPULATION | Z | ANTIRETROVIRALS | OUTCOMES[A] | EMERGENT DTG RESISTANCE MUTATIONS |
|---|---|---|---|---|---|
| **SAILING** | Resistance to ≥1 drug in ≥2 classes | | DTG (n=354) RAL (n=361) | At 48 weeks DTG 71% RAL 64% | R263R (FC 1.12) R263R (FC 1.93) R263R (FC 1.1) R263R (FC 1.9) E138T/A + T97A (FC > max) V151I (FC 0.92) |
| **VIKING,**[C] | RAL resistance and ≥1 drug in ≥3 classes | | DTG daily (n=27) DTG twice daily (n=24) | At 24 weeks DTG daily 41% DTG twice daily 75% | L74I/M, E138A (FC 38) L74M/I, T97A, G140S, Q148H (FC 68) N155H (FC 6.6) N155H (FC 8.4) T97A, E138K, N155H (FC |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | 93)<br>E92Q, T97A (FC 42)<br>E138K, N155H (FC 63) |
| **VIKING-3** | RAL/ELV resistance and ≥1 drug in ≥3 classes | | DTG twice daily (n=183) | At 24 weeks DTG 69% | Not available |
| **VIKING-4** | RAL/ELV resistance and ≥1 drug in ≥2 classes | | DTG twice daily (n=30) | At 24 weeks DTG 47% | L74L/M[b]<br>T97A<br>T97A<br>T97A<br>E138K<br>S147G<br>N155H |

**Notes:**

[a]Percentage of cohort achieving HIV RNA <50 copies/mL at specified dates.

[b]FC not provided.

[c]Adapted from Eron JJ, Clotet B, Durant J, et al; VIKING Study Group. Safety and efficacy of dolutegravir in treatment-experienced subjects with ralte gravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. *J Infect Dis*. 2013;207(5):740–748.

**Abbreviations:** RAL, raltegravir; DTG, dolutegravir; ELV, elvitegravir; FC, fold change in phenotype resistance; max, maximum.

STR with dolutegravir

The bioequivalence of the co-formulated tablet leaves little doubt as to the potential efficacy of an STR containing dolutegravir. Given that there have been no published studies of dolutegravir as an STR and the consistent under-representation of women in the aforementioned trials, the Antiretroviral Therapy in Naïve Women (ARIA) trial was conducted, and the results are forthcoming. ARIA will compare the dolutegravir–abacavir–lamivudine STR against atazanavir–ritonavir with tenofovir–emtricitabine in treatment-naïve

women. Further studies will address the feasibility of switching to the dolutegravir–abacavir–lamivudine STR from either an INSTI-free regimen or from nevirapine with abacavir–lamivudine.,

**Safety of dolutegravir[2]**

Adverse events

Amalgamating the adverse event profiles accrued from the randomized controlled trials of dolutegravir provides a robust evidence base. The total incidence of adverse effects approaches 90%, but this liberal estimate consists of predominantly mild reactions that largely remit with time and may not entirely be drug related. Common adverse events include headache, nausea, and diarrhea, but the proportion with severe reactions (grade III or IV) is 1%. In SINGLE, as compared to SPRING and SAILING, the prevalence of insomnia was higher, which may be related to the specific study questionnaire that had not been employed in the previous trials. In a meta-analysis, there were significantly fewer adverse events with dolutegravir as compared to atazanavir–ritonavir, lopinavir–ritonavir, and efavirenz, while no differences between darunavir–ritonavir, elvitegravir–cobicistat, raltegravir, and rilpivirine were observed. Furthermore, adverse events ascribed to dolutegravir infrequently led to treatment cessation, occurring in less than 2%, comparable to raltegravir and lower than efavirenz and PI-based regimens. When compared to raltegravir in treatment-experienced patients, there was no difference in the overall frequency of adverse events nor in the frequency of adverse events leading to drug discontinuation. Dolutegravir has not been associated with an increase in cardiovascular risk.,, Further proof of the tolerability of dolutegravir is the similar side effect profile observed when given twice daily, even among those with advanced immunosuppression.,

With respect to biochemical perturbations due to dolutegravir, the most consistently observed is creatinine elevation. This typically occurs within a week of initiation followed by a plateau at an average increase of 11 mmol/L. This rise is mediated through inhibition of the renal transporter OCT-2, but the reduced creatinine secretion does not translate into a lower glomerular filtration rate. Elevations in transaminases occur in 5%, are generally mild, and occur at a similar rate as with raltegravir, darunavir–ritonavir, and efa-virenz. In the limited number of patients with hepatitis B or C coinfection, the incidence of transaminase elevation rises to 16%, most likely reflecting immune reconstitution, and is lower than that observed with raltegravir and efavirenz, but higher than that with darunavir–ritonavir. Elevation in total cholesterol, low-density lipoprotein, and triglycerides observed with PIs is absent with

dolutegravir. Creatine kinase elevations are common, largely asymptomatic, and mild, with only 5% being grade III or IV in severity. Hypersensitivity reactions were extremely uncommon, occurring in less than 1%, and tend to occur shortly after treatment initiation.

Special populations

There is a paucity of information regarding the use of dolutegravir in pediatric and pregnant populations. In animal studies, dolutegravir crosses the placenta, but this had no impact on fetal development in rats and rabbits despite exposure to supratherapeutic doses, resulting in an FDA class B classification. Ongoing clinical trials evaluating dolutegravir in treatment-experienced children and pregnant women will clarify the safety and efficacy of dolutegravir in these populations., In the interim, dolutegravir is not recommended in pregnancy unless alternative agents are unavailable.

Resistance profile

Another advantage of dolutegravir relates to the barrier to resistance. When analyzing those experiencing virologic failure while on dolutegravir as first-line therapy, no resistance mutations were discovered. This contrasts with the four of 281 patients who developed raltegravir resistance in STARTMRK at 5 years and one of 411 patients in SPRING-2 at 96 weeks., In comparison, at week 144, elvitegravir-resistant virus was observed in nine of 348 patients and six of 353 patients in studies comparing it to efavirenz and atazanavir–ritonavir, respectively., It is unclear as to whether the resistance barrier to dolutegravir is similar to or surpasses that of PIs, as virologic failure due to resistance was not observed in FLAMINGO.

Dolutegravir has induced mutations within the integrase enzyme, but these are infrequent and have minimal effect clinically. Dolutegravir can select for a R263K mutation that attenuates its activity, but not to an extent that allows for viral rebound. Continual dolutegravir selection pressure allows for the development of sequential mutations, generally in the same R263K pathway, but again these do not substantially impact antiviral activity and may in fact confer reduced HIV replication fitness.,–

It is important to note that the randomized clinical trials evaluating dolutegravir test for resistance upon detection of viral rebound, which often differs from clinical practice, where patients can remain on failing regimens for longer before genotype analysis is undertaken. This allows for additional selection pressure and may serve to increase the incidence of dolutegravir resistance. Given that adherence may be less optimal outside the rigor of clinical trials, over time the increasing use of dolutegravir may result in the emergence of novel mutations.

Recently, a patient with known N155H, S119R, and E157Q mutations who achieved suppression with dolutegravir experienced virologic rebound conferred by novel mutations, T97A and S147G. This further confirms the importance of modifying a failing regimen urgently to avoid the accumulation of mutations that may compromise therapy.

Patient-reported outcomes

Not captured in the randomized trials of dolutegravir are subjective measures of a patient's health – termed "patient-reported outcomes". A number of assessment tools have been evaluated, principally among those receiving NNRTI-or PI-based regimens, but none are sufficiently robust for widespread adoption. When these infrequently ascertained measures are assessed, as in SINGLE, dolutegravir is not inferior to tenofovir–emtricitabine–efavirenz.

Maximizing adherence to antiretroviral treatment is vital and became even more important following the recognition that multiple antiretrovirals with varying mechanisms of action were required for continual HIV suppression., Strategies to improve adherence, including reducing pill burden to simplify regimens, should translate into improved quality of life. As an added benefit, co-formulated STRs, when compared to the component antivirals taken separately, may potentially reduce the development of resistance mutations.– Furthermore, an initial highly successful regimen obviates the need to switch therapy, which may result in experiencing new side effects that negatively impact quality of life., As the initial antiretroviral regimen predicts successful long-term virologic suppression, selecting the correct therapy is critically important.

**HIV treatment today[3]**

The accepted standard of care in HIV treatment involves using a combination of three active drugs from at least two different classes. This approach has demonstrated durable viral suppression and consequent immune reconstitution, resulting in a dramatic reduction in morbidity and mortality and near-normal life expectancy. Further, an undetectable viral load prevents HIV sexual transmission, with major implications in terms of public health and individual wellbeing.

Regimen selection is based on virologic efficacy, potential for adverse effects, pill burden and dosing frequency, drug-drug interaction potential, resistance test results, comorbid conditions and cost. Given the importance of lifelong treatment adherence to maintain durable virologic suppression, fixed-dose combinations that include two or three drugs are now commonly used.

Current treatment guidelines recommend first-line regimens comprising of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus a third drug from one of three

Drug classes: integrase strand transfer inhibitors (InSTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), or protease inhibitors (PIs). The European AIDS Clinical Society (EACS) guidelines were the first to include a two-drug regimen, dolutegravir (DTG) plus lamivudine (3 TC), as a recommended first-line treatment option, though still lists two NRTI combined with an InSTI as preferred. The US Department of Health and Human Services (DHHS) followed, including DTG plus 3 TC as one of the recommended initial regimens for most people. Thus, NRTIs form the backbone of, the still largely preferred, triple ART, and first-line dual ART approaches to treatment.

Table 3. Branded and generic three-drug fixed-dose combinations (FDC) available today.

| | |
|---|---|
| **1.** | **TDF + FTC + efavirenz (branded)** |
| **2.** | TDF + 3 TC + efavirenz (generic) |
| **3.** | TAF + FTC + bictegravir (branded) |
| **4.** | TAF + FTC + darunavir + cobicistat (branded) |
| **5.** | TDF + FTC + elvitegravir + cobicistat (branded) |
| **6.** | TAF + FTC + elvitegravir + cobicistat (branded) |
| **7.** | TDF + FTC + rilpivirine (branded) |
| **8.** | TAF + FTC + rilpivirine (branded) |
| **9.** | TDF + 3 TC + dolutegravir (generic) |
| **10.** | TDF + 3 TC + doravirine (combination of brand new compound and generic backbone) |

TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, FTC = emtricitabine, 3 TC = lamivudine.

**Nucleoside reverse transcriptase class evolution[3]**

The first ARV drug for clinical use was the NRTI zidovudine (ZDV) licensed by the US FDA in 1987. The timeline for the US FDA approval of the NRTI class of drugs is depicted in . In 2001, the first nucleotide reverse transcriptase inhibitor (NtRTI), i.e. TDF was introduced. TDF has now become one of the most frequently prescribed drugs for HIV treatment. In 2009, it

was estimated that if ART had saved three million lives, tenofovir alone may be responsible for two-thirds of the three million years of life saved. TDF description is beyond the scope of this review article and its efficacy and safety profiles are extensively described in the literature.

Table 2. Current recommendations for first-line antiretroviral regimens., ,

| **EACS 2020** | **DHHS 2019** | **IAS 2018** |
|---|---|---|
| **Preferred regimens**<br>**• ABC/3TC/DTG**<br>**• (TAF/FTC or TDF/FTC or TDF/3 TC) Plus (DTG or RAL TAF/FTC/BIC**<br>**1 NRTI + 1 INSTI**<br>**3TC/DTG** | Recommended initial regimens for most people with HIV<br>• BIC/TAF/FTC<br>• DTG/ABC/3 TC<br>• DTG + (TAF or TDF) + (FTC or 3 TC)<br>• DTG + 3 TC<br>• RAL + (TAF or TDF) + (FTC or 3 TC) | Generally recommended initial regimens<br>• BIC/TAF/FTC<br>• DTG/ABC/3 TC<br>• DTG + TAF/FTC<br>Recommended Initial Regimens for Individuals for Whom Generally Recommended Regimens Are Not Available or Not an Option |
| **Alternative regimens**<br>**• ABC/3 TC + RAL**<br>**• TAF/FTC OR TDF/FTC OR TDF/3 TC + DOR OR RPV**<br>**• TDF/FTC/EVG/c**<br>**• TAF/FTC/EVG/c**<br>**• ABC/3 TC + EFV**<br>**• (TAF/FTC or TDF/FTC or TDF/3 TC) + EFV**<br>**• TDF/FTC/EFV**<br>**• ABC/3 TC + (ATV/c or ATV/r)** | Recommended initial regimens in certain clinical situations<br>• EVG/c/(TAF or TDF)/FTC<br>• (DRV/c or DRV/r) + (TAF or TDF) + (FTC or 3 TC)<br>• (ATV/c or ATV/r) + (TAF or TDF) + (FTC or 3 TC)<br>• (DRV/c or DRV/r) + | • DRV/c + TAF (or TDF)/FTC<br>• DRV/r + TAF (or TDF)/FTC<br>• EFV/TDF/FTC<br>• ELT/c/TAF (or TDF)/FTC<br>• RAL + TAF (or TDF)/FTC<br>• RPV/TAF (or TDF)/FTC |
| **ABC/3 TC + (DRV/c or DRV/r)**<br>**(TAF/FTC or TDF/FTC or** | ABC/3 TC<br>DOR/TDF/3 TC or DOR +<br>TAF/FTC | (if pretreatment HIV RNA level is < 100 000 copies/mL and CD4 cell count is > 200/μL) |

| | | |
|---|---|---|
| **TDF/3 TC) + (ATV/c or ATV/r)** | EFV + (TAF or TDF) + (FTC or 3 TC)<br>o EFV 600 mg + TDF + (FTC or 3 TC) o EFV 400 mg/TDF/3 TC<br>o EFV 600 mg + TAF/FTC<br>RPV/(TAF or TDF)/(FTC<br>DTG/3 TC<br>DRV/r + RAL bd<br>DRV/r od + 3 TC | |

EVG/c: boosted elvitegravir with cobicistat; DOR: doravirine; TAF; tenofovir alafenamide; FTC: emtricitabine; BIC: bictegravir; RAL: raltegravir; RPV: rilpivirine; EFV: efavirenz; ATV/c: boosted atazanavir with cobicistat; ATV/r: boosted atazanavir with ritonavir; ABC: abacavir; 3 TC: lamivudine; DRV/c: darunavir and cobiscistat; DRV/r: darunavir and ritonavir; DTG: dolutegravir.

Both NRTIs and NtRTIs interact with the catalytic site of the HIV reverse transcriptase enzyme. Before these drugs can interact with the substrate-binding site, they need to be phosphorylated intracellularly to the triphosphate and diphosphate forms, respectively. The phosphorylated forms then act as a competitive inhibitor/alternate substrate causing chain termination.

As new drug classes became available, the combination of two NRTI plus an agent from a different class was proven to be the optimal 'recipe' for sustained viral suppression and the two NRTI backbone established itself as the cornerstone of regimens recommended by consensus guidelines globally. Further, extensive use of potent triple regimens resulted in increased life expectancy, and the realisation that regimens needed to be friendlier – in terms of tolerability, pill burden, frequency of dosing and that co-formulations improve patient adherence.

The first two NRTI fixed-dose combination (FDC) of ZDV+ 3 TC was licensed by the US FDA in 1997. This was followed by abacavir (ABC) + 3 TC and TDF + FTC, both in 2004. Importantly, TDF + 3 TC was also approved for use by the US FDA under the President's

Emergency Programme for AIDS Relief (PEPFAR) programme in 2011, and tenofovir alafenamide (TAF) + FTC in 2016.

**Safety[3]**

Pollock et al. assessed the incidence of FTC-associated adverse events by switching 158 patients on a sable 3 TC-containing regimen to FTC, without altering any other drugs in the triple regimen. Switches were made between May 2004 and July 2005 based on patient and/or physician preferences. Overall, switch to FTC was well tolerated with no Grade 3 or 4 toxicities reported.

However, within a month of switch to FTC, 13 patients had re-initiated 3 TC. In 11 patients, this was triggered by patient-reported adverse effects, and resolution of clinical symptoms was reported by all 11 cases within 72 h of re-initiating 3 TC. This translates into a 7% incidence of intolerance to FTC in this cohort (11 out of 158). Six of the 11 cases reported Grade II central nervous system (CNS) toxicity – feeling strange or unwell. This has not been assessed in the randomised trials that predated this cohort.

Hyperpigmentation has been reported with FTC, with an overall incidence of 3.4%, usually affecting the palms of the hands or the soles of the feet. Similarly, an incidence of 3.9% has been reported by a study in 155 Japanese patients.

In pooled data from adults, aspartate transaminase (AST) increase, alanine transaminase (ALT) increase, and pneumonia have been reported as the most serious adverse effects with FTC. The majority of these were felt to be unrelated to FTC. Adverse events most frequently leading to study discontinuation were AST increase (2 versus 2.3% control), ALT increase (2% versus 2.3% control), hyperamylasaemia (0.6% versus 1.2% control) and rash (0.7% versus 0.8% control).

Finally, Venhoff et al. investigated the mitochondrial toxicity of various NRTI backbones. TDF plus 3 TC was the only combination with no additive or synergistic toxic effects, while a dose-dependent reduction in cell proliferation was observed with the TDF plus FTC combination.

Resistance

Data from the UK HIV Drug Resistance Database (HDRD) and the UK Collaborative HIV Cohort (CHIC).

Study was analysed to investigate the prevalence of genotypic resistance profiles in patients failing.

TDF, EFV and either 3 TC or FTC. The UK HDRD is a central repository of resistance tests performed as part of routine clinical care in the UK, whereas the UK CHIC Study is an observational cohort of HIV-infected individuals attending some of the largest HIV clinical centres in the UK.

The endpoints analysed were detection of K65R, M184V or both. Person-time was calculated from the start date of the regimen to detection of the mutation(s) being analysed. An event was defined as detection of a mutation, and the rate of an event (according to whether the regimen contained 3 TC or FTC) was calculated by dividing number of number of events by the person-time. FTC- based regimens (n = 5190) were used more commonly than 3 TC-based regimens (n = 1228).

The overall event rate for detection of M184V was 0.38/100 PYFU. Although patients on 3 TC were more likely to develop resistance, this was not statistically significant in univariable (OR 1.85, p = 0.09) or multivariable analyses (OR 1.89, p = 0.1). The study concluded that there was no evidence of an increased risk of development of M184V and K65R at failure of 3 TC-based, as compared to FTC-based, ART. Other studies, have shown statistically significant differences between FTC and 3 TC but these were small and retrospective.

**Pharmacokinetics[3]**

3 TC and FTC share an intracellular mode of action against HIV reverse transcriptase and are pharmacokinetically very similar. They are both cytosine analogues which are phosphorylated intracellularly to interfere with HIV viral RNA-dependent DNA polymerase resulting in inhibition of viral replication.

The main difference between the two drugs is their intracellular half-life, which is approximately 38 h for FTC triphosphate, compared with approximately 16 h for 3 TC triphosphate.

However, both drugs can be administered once daily and when co-administered with TDF are able to provide sufficient symmetry to the ARV combination, especially with third agents characterised by similarly prolonged plasma half-lives.

Finally, because renal excretion of unchanged drug is the principal route of FTC and 3 TC elimination, the potential for these drugs to cause metabolic drug interactions is low and to date, no specific drug interactions have been reported in the literature.

FTC and 3 TC in combination with TAF versus TDF

One limitation is the inability to use 3 TC in combination with TAF, since all TAF products for HIV are co-formulated with FTC. Although the International Antiviral Society-USA (IAS-

USA) guidelines express a preference for TAF over TDF, DHHS and EACS guidelines do not. Although TDF is associated with changes in renal and bone biomarkers, differences in clinical end-points seem to be largely limited to when TDF is combined with a boosted 3rd agent.' In addition, TAF is associated with a less favourable lipid profile than TDF and, although lipid difference in trials were small, they may be more pronounced and of clinical consequence in real-life populations.

**Recommendations from international guidelines[3]**

In 2012, the World Health Organisation (WHO) published a Technical Update on the pharmacological equivalence and clinical interchangeability of 3 TC and FTC. This was based on a comprehensive review that examined preclinical studies, efficacy and safety data from clinical trials, comparative data concerning the development of resistance, considerations of patent barriers, comparative cost analysis and the availability of FDCs, and concluded that the available data support the clinical and programmatic interchangeability of 3 TC and FTC.

Furthermore, the 2019 DHHS (December 2019) and EACS antiretroviral guidelines recommend that 3 TC and emtricitabine may be considered interchangeable.

NRTI backbones in current use

International guidelines, recommend the NRTI backbones illustrated in , in combination with a third agent, for initiation of ART.

Today, tenofovir-based two-NRTI backbones are the cornerstone in the treatment of HIV. Several tenofovir-based regimens are available as fixed dose combinations (FDC), of which some are branded and some generic formulations and some are composed by the mixture of the two.

Table 3. Timeline of US FDA approvals for the N(t)RTI class of antiretrovirals 10.

| **Year** | **NRTI/NtRTI** |
|---|---|
| **1987** | Zidovudine |
| **1991** | Didanosine |
| **1992** | Zalcitabine |
| **1994** | Stavudine |
| **1995** | Lamivudine |
| **1997** | “Combivir” (FDC of zidovudine 300 mg + lamivudine 300 mg) |
| **1998** | Abacavir |

| | |
|---|---|
| **2000** | Didanosine EC |
| **2001** | Tenofovir DF |
| **2003** | Emtricitabine |
| **2004** | “Epzicom” (FDC of abacavir 300 mg + lamivudine 300 mg) |
| **2004** | “Truvada” (FDC of tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg) |
| **2011** | Tenofovir 300 + Lamivudine 300 mg tablets (FDC) |
| **2016** | “Descovy” (FDC of tenofovir alafenamide 25 mg + emtricitabine 200 mg) |

A drawback to branded FDC is that they traditionally come at an increased cost. However, as more components of first-line regimens become generic, clinicians and third-party payers will need to define the true cost-benefit associated with using some generics, and the clinical relevance of taking a single pill compared to multiple pills once daily.

The availability of generic formulations has facilitated the “unbundling” of prescriptions, i.e. using individual generic formulations of the FDC to cut costs. Published evidence from the National Health Service (NHS) cohort in the UK indicates a favourable experience when the FDC of.

TDF/FTC/efavirenz was replaced with one pill of TDF/FTC plus one pill of EFV. Of 230 patients who were switched away from the single-tablet regimen between December 2016 and October 2017, 177 (77%) patients remained on TDF/FTC + EFV at December 2018. Although the increased pill burden was a significant

Concern for prescribers, this was not reflected in the attitude of patients. The authors concluded that pill burden is not a major consideration for switching stable patients.

**TDF/3 TC as a viable option**

Data from clinical studies support the efficacy ands safety of the combination of TDF + 3 TC. Further, this combination has been used extensively as per WHO guidelines in various triple combination formulations with EFV and DTG. Recently, the TDF/3TC/DOR fixed-dose combination has received EMA and US FDA approval. Within Europe, the TDF/3 TC fixed-dose combination has received marketing authorisation in different European countries.

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1. Aprilianti S, Utami AM, Suwantika AA, Zakiyah N, Azis VI. The Cost-Effectiveness of Dolutegravir in Combination with Tenofovir and Lamivudine for HIV Therapy: A Systematic Review. *Clinicoecon Outcomes Res*. 2024;16:25-34.
2. Kandel CE, Walmsley SL. Dolutegravir - a review of the pharmacology, efficacy, and safety in the treatment of HIV. *Drug Des Devel Ther*. 2015;9:3547-3555.
3. Waters L, Mehta V, Gogtay J, Boffito M. The evidence for using tenofovir disoproxil fumarate plus lamivudine as a nucleoside analogue backbone for the treatment of HIV. *J Virus Erad*. 2021;7(1):100028.

# Survey Form

**1) In routine clinical practice, how frequent testing for viral load would you recommend after initiation of ART?**

a. Monthly
b. Quarterly
c. Six monthly
d. Six monthly for 1 year, followed by yearly

**2) According to your opinion, which is/are the significant predictor/s for first line ART failure?**

a. Inadequate adherence
b. Presence of ART drug toxicities
c. WHO clinical stage 3 and stage 4
d. Drug resistance

**3) In your clinical practice how many percentage of patients are put on Fixeddose combination of Dolutegravir (DTG), Tenofovir disoproxil (TDF) and Lamivudine (3TC)?**

a. 40-50%
b. 50-60%
c. 60-70%
d. >70%

**4) In your clinical practice, which 2 NRTIs do you prefer in combination with dolutegravir (DTG) as the first line regimen for HIV patients?**

a. Tenofovir disoproxil (TDF)
b. Tenofovir alafenamide (TAF)
c. Lamivudine (3TC)
d. Abacavir (ABC)

**5) In your clinical practice, what percentage of patients attain HIV-1 RNA < 50 copies/mL with the DTG, TDF and 3TC fixed-dose combination, after a treatment period of 24 weeks?**

a. 40-50%
b. 50-60%
c. 70-80%
d. 80-90%

**6) In your clinical practice, which is the most common side effect reported with DTG, TDF and 3TC fixed-dose combination?**

a. Insomnia
b. Headache
c. Fatigue
d. Nausea

**7) In your clinical experience, which of the following can have a potential drug interaction with DTG, TDF and 3TC FDC?**

a. Rifampicin
b. Metformin
c. Oral calcium or iron supplements
d. Oral contraceptives

**8) In your clinical practice, which of the following laboratory tests is essential for monitoring patients on FDC of DTG, TDF and 3TC?**

a. Liver function tests
b. Renal function tests
c. Lipid profile
d. Blood sugar

**9) In your clinical practice, in which category of HIV patient would you prefer the ART containing FDC of DTG, TDF and 3TC?**

a. Treatment naïve patients
b. Treatment experienced patients

**10) In which regimen will you use Dolutegravir in the treatment of HIV?**

a. First line regimen
b. Second line regimen
c. Third line regimen

**11) Which of the following drug combinations is commonly used as first-line therapy for HIV-1 infection?**

a. Abacavir + Lamivudine + DTG
b. Tenofovir disoproxil + Lamivudine + Efavirenz
c. Lamivudine + Dolutegravir
d. Dolutegravir + Tenofovir Disoproxil fumarate + Lamivudine

**12) According to your expert opinion, what are the advantages of Dolutegravir in your clinical practice**

a. High rates of viral suppression, low rates of treatment discontinuation
b. Rare severe side effects
c. Low rates of drug-drug interactions

**13) According to your opinion, which of the following parameters need to be checked while assessing treatment adherence to FDC of Dolutegravir + Lamivudine + Tenofovir Disoproxil Fumarate?**

a. Number of doses missed since last visit
b. Whether doses are taken at correct time interval
c. Timings and dose of concurrent medications

**14) How much is the compliance to treatment with FDC of Dolutegravir, Tenofovir disoproxil fumarate, Lamivudine tablets in your clinical practice?**

a. 60-70%
b. 70-80%
c. 80-90%
d. 90-100%

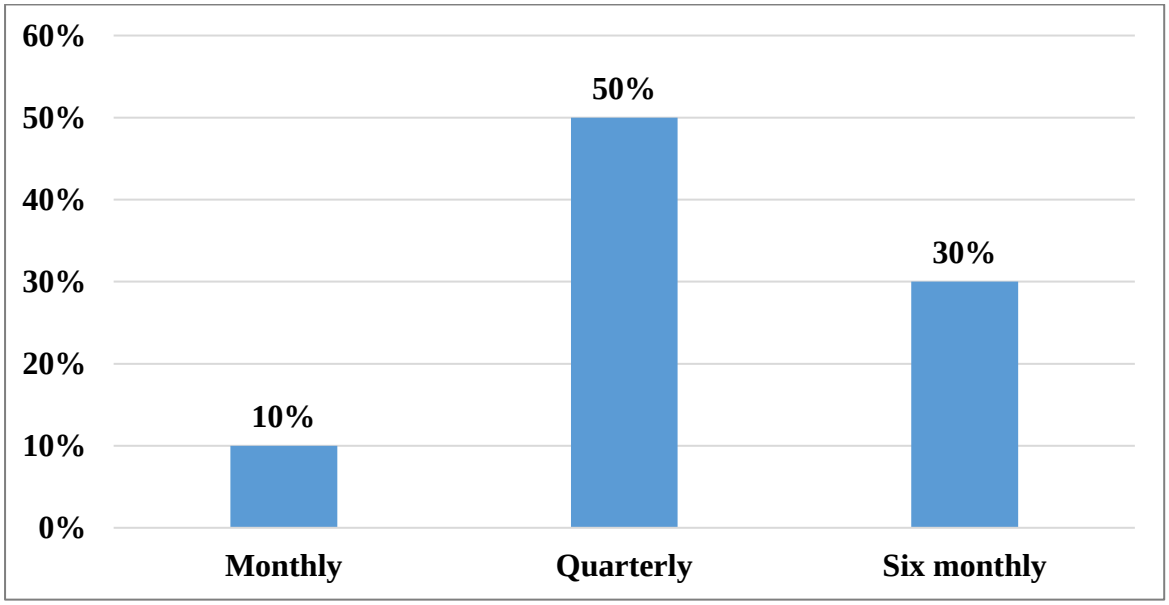
**15) In your opinion, how do you rate the efficacy of FDC of Dolutegravir, Tenofovir disoproxil fumarate, Lamivudine tablets for the patients with HIV as ART treatment?**

a. Excellent
b. Good
c. Average
**d.** Poor

# Survey Findings

**1) In routine clinical practice, how frequent testing for viral load would you recommend after initiation of ART?**

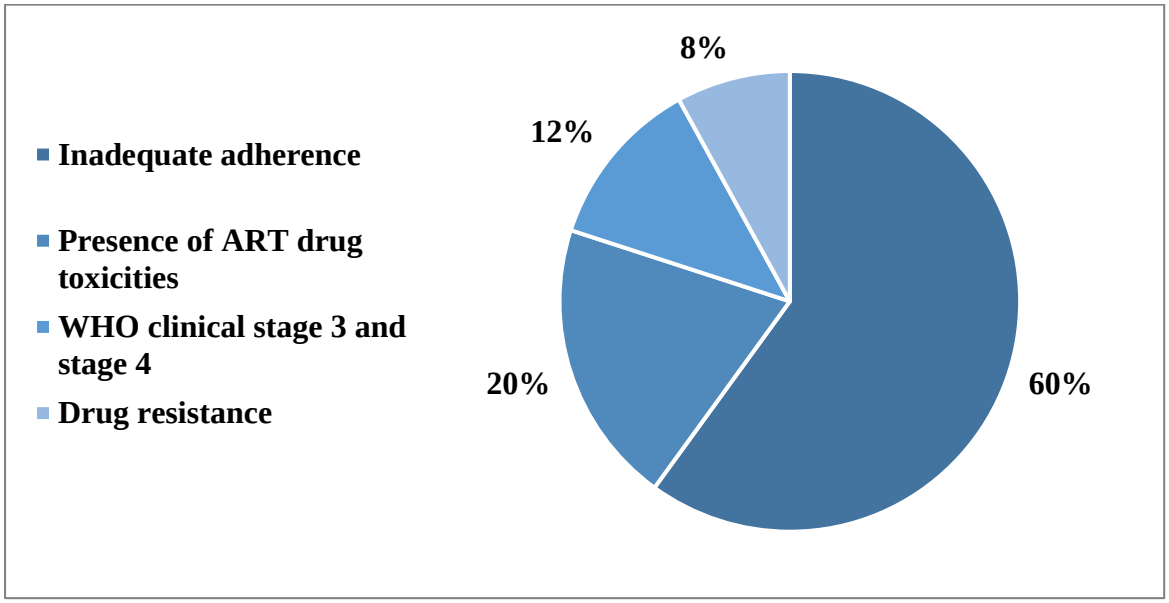
a. Monthly
b. Quarterly
c. Six monthly
d. Six monthly for 1 year, followed by yearly




According to 50% of doctors, they would recommend quarterly testing for viral load after initiation of ART.

**2) According to your opinion, which is/are the significant predictor/s for first line ART failure?**

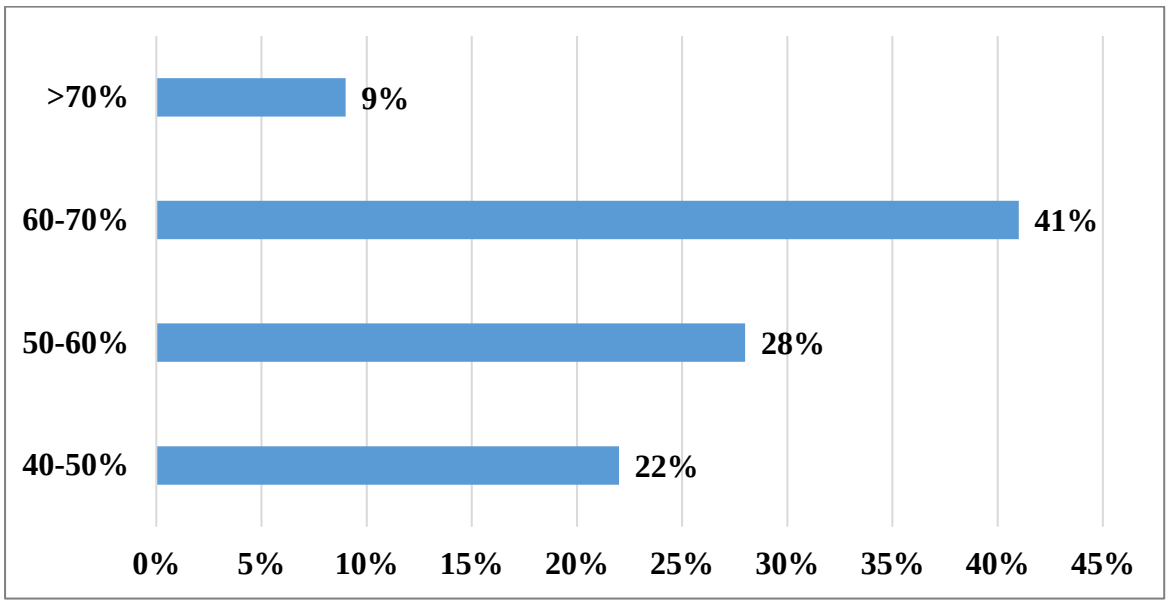
a. Inadequate adherence
b. Presence of ART drug toxicities
c. WHO clinical stage 3 and stage 4
d. Drug resistance




In the opinion of 60% of doctors, inadequate adherence is the significant predictor/s for first line ART failure.

**3) In your clinical practice how many percentages of patients are put on Fixeddose combination of Dolutegravir (DTG), Tenofovir disoproxil (TDF) and Lamivudine (3TC)?**

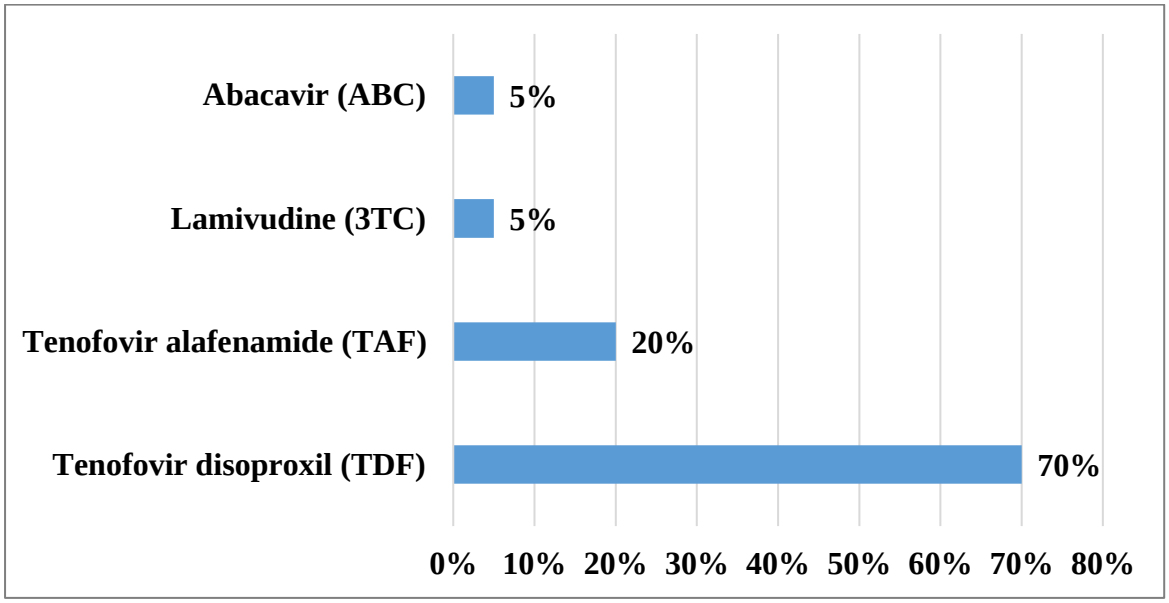
a. 40-50%
b. 50-60%
c. 60-70%
d. >70%




According to 41% of doctors, 60-70% of patients are put on Fixeddose combination of Dolutegravir (DTG), Tenofovir disoproxil (TDF) and Lamivudine (3TC).

**4) In your clinical practice, which 2 NRTIs do you prefer in combination with dolutegravir (DTG) as the first line regimen for HIV patients?**

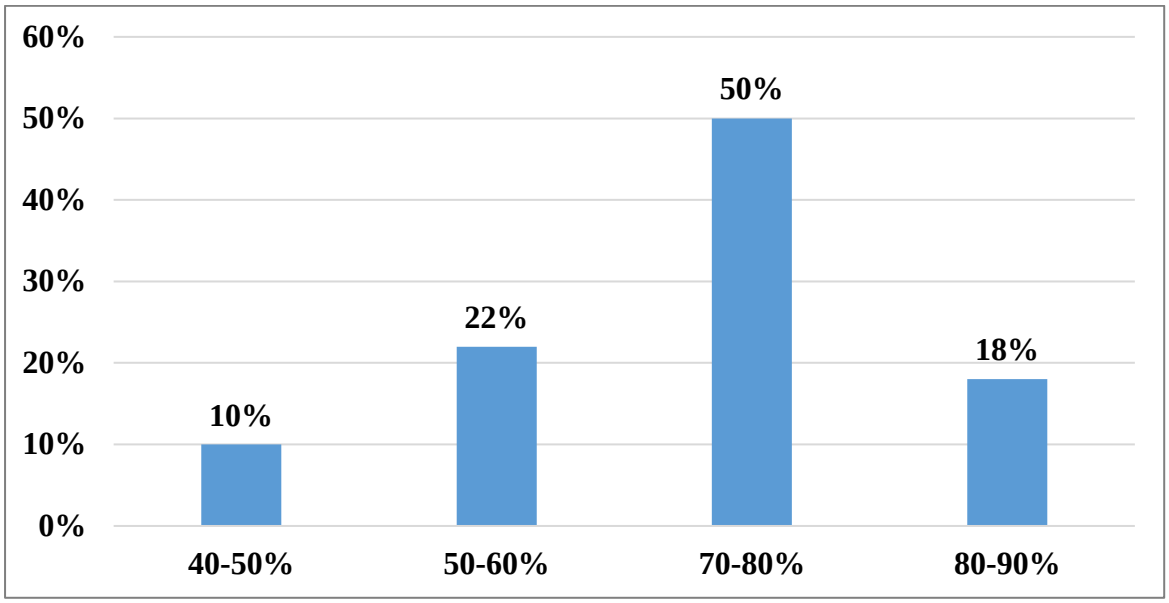
a. Tenofovir disoproxil (TDF)
b. Tenofovir alafenamide (TAF)
c. Lamivudine (3TC)
d. Abacavir (ABC)




Majority of doctors (70%) prefer Tenofovir disoproxil (TDF) in combination with dolutegravir (DTG) as the first line regimen for HIV patients.

**5) In your clinical practice, what percentage of patients attain HIV-1 RNA < 50 copies/mL with the DTG, TDF and 3TC fixed-dose combination, after a treatment period of 24 weeks?**

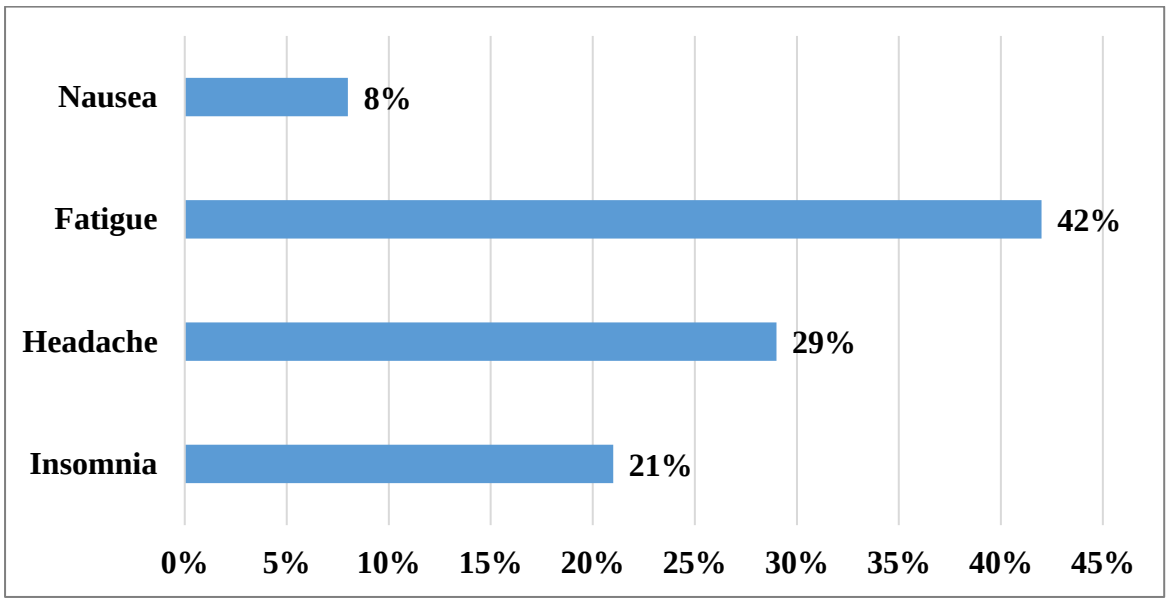
a. 40-50%
b. 50-60%
c. 70-80%
d. 80-90%




According to 50% of doctors, 70-80% of patients attain HIV-1 RNA < 50 copies/mL with the DTG, TDF and 3TC fixed-dose combination, after a treatment period of 24 weeks.

**6) In your clinical practice, which is the most common side effect reported with DTG, TDF and 3TC fixed-dose combination?**

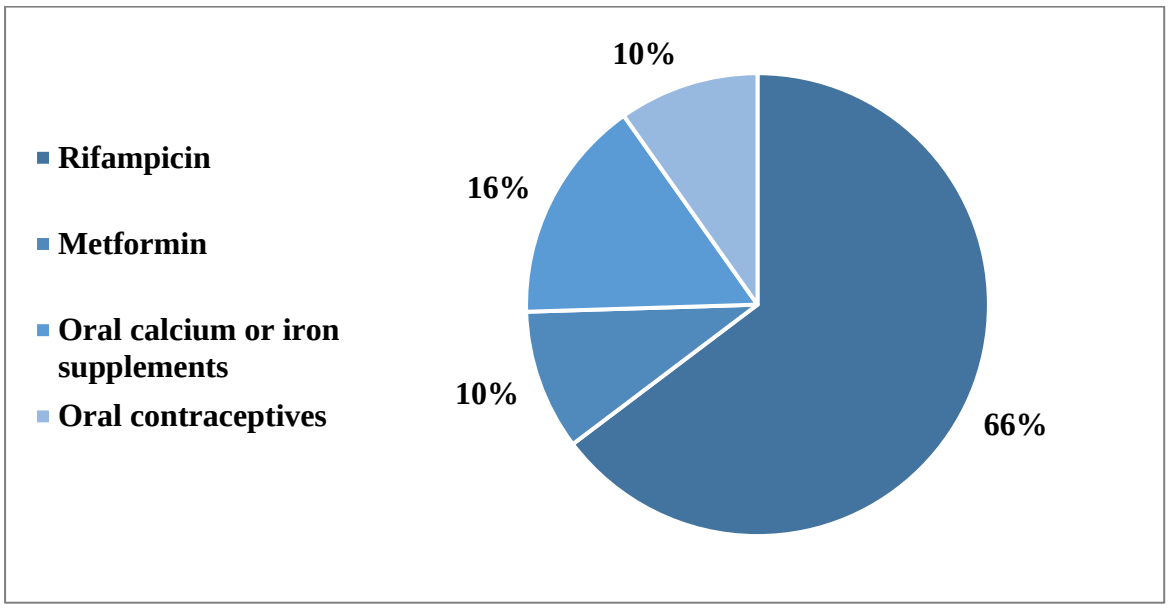
a. Insomnia
b. Headache
c. Fatigue
d. Nausea




42% of doctors consider fatigue to be the most common side effect reported with DTG, TDF and 3TC fixed-dose combination.

**7) In your clinical experience, which of the following can have a potential drug interaction with DTG, TDF and 3TC FDC?**

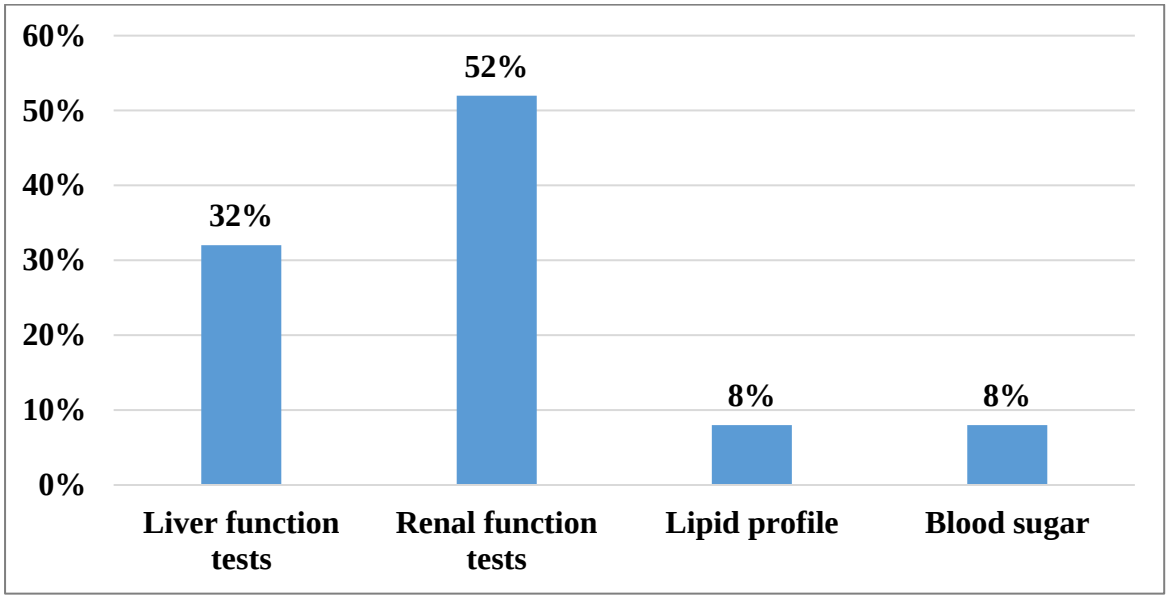
a. Rifampicin
b. Metformin
c. Oral calcium or iron supplements
d. Oral contraceptives




According to 66% of doctors, Rifampicin can have a potential drug interaction with DTG, TDF and 3TC FDC.

**8) In your clinical practice, which of the following laboratory tests is essential for monitoring patients on FDC of DTG, TDF and 3TC?**

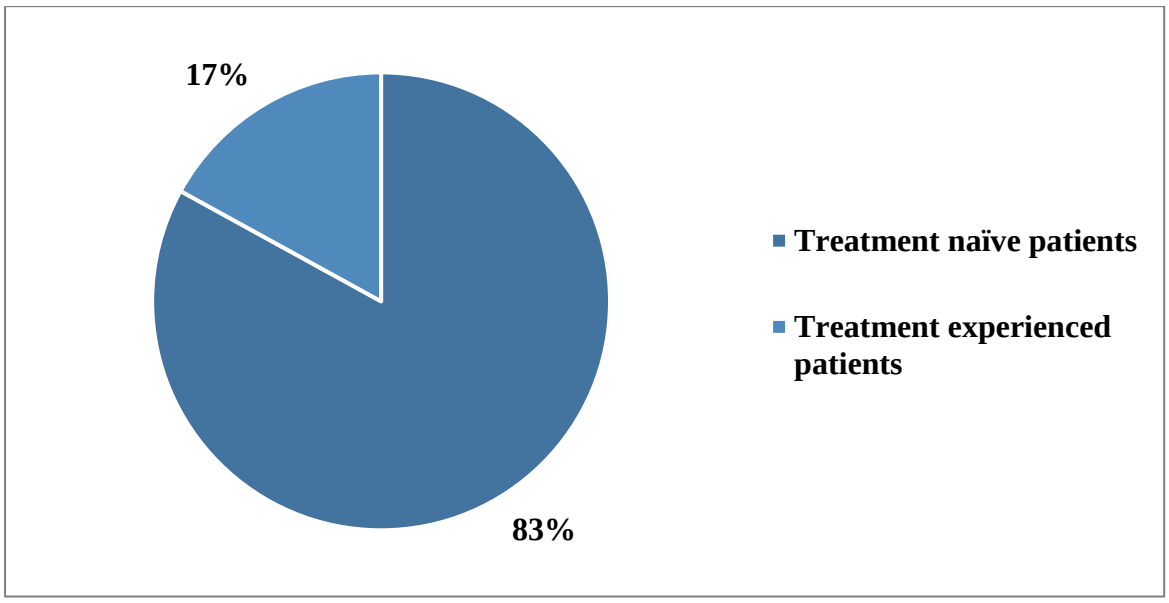
a. Liver function tests
b. Renal function tests
c. Lipid profile
d. Blood sugar




As per 52% of doctors, renal function test is essential for monitoring patients on FDC of DTG, TDF and 3TC.

**9) In your clinical practice, in which category of HIV patient would you prefer the ART containing FDC of DTG, TDF and 3TC?**

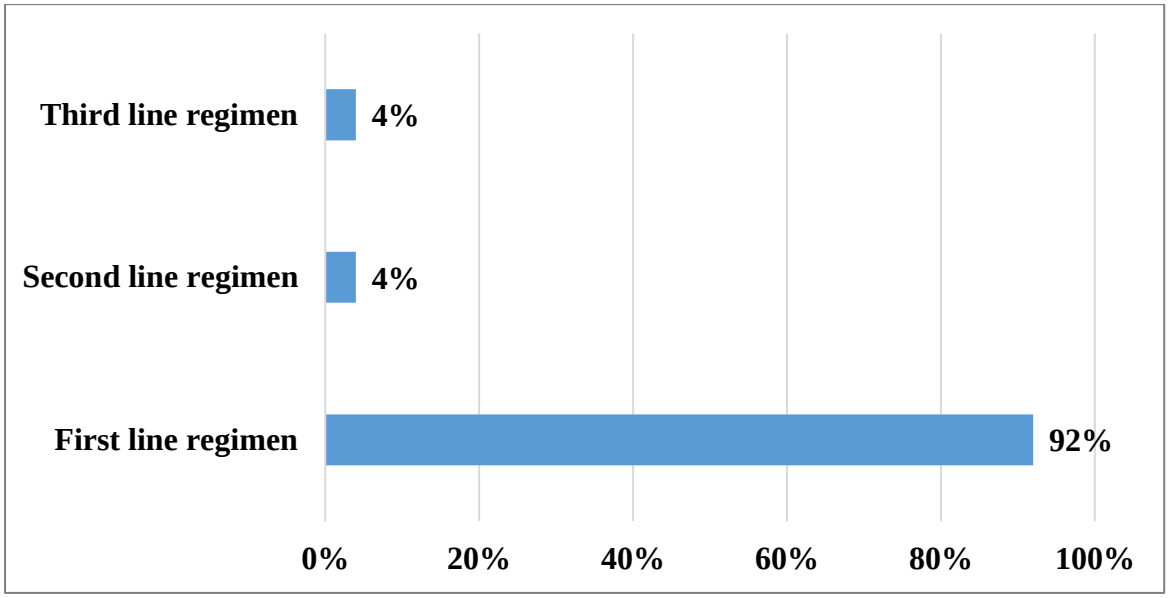
a. Treatment naïve patients
b. Treatment experienced patients




Majority of doctors, 83%, would prefer the ART containing FDC of DTG, TDF and 3TC in the category of treatment naïve HIV patients.

**10) In which regimen will you use Dolutegravir in the treatment of HIV?**

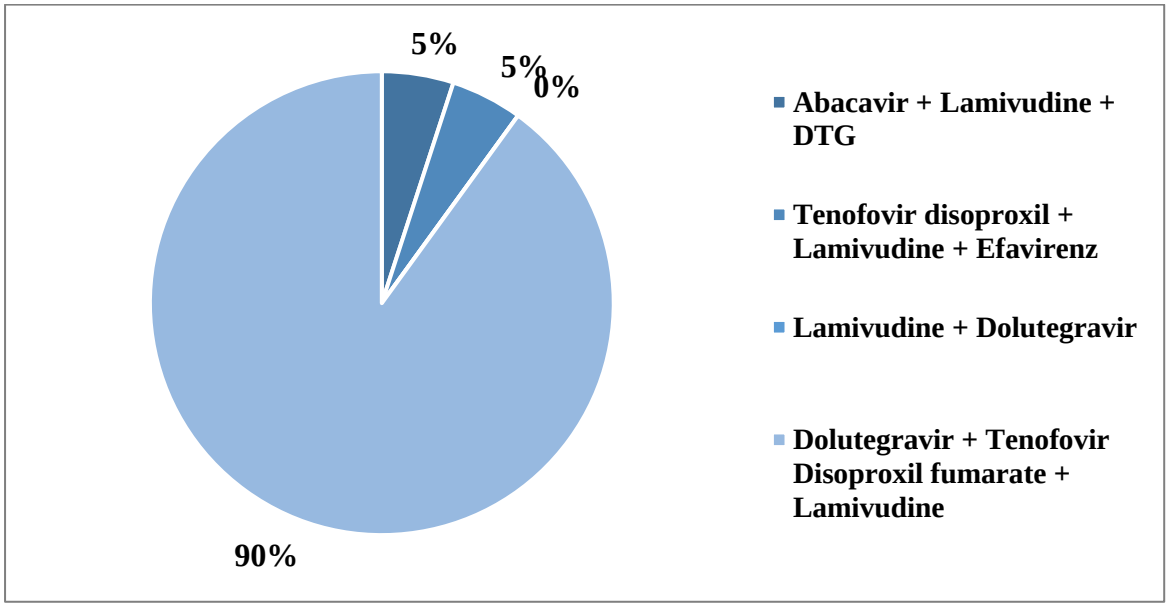
a. First line regimen
b. Second line regimen
c. Third line regimen




Majority of doctors, 92%, will use Dolutegravir in first line regimen in the treatment of HIV.

**11) Which of the following drug combinations is commonly used as first-line therapy for HIV-1 infection?**

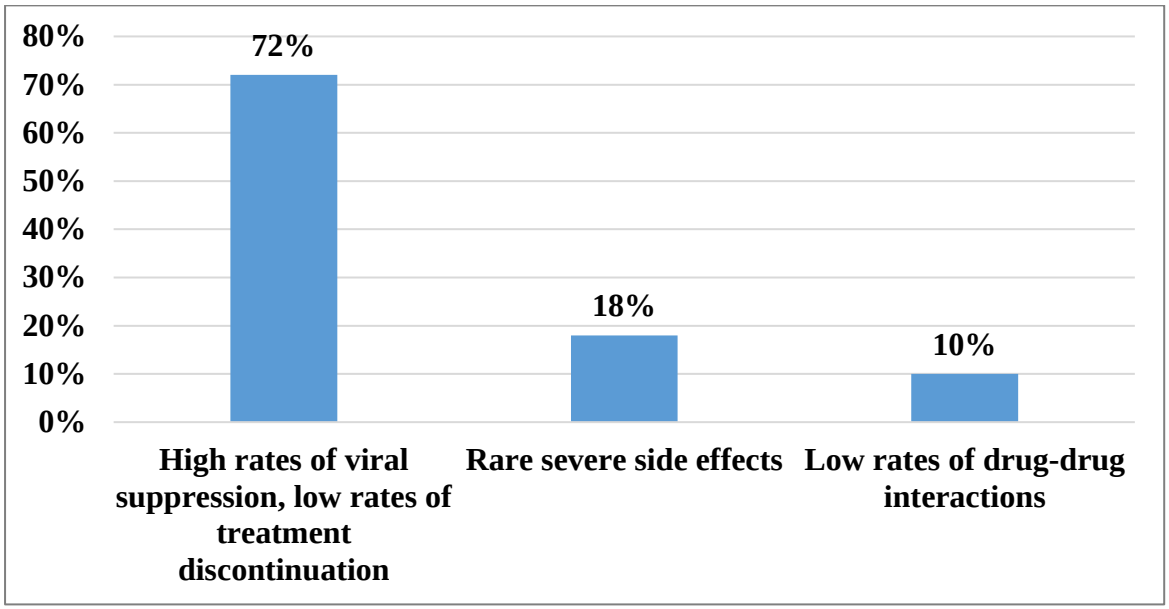
a. Abacavir + Lamivudine + DTG
b. Tenofovir disoproxil + Lamivudine + Efavirenz
c. Lamivudine + Dolutegravir
d. Dolutegravir + Tenofovir Disoproxil fumarate + Lamivudine




According to majority of doctors, 90%, Dolutegravir + Tenofovir Disoproxil fumarate + Lamivudine drug combinations is commonly used as first-line therapy for HIV-1 infection.

**12) According to your expert opinion, what are the advantages of Dolutegravir in your clinical practice**

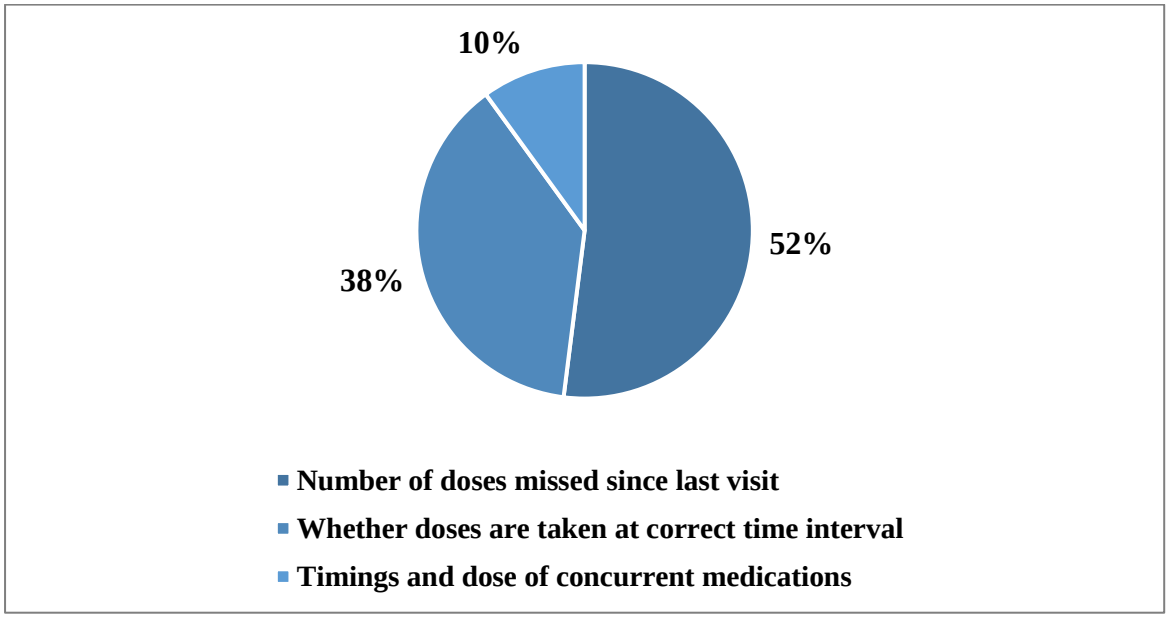
a. High rates of viral suppression, low rates of treatment discontinuation
b. Rare severe side effects
c. Low rates of drug-drug interactions




As per 72% of doctors, the advantages of Dolutegravir in their clinical practice is high rates of viral suppression, low rates of treatment discontinuation.

**13) According to your opinion, which of the following parameters need to be checked while assessing treatment adherence to FDC of Dolutegravir + Lamivudine + Tenofovir Disoproxil Fumarate?**

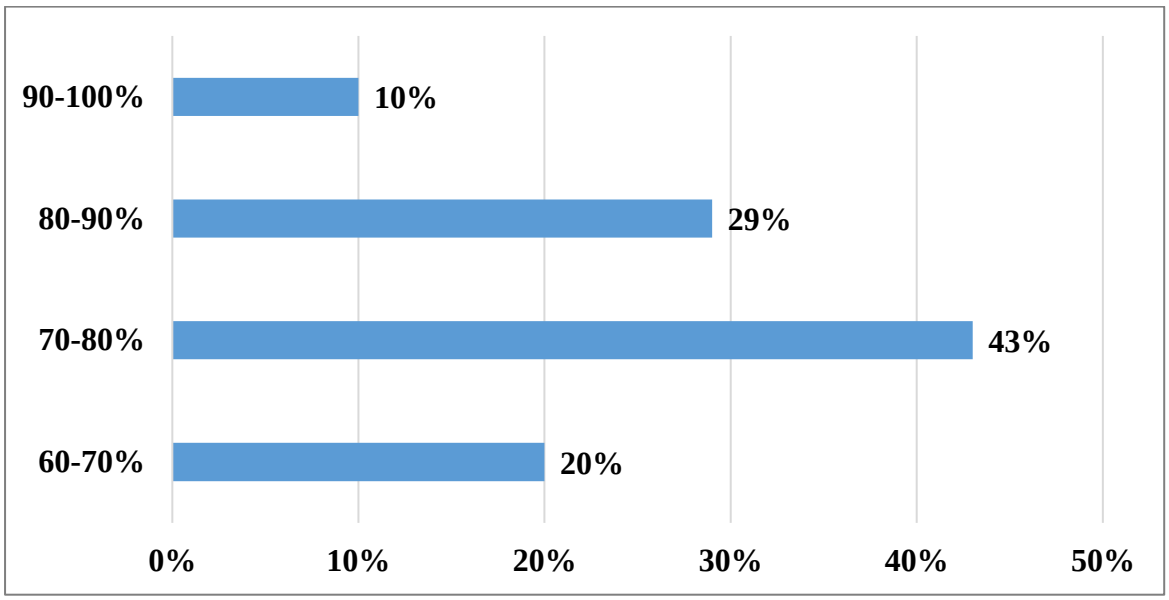
a. Number of doses missed since last visit
b. Whether doses are taken at correct time interval
c. Timings and dose of concurrent medications




In the opinion of 52% of doctors, the parameter of number of doses missed since last visit need to be checked while assessing treatment adherence to FDC of Dolutegravir + Lamivudine + Tenofovir Disoproxil Fumarate.

**14) How much is the compliance to treatment with FDC of Dolutegravir, Tenofovir disoproxil fumarate, Lamivudine tablets in your clinical practice?**

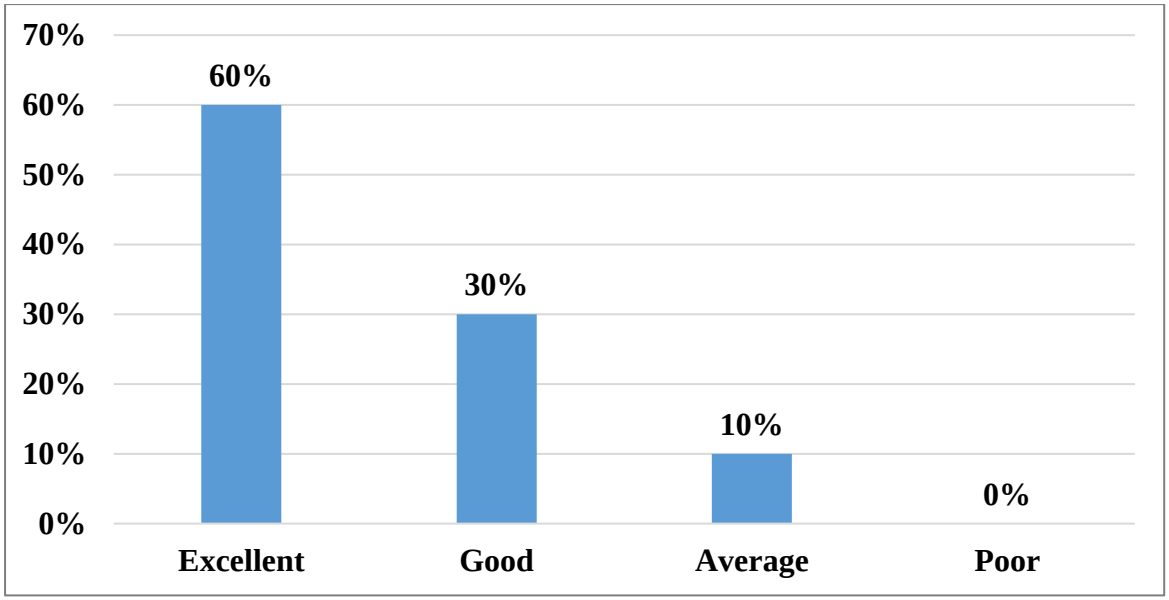
a. 60-70%
b. 70-80%
c. 80-90%
d. 90-100%




As per 43% of doctors, the compliance to treatment with FDC of Dolutegravir, Tenofovir disoproxil fumarate, Lamivudine tablets is 70-80%.

**15) In your opinion, how do you rate the efficacy of FDC of Dolutegravir, Tenofovir disoproxil fumarate, Lamivudine tablets for the patients with HIV as ART treatment?**

a. Excellent
b. Good
c. Average
d. Poor




60% of doctors rate the efficacy of FDC of Dolutegravir, Tenofovir disoproxil fumarate, Lamivudine tablets for the patients with HIV as ART treatment as excellent.

# Summary

- According to 50% of doctors, they would recommend quarterly testing for viral load after initiation of ART.
- In the opinion of 60% of doctors, inadequate adherence is the significant predictor/s for first line ART failure.
- According to 41% of doctors, 60-70% of patients are put on Fixeddose combination of Dolutegravir (DTG), Tenofovir disoproxil (TDF) and Lamivudine (3TC).
- Majority of doctors (70%) prefer Tenofovir disoproxil (TDF) in combination with dolutegravir (DTG) as the first line regimen for HIV patients.
- According to 50% of doctors, 70-80% of patients attain HIV-1 RNA < 50 copies/mL with the DTG, TDF and 3TC fixed-dose combination, after a treatment period of 24 weeks.
- 42% of doctors consider fatigue to be the most common side effect reported with DTG, TDF and 3TC fixed-dose combination.
- According to 66% of doctors, Rifampicin can have a potential drug interaction with DTG, TDF and 3TC FDC.
- As per 52% of doctors, renal function test is essential for monitoring patients on FDC of DTG, TDF and 3TC.
- Majority of doctors, 83%, would prefer the ART containing FDC of DTG, TDF and 3TC in the category of treatment naïve HIV patients.
- Majority of doctors, 92%, will use Dolutegravir in first line regimen in the treatment of HIV.
- According to majority of doctors, 90%, Dolutegravir + Tenofovir Disoproxil fumarate + Lamivudine drug combinations is commonly used as first-line therapy for HIV-1 infection.
- As per 72% of doctors, the advantages of Dolutegravir in their clinical practice is high rates of viral suppression, low rates of treatment discontinuation.
- In the opinion of 52% of doctors, the parameter of number of doses missed since last visit need to be checked while assessing treatment adherence to FDC of Dolutegravir + Lamivudine + Tenofovir Disoproxil Fumarate.

- As per 43% of doctors, the compliance to treatment with FDC of Dolutegravir, Tenofovir disoproxil fumarate, Lamivudine tablets is 70-80%.
- 60% of doctors rate the efficacy of FDC of Dolutegravir, Tenofovir disoproxil fumarate, Lamivudine tablets for the patients with HIV as ART treatment as excellent.

# Consultant Opinion

Market Opportunities:

There is a market opportunity for pharmaceutical companies to develop and promote fixed-dose combinations (FDCs) of antiretroviral therapy (ART) that are highly effective, well-tolerated, and convenient to administer. Products that offer simplified dosing regimens and minimal side effects could address unmet needs in HIV treatment and improve patient adherence and outcomes.

Value for Healthcare Professionals:

Healthcare professionals should receive education and training on the latest guidelines and recommendations for HIV treatment, including the use of FDCs containing dolutegravir, tenofovir disoproxil fumarate, and lamivudine as first-line therapy. Training programs can help providers stay informed about emerging treatment options and best practices in managing HIV.

Adverse Effect Management:

Healthcare providers should be aware of potential drug interactions and side effects associated with ART, particularly FDCs containing dolutegravir, tenofovir disoproxil fumarate, and lamivudine. Regular monitoring of patients' renal function and adherence to treatment guidelines can help mitigate risks and optimize patient safety.

Withdrawal Management:

Clear guidelines should be established for monitoring patients' viral load and treatment adherence during ART, including recommendations for routine testing intervals and assessment parameters. Standardized protocols can help healthcare providers identify and address treatment failure or non-adherence promptly to prevent disease progression and development of drug resistance.

Market Positioning:

Pharmaceutical companies should position FDCs containing dolutegravir, tenofovir disoproxil fumarate, and lamivudine as preferred first-line therapy options for treatment-naive HIV patients. Marketing strategies should emphasize the high rates of viral suppression, low rates of treatment discontinuation, and overall efficacy of these combinations to differentiate them from other ART regimens.

Personalized Treatment Decisions:

Treatment decisions should be tailored to each patient's individual needs, preferences, and comorbidities. Healthcare providers should assess factors such as renal function, drug interactions, and treatment adherence when selecting the most appropriate ART regimen for their patients with HIV.

Improving Patient Outcomes:

Patient education and support are essential for optimizing outcomes in HIV treatment. Healthcare providers should engage patients in shared decision-making, provide comprehensive counseling on treatment goals and expectations, and offer ongoing support to promote adherence and self-management. Additionally, access to support services, such as adherence counseling and peer support groups, can help patients navigate the challenges of living with HIV and maintain optimal health.

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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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