Survey Report

Role of Darunavir-Ritonavir (600 mg - 100 mg) in the treatment of HIV

Version No.: 1.1

The study was conducted according to the approved protocol and in compliance with the protocol, Good Clinical Practice (GCP), and other applicable local regulatory requirements.

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INTRODUCTION

Human immunodeficiency virus (HIV) infection most likely spread randomly from non-human primates to humans during the 1900s [1]. Within two years of the initial report known to us was a acquired immune deficiency syndrome (AIDS) from where scientists isolated the causal virus HIV. HIV has infected more than 75 million individuals worldwide, with an estimated 37 million currently infected. HIV infection is one of the leading causes of illness and mortality globally [2]. HIV's primary target is CD4+ T cells. Following a transmission event, HIV enters the mucosal tissues and spreads to the lymphoid organs within a few days [3]. The virus becomes detected in the blood on day 10 and then spreads exponentially over the next few weeks, frequently peaking around day 30, when HIV antibody levels become detectable. The immune system eventually obtains some degree of control and establishes a set point in which the level of HIV replication remains relatively steady, typically for years [4].

Antiretroviral therapy (ART) has been used to treat HIV infection for nearly 20 years. When administered correctly, ART is extremely effective—totally or nearly entirely suppressing HIV replication, boosting immunological function, and significantly lowering the chance of getting AIDS. However, ART is not curative; if medications are discontinued, the virus nearly often recovers within weeks [5]. Darunavir, in combination with ritonavir (600mg/100mg), is an important regimen in the treatment of HIV-1 infection, particularly in treatment-experienced patients. Darunavir is an HIV-1 protease inhibitor that works by blocking the enzyme necessary for viral replication [6]. Orally administered DRV/r 600/100 mg twice daily is rapidly absorbed, reaching peak plasma concentrations within 2.5 to 4 hours [7]. Studies have shown that darunavir/ritonavir, when used as part of an optimized antiretroviral therapy regimen, effectively reduces viral load and helps manage HIV infection in treatment-experienced patients [8]. The absolute oral bioavailability of one single 600 mg dose of darunavir alone and with 100 mg of ritonavir twice a day was 37% and 82%, respectively. Exposure to darunavir in boosted patients is 11 times higher than in unboosted patients [9]. Darunavir-ritonavir (600mg-100 mg) combination is very effective in the management of HIV.

This study aimed to provide a comprehensive overview of antiretroviral strategies to prevent HIV infection among the Indian population. This questionnaire emphasizes

the choice of agents, dosing regimens, and management of complications. By elucidating patterns of practice, areas of consensus, and variations in approach, this research seeks to inform evidence-based guidelines tailored to the Indian context.

RATIONALE OF THE STUDY

The need for this study arose from a significant knowledge gap in the prevention of HIV among the Indian population. The rationale was to gather comprehensive insights into the clinical use and dosage regimen of darunavir-ritonavir (600 mg - 100 mg) for HIV prevention in Indian patients. By understanding prescribing patterns, prevalence, impact, preferred dose, frequency, and perceived efficacy among physicians, the study aimed to optimize therapeutic strategies and improve patient outcomes.

The purpose of the study was to evaluate the role of darunavir-ritonavir (600 mg - 100 mg dose) in Indian patients dealing with HIV. The investigation sought to assess its preferred dose, enhance patient compliance, and determine its long-term safety profile.

STUDY OBJECTIVE

The study aimed to evaluate and characterize the current antiretroviral therapies and preferences among HIV patients in India, focusing on the choice of agents, dosing strategies, and management of complications across diverse patient populations.

METHODS

This study was designed as a cross-sectional, questionnaire-based investigation targeting Indian physicians who manage patients with HIV infection. The primary objective was to explore physicians' clinical experience, prescribing practices, and perceptions regarding darunavir-ritonavir use in Indian patients with AIDS.

Physicians were identified and invited to participate through professional networks and medical associations. Prior to participation, detailed information about the study was provided to ensure informed consent. An electronic survey comprising 15 questions was administered to capture data on physicians’ experiences and views

concerning darunavir-ritonavir. The survey was designed to be convenient and accessible, enhancing participant engagement. The responses were collected electronically and stored securely to ensure confidentiality. Data analysis involved both descriptive and inferential statistics. Descriptive statistics summarized the demographic characteristics of the participants and the frequency of their responses. Inferential statistics, including chi-square tests and logistic regression, were employed to examine potential associations between physician characteristics and their perceptions and prescribing behaviors.

The target sample size was 70 physicians, chosen to provide a representative sample for meaningful statistical analysis. Ethical considerations were strictly adhered to, following the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from an Independent Ethics Committee. Participants were assured of their right to withdraw from the study at any time without facing any negative consequences. All responses were anonymized to uphold participant confidentiality. The findings were compiled into a comprehensive report, which was intended for dissemination through scientific publications and/or presentations at relevant conferences, if deemed appropriate. This approach ensured a thorough evaluation of the study's objectives and the effective communication of its results.

RESULTS

A total of 70 HCPs participated in the survey. Below is the summary of the responses.

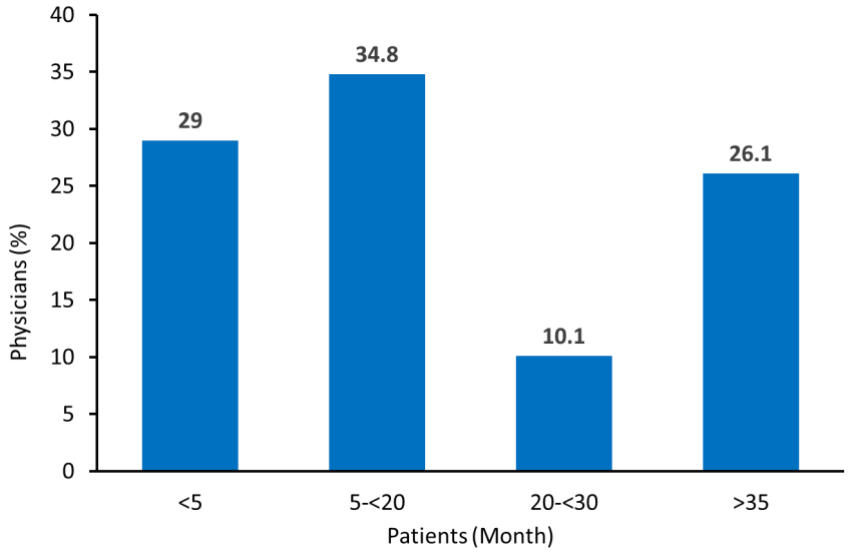
Question 1: In your clinical practice, how many newly diagnosed patients with HIV present with opportunistic infections in a month?

A) <5

B) 5 - <20

C) 20 - <30

D) ≥ 35



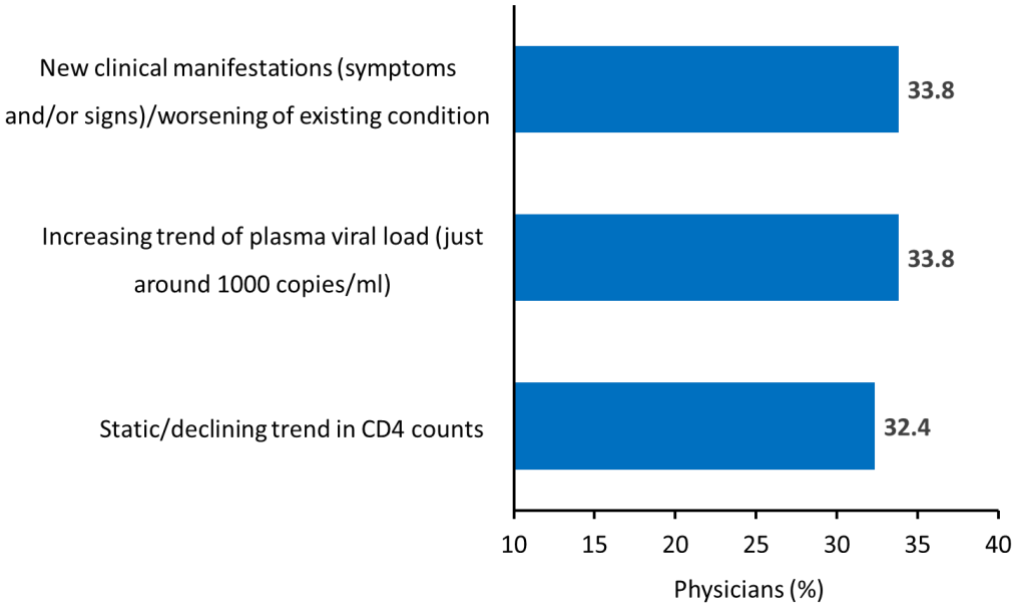
- About 34.8% of the physicians observed that five to fewer than 20 newly diagnosed patients with HIV presented with opportunistic infections in a month during their clinical practice.
- Approximately 29% of physicians observed fewer than five newly diagnosed patients with HIV presenting with opportunistic infections in a month during their clinical practice.
- About 26.1% of physicians observed 35 or more newly diagnosed HIV patients with opportunistic infections monthly. Only, 10.1% of physicians noted that 20 to fewer than 30 newly diagnosed HIV patients presented with opportunistic infections each month.

Question 2: According to NACO, treatment failure to the current regimen is suspected whenever a patient is found to have _____.

A) Increasing trend of plasma viral load (just around 1000 copies/m

B) Static/declining trend in CD4 counts

C) New clinical manifestations (symptoms and/or signs)/worsening of existing condition



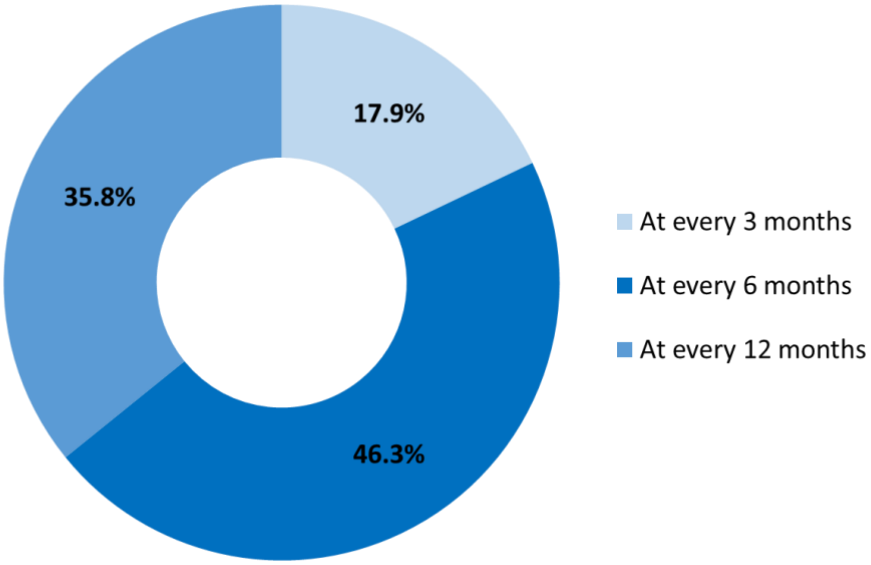
- About 33.8% of physicians observed that, according to NACO guidelines, treatment failure of the current regimen was suspected whenever a patient had an increasing trend in plasma viral load, even if it was around 1000 copies/ml.
- Similarly, 33.8% of physicians observed that, according to NACO guidelines, treatment failure was suspected whenever a patient developed new clinical manifestations (symptoms and/or signs) or experienced worsening of an existing condition.
- Meanwhile, 32.4% of physicians observed that, according to NACO guidelines, treatment failure was suspected whenever a patient had a static or declining trend in CD4 counts.

Question 3: In your clinical practice, what is the frequency of plasma viral load testing for patients on second/third-line ART?

A) At every 3 months 17.9%

B) At every 6 months 46.3%

C) At every 12 months 35.8%



- About 46.3% of physicians observed that plasma viral load testing for patients on second/third-line ART was performed in every 6 months in their clinical practice.
- Meanwhile, 35.8% of physicians observed that plasma viral load testing for these patients was conducted in every 12 months.
- Approximately 17.9% of physicians observed that plasma viral load testing was performed in every 3 months in their clinical practice.

Question 4: According to your expert opinion, rational sequencing of drugs for the antiretroviral treatment in HIV is to _____ .

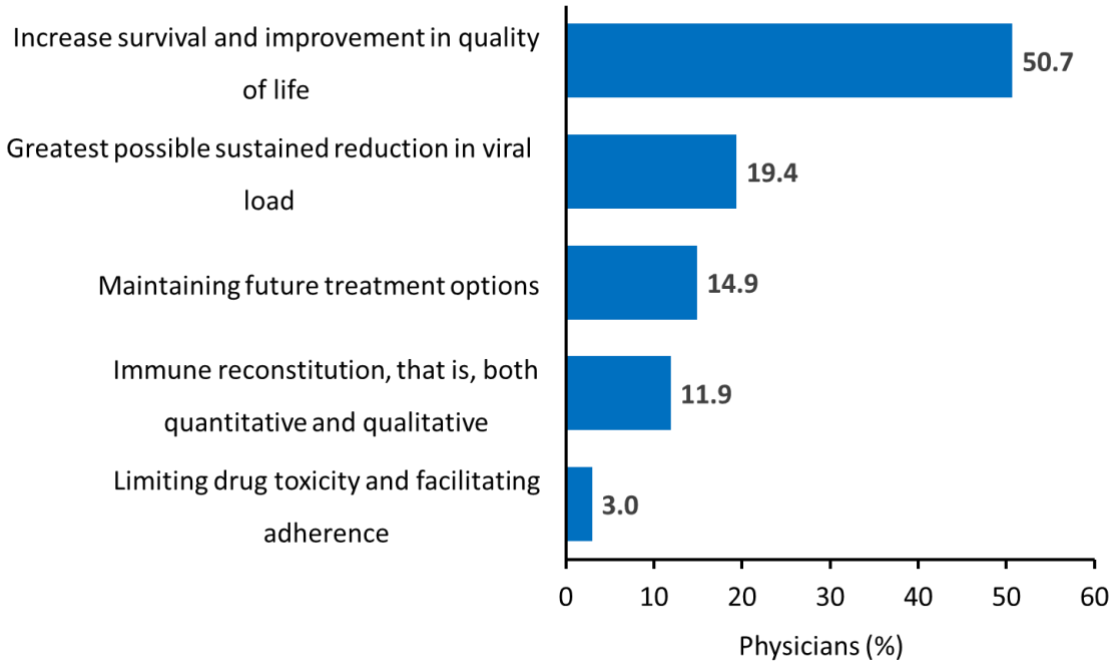
A) Increase survival and improvement in quality of life 50.7%

B) Greatest possible sustained reduction in viral load 19.4%

C) Immune reconstitution, that is, both quantitative and qualitative 11.9%

D) Maintaining future treatment options 14.9%

E) Limiting drug toxicity and facilitating adherence 3.0%



- The majority of physicians (50.7%) believed that the primary goal of rational drug sequencing for antiretroviral treatment in HIV was to increase survival and improve quality of life.
- About 19.4% of physicians felt that the greatest possible sustained reduction in viral load was the key objective.
- Following this, 14.9% of physicians prioritized maintaining future treatment options, 11.9% focused on immune reconstitution (both quantitative and qualitative), and only 3% emphasized limiting drug toxicity and facilitating adherence.

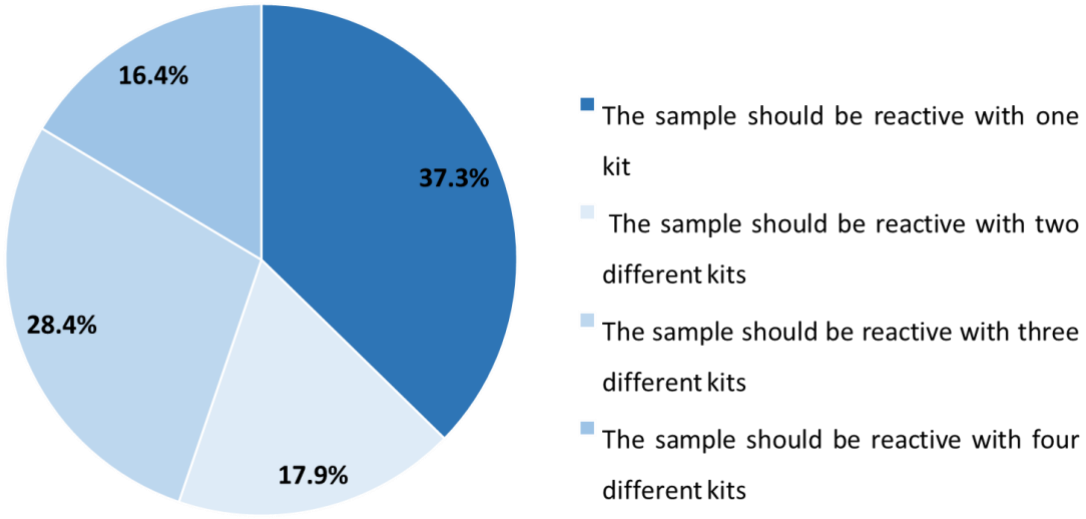
Question 5: According to NACO, in clinically symptomatic individuals, for the HIV testing and diagnosis in adults and children above the age of 18 months, _____.

A) The sample should be reactive with one kit

B) The sample should be reactive with two different kits

C) The sample should be reactive with three different kits

D) The sample should be reactive with four different kits



- According to NACO guidelines for HIV testing and diagnosis in clinically symptomatic individuals aged 18 months and older, specific criteria for confirming HIV status involve test reactivity.
- About 37.3% of physicians adhered to the guideline that the sample should be reactive with one kit.
- Meanwhile, 28.4% of physicians followed the guideline that the sample should be reactive with three different kits.
- Approximately 17.9% of physicians adhered to the guideline that the sample should be reactive with two different kits.
- Only 16.4% of physicians followed the guideline that the sample should be reactive with four different kits.

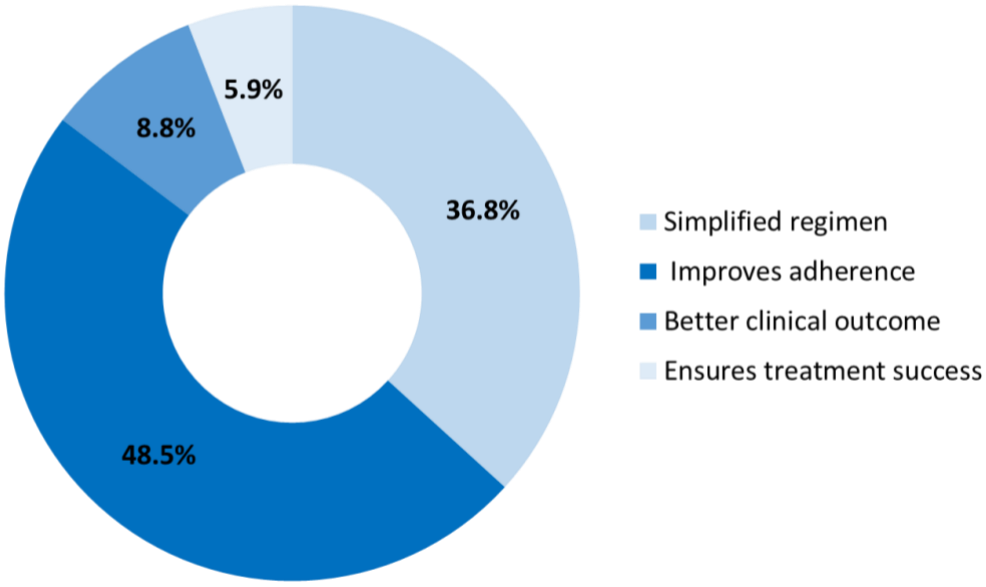
Question 6: In your opinion, what are the benefits of fixed dose combination drugs like DRV/r?

A) Simplified regimen

B) Improves adherence

C) Better clinical outcome

D) Ensures treatment success

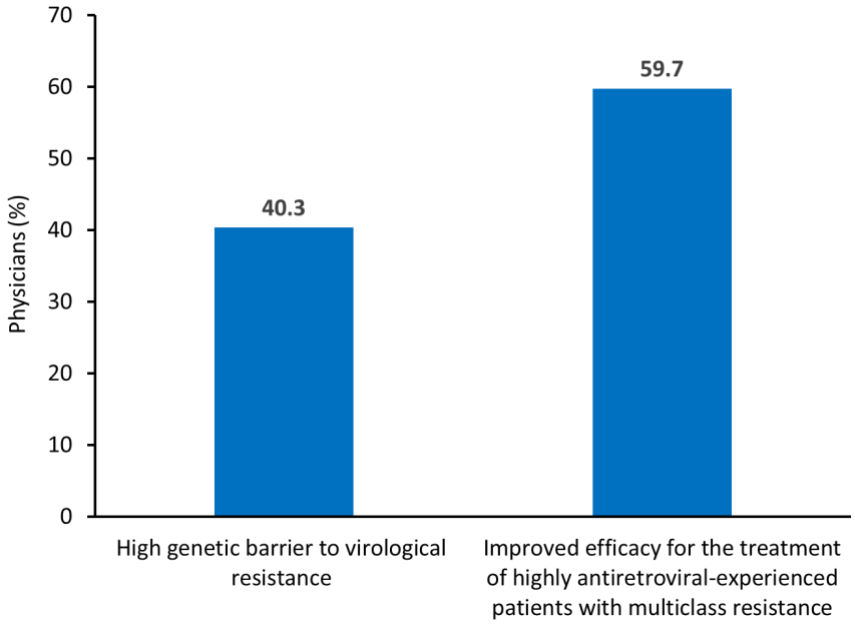


- Around 48.5% of physicians considered improved adherence as the primary benefit of fixed-dose combination drugs like DRV/r.
- About 36.8% of physicians viewed simplified regimens as the main advantage of these drugs.
- Meanwhile, 8.8% of physicians believed that better clinical outcomes were the key benefit.
- Only 5.9% of physicians thought that ensuring treatment success was the primary benefit of fixed-dose combination drugs like DRV/r.

Question 7: As per your expert view, Darunavir is preferred treatment option over other protease inhibitors because of _____ .

A) High genetic barrier to virological resistance

B) Improved efficacy for the treatment of highly antiretroviral-experienced patients with multiclass resistance

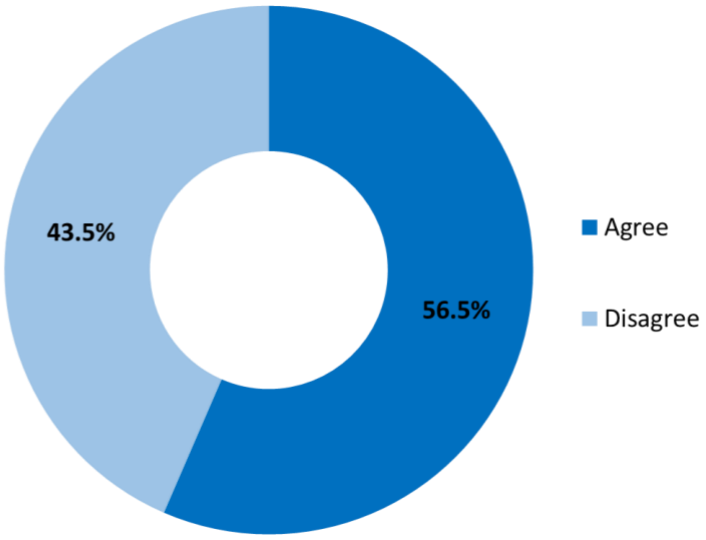


- According to 59.7% physicians' expert views, Darunavir is preferred over other protease inhibitors primarily due to its improved efficacy for treating highly antiretroviral-experienced patients with multiclass resistance.
- Meanwhile, 40.3% of physicians preferred Darunavir because of its high genetic barrier to virological resistance.

Question 8: As per your opinion, an ARV's intrinsic antiviral potency combined with its genetic barrier to resistance influences its ability to protect an ART regimen from virological failure?

A) Agree

B) Disagree

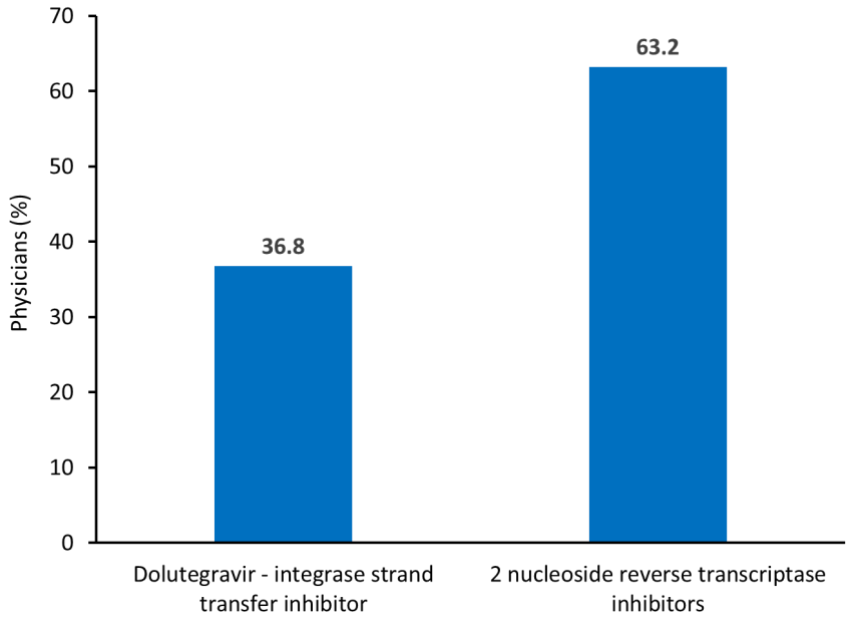


- Majority (56.5%) of physicians agreed that an ARV's intrinsic antiviral potency, combined with its genetic barrier to resistance, influences its ability to protect an ART regimen from virological failure. In contrast, 43.5% of physicians disagreed with this perspective.

Question 9: In your clinical practice, which is the preferred combination with Ritonavir-boosted Darunavir?

A) Dolutegravir - integrase strand transfer inhibitor (INSTI),

B) 2 nucleoside reverse transcriptase inhibitors (2NRTI)

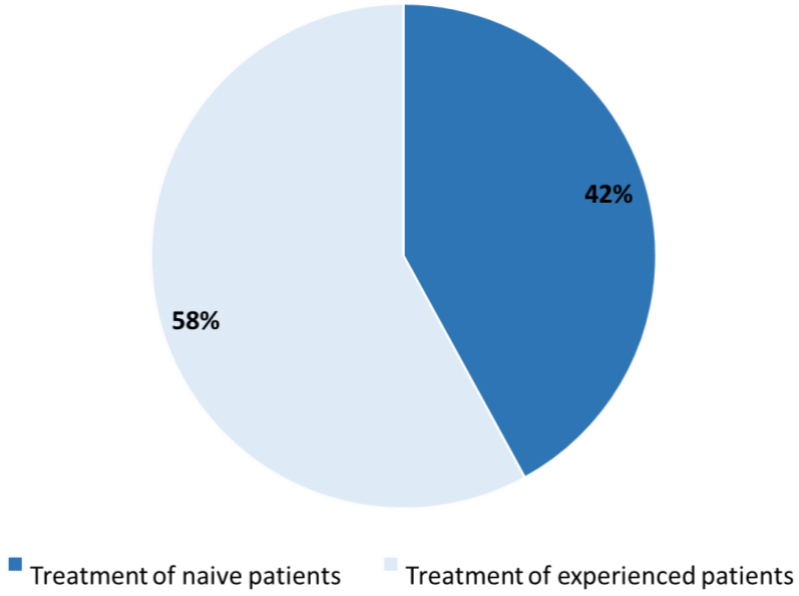


- Majority of physicians (63.2%) the preferred combination with Ritonavir-boosted Darunavir predominantly involves two nucleoside reverse transcriptase inhibitors (2NRTIs) in their clinical practices.
- However, 36.8% of physicians prefer using Dolutegravir, an integrase strand transfer inhibitor (INSTI), with Ritonavir-boosted Darunavir during their clinical practices.

Question 10: In your clinical practice, in which group of HIV patients would you prefer the ART containing Darunavir/Ritonavir (600/100 mg twice daily)?

A) For the treatment of naive patients

B) For the treatment of experienced patients



- The majority of physicians (58%) preferred using ART containing Darunavir/Ritonavir (600/100 mg twice daily) for the treatment of experienced HIV patients.
- In contrast, 42% of physicians preferred using ART containing Darunavir/Ritonavir (600/100 mg twice daily) for the treatment of naive HIV patients.

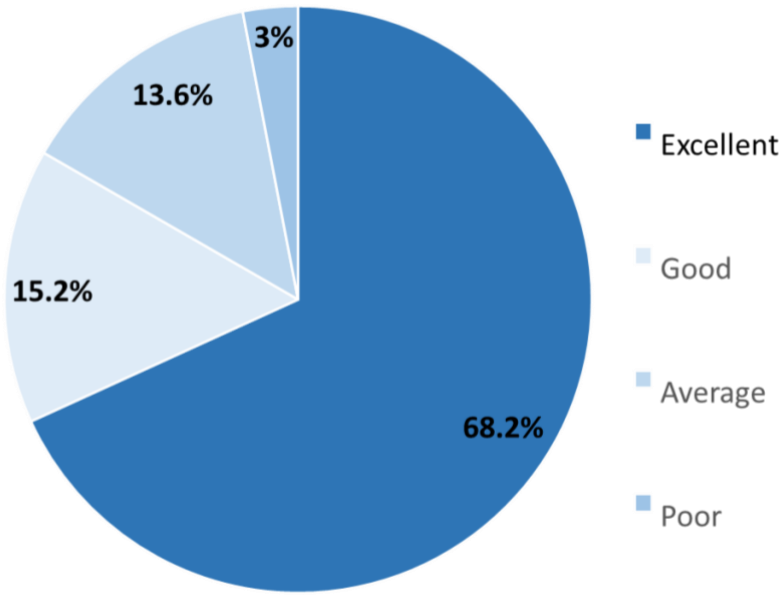
Question 11: In your opinion, how do you rate the efficacy of Darunavir/Ritonavir (600/100 mg) in the treatment of HIV?

A) Excellent

B) Good

C) Average

D) Poor

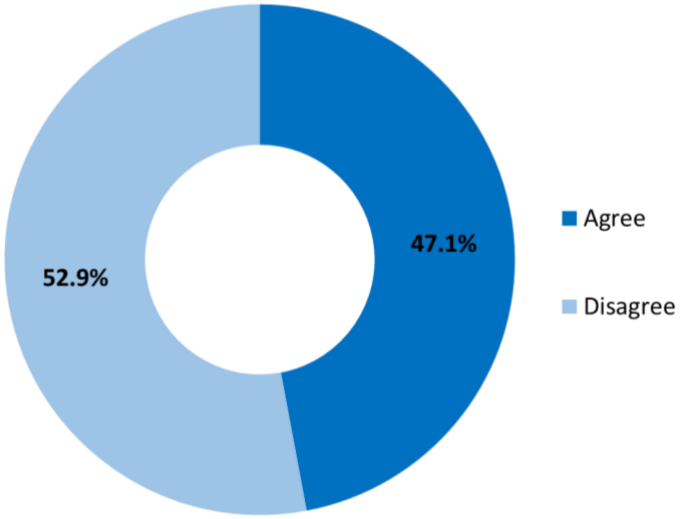


- The majority of physicians (68.2%) rated the efficacy of Darunavir/Ritonavir (600/100 mg) in the treatment of HIV as excellent.
- This was followed by 15.2% who rated it as good, approximately 13.6% who rated it as average, and only 3% who rated it as poor.

Question 12: In your opinion, do you agree compliance is an issue for Darunavir/Ritonavir (600/100) in ART?

A) Agree

B) Disagree



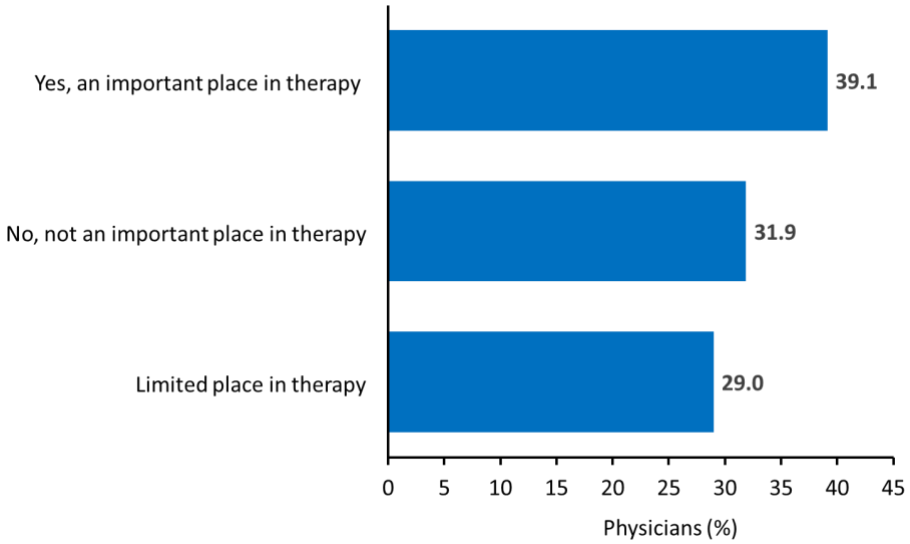
- The majority (52.9%) of physicians disagreed that compliance is an issue for Darunavir/Ritonavir (600/100) in ART.
- In contrast, 47.1% of physicians agreed that compliance is an issue for Darunavir/Ritonavir (600/100) in ART.

Question 13: As per your expert opinion, what is the place of Darunavir/Ritonavir (boosted protease inhibitor) in the long-term treatment of HIV?

A) Yes, an important place in therapy

B) No, not an important place in therapy

C) Limited place in therapy



- About 39.1% of physicians gave their expert opinion that Darunavir/Ritonavir (boosted protease inhibitor) holds an important place in the long-term treatment of HIV.
- Similarly, 31.9% of physicians believed that Darunavir/Ritonavir does not hold an important place in therapy.
- Approximately 29% of physicians believed that Darunavir/Ritonavir has a limited place in the long-term treatment of HIV.

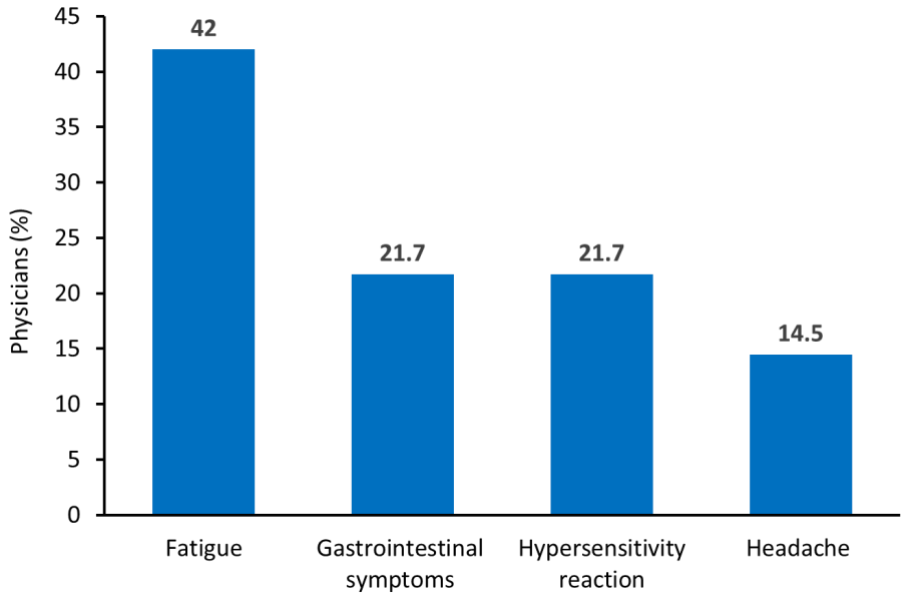
Question 14: In your clinical practice, which is the most common side effect reported with Darunavir based regimen?

A) Headache

B) Gastrointestinal symptoms

C) Hypersensitivity reaction

D) Fatigue



- About 42% of physicians reported fatigue as the most commonly experienced side effect with Darunavir-based regimens during their clinical practice.
- Approximately 21.7% of physicians noted gastrointestinal symptoms as the most commonly reported side effect.
- Similarly, 21.7% of physicians observed hypersensitivity reactions as the most common side effect.
- Around 14.5% of physicians experienced headaches as the most frequently reported side effect with Darunavir-based regimens during their clinical practice.

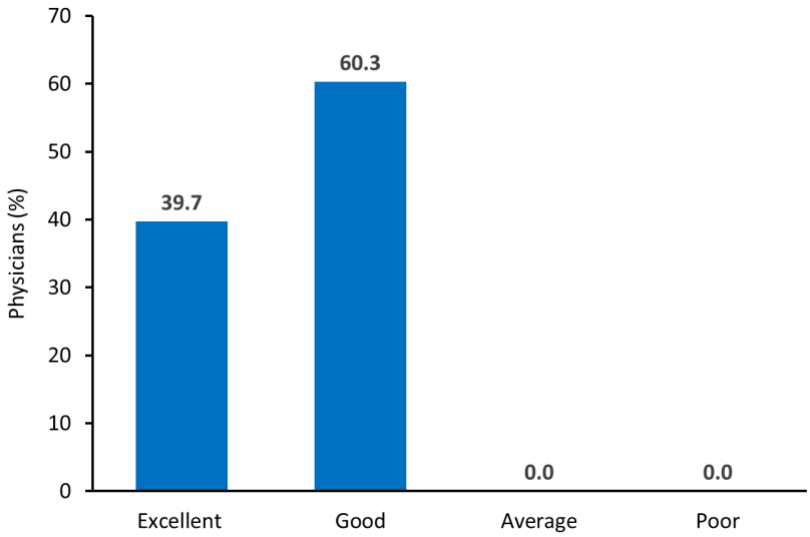
Question 15: In your opinion, how do you rate the safety of Darunavir/Ritonavir combination for the patients with HIV as ART treatment?

A) Excellent

B) Good

C) Average

D) Poor



- The majority of physicians (60.3%) rated the safety of the Darunavir/Ritonavir combination for patients with HIV as good.
- About 39.7% of physicians rated its safety as excellent.
- No physicians rated its safety as average or poor, suggesting that Darunavir/Ritonavir is perceived as a safe and reliable option for ART.

SUMMARY

The study aimed to understand the perspectives and experiences of Indian physicians regarding the use of Darunavir/Ritonavir (600/100 mg) in treating HIV patients. Approximately 34.8% of physicians observed that five to fewer than 20 newly diagnosed HIV patients presented with opportunistic infections each month, while 29% observed fewer than five, 26.1% observed 35 or more, and 10.1% observed 20 to fewer than 30 such patients monthly. About 33.8% of physicians reported that, according to NACO guidelines, treatment failure was suspected with an increasing trend in plasma viral load around 1000 copies/ml. A similar percentage observed treatment failure due to new clinical manifestations or worsening conditions, while 32.4% cited static or declining CD4 counts as indicative of failure. Plasma viral load testing for patients on second/third-line ART was conducted every six months by 46.3% of physicians, every 12 months by 35.8%, and every three months by 17.9%. The majority (50.7%) of physicians believed the primary goal of rational drug sequencing in HIV treatment was to increase survival and improve quality of life, with 19.4% emphasizing sustained viral load reduction, 14.9% prioritizing future treatment options, 11.9% focusing on immune reconstitution, and 3% on limiting drug toxicity. According to NACO guidelines, 37.3% of physicians adhered to using one reactive kit for HIV testing, 28.4% used three kits, 17.9% used two kits, and 16.4% used four kits.

About 48.5% of physicians considered improved adherence as the main benefit of fixed-dose combination drugs like DRV/r, 36.8% viewed simplified regimens as beneficial, 8.8% highlighted better clinical outcomes, and 5.9% focused on treatment success. Darunavir was preferred by 59.7% of physicians due to its efficacy in highly antiretroviral-experienced patients, while 40.3% valued its high genetic barrier to resistance. The majority (56.5%) believed an ARV's antiviral potency and genetic barrier to resistance protected ART regimens from failure, although 43.5% disagreed. About 63.2% preferred combining Ritonavir-boosted Darunavir with two NRTIs, while 36.8% preferred using Dolutegravir. Most physicians (58%) preferred Darunavir/Ritonavir for experienced HIV patients, whereas 42% preferred it for naive patients. The efficacy of Darunavir/Ritonavir was rated as excellent by 68.2% of physicians, good by 15.2%, average by 13.6%, and poor by 3%. While 52.9% disagreed that compliance was an issue, 47.1% agreed. About 39.1% believed

Darunavir/Ritonavir held an important place in long-term HIV treatment, 31.9% did not, and 29% saw it as having a limited role. Common side effects included fatigue (42%), gastrointestinal symptoms (21.7%), hypersensitivity reactions (21.7%), and headaches (14.5%). The safety of Darunavir/Ritonavir was rated as good by 60.3% and excellent by 39.7%, with no ratings of average or poor, indicating it was perceived as a safe and reliable ART option.

DISCUSSION

The survey revealed significant insights into the clinical use of Darunavir/Ritonavir (DRV/r) among Indian physicians treating HIV patients. A majority of physicians (68.2%) rated the efficacy of DRV/r as excellent, with a notable portion (60.3%) also rating its safety as good. Compliance issues were not widely seen as a problem by most physicians (52.9%). Fatigue was the most commonly reported side effect (42%), followed by gastrointestinal symptoms and hypersensitivity reactions (21.7% each). The preference for using DRV/r was higher among experienced HIV patients (58%) compared to naive patients (42%). Physicians favored its use primarily due to its improved efficacy in highly antiretroviral-experienced patients with multiclass resistance (59.7%) and its high genetic barrier to virological resistance (40.3%). The data indicated that the majority of physicians (56.5%) agreed that an ARV's antiviral potency and genetic barrier significantly influence the protection of an ART regimen from virological failure.

CLINICAL RECOMMENDATIONS

- Enhanced adherence: Emphasize the use of fixed-dose combination drugs like DRV/r to improve adherence, as supported by 48.5% of physicians. This can lead to better patient compliance and overall treatment success.
- Efficacy of Darunavir/Ritonavir: Highlight the strong efficacy of Darunavir/Ritonavir (600/100 mg) in treating HIV, as 68.2% of physicians rated its efficacy as excellent. This supports its use as a preferred treatment option for both naive and experienced HIV patients.

- Safety profile: Consider the safety profile of Darunavir/Ritonavir, with 60.3% of physicians rating it as good and 39.7% as excellent. No physicians rated it as average or poor, indicating it is a safe and reliable option for ART.
- Preferred combination therapy: Recommend the use of Ritonavir-boosted Darunavir with two nucleoside reverse transcriptase inhibitors (2NRTIs), preferred by 63.2% of physicians, to enhance treatment outcomes.
- Plasma viral load testing frequency: Advocate for plasma viral load testing every 6 months for patients on second/third-line ART, as preferred by 46.3% of physicians, to monitor treatment effectiveness and detect any potential treatment failures.
- Management of opportunistic infections: Note that a significant portion of physicians observed frequent opportunistic infections in newly diagnosed HIV patients. This highlights the need for vigilant monitoring and timely intervention to manage these infections effectively.
- Side effects monitoring: Be aware of common side effects associated with Darunavir-based regimens, including fatigue (42%), gastrointestinal symptoms (21.7%), hypersensitivity reactions (21.7%), and headaches (14.5%). Regular monitoring and management of these side effects can improve patient comfort and adherence to therapy.
- Darunavir's role in long-term treatment: Recognize Darunavir/Ritonavir’s important role in long-term HIV treatment, as indicated by 39.1% of physicians, while also considering its limitations as noted by 29% of physicians. This can guide treatment choices based on individual patient needs and resistance profiles.
- Compliance and resistance: Address compliance issues and resistance concerns, as 52.9% of physicians disagreed that compliance is an issue for Darunavir/Ritonavir, whereas 47.1% agreed. Tailoring adherence support and resistance management strategies can enhance treatment success.

CONSULTANT OPINION

Based on the data, Darunavir/Ritonavir is highly regarded among physicians for its efficacy and safety in HIV treatment. The majority of physicians (68.2%) rated its efficacy as excellent, and 60.3% considered its safety as good, with no physicians rating it as average or poor. This suggests a strong confidence in the drug's effectiveness and safety profile. Physicians primarily value Darunavir/Ritonavir for its improved efficacy in treating highly antiretroviral-experienced patients with multiclass resistance (59.7%), as well as its high genetic barrier to virological resistance (40.3%). The drug’s fixed-dose combination is noted for benefits like improved adherence (48.5%) and simplified regimens (36.8%). However, a portion of physicians (47.1%) still perceive compliance as an issue, though a majority (52.9%) disagreed with this concern.

The adherence to NACO guidelines varies, with 37.3% of physicians following the guideline that a reactive sample with one kit is sufficient, while others adhere to more stringent criteria involving multiple kits. Plasma viral load testing frequencies also vary, with 46.3% of physicians testing every 6 months and 17.9% testing every 3 months. This variability underscores differing practices in monitoring and managing HIV treatment. Overall, while Darunavir/Ritonavir is preferred for its efficacy and safety, issues like compliance and the interpretation of testing guidelines reflect areas where further standardization and education could be beneficial. The data highlights Darunavir/Ritonavir's role as a cornerstone in ART, especially for experienced patients, but also indicates ongoing discussions about its place in therapy and the importance of balancing efficacy with practical considerations.

MARKET OPPORTUNITIES

The data highlights significant market opportunities for Darunavir/Ritonavir in the HIV treatment landscape. With 68.2% of physicians rating its efficacy as excellent and 60.3% rating its safety as good, Darunavir/Ritonavir is perceived as a highly effective and reliable option for ART. The preference for Darunavir, driven by its efficacy in treating highly antiretroviral-experienced patients and its high genetic barrier to resistance, underscores its market potential. The majority of physicians (58%) prefer using ART containing Darunavir/Ritonavir for experienced patients, indicating a strong demand for this combination in advanced stages of HIV. Additionally, with a significant proportion of physicians noting improved adherence and simplified regimens as key benefits, there is an opportunity to further promote Darunavir/Ritonavir as a preferred choice in both new and experienced patient populations. Addressing concerns about compliance and side effects could further enhance its market position.

MARKET POSITIONING

- About 68.2% of physicians rated the efficacy of Darunavir/Ritonavir (600/100 mg) as excellent, indicating strong confidence in its effectiveness for HIV treatment.
- The majority of physicians (60.3%) rated the safety of Darunavir/Ritonavir as good, with 39.7% rating it as excellent, suggesting it is viewed as a reliable option for ART.
- About 48.5% of physicians identified improved adherence as a key benefit of fixed-dose combinations like Darunavir/Ritonavir, highlighting its positive impact on patient compliance.
- Majority 50.7% of physicians prioritized increasing survival and improving quality of life as the main goal of rational drug sequencing, reflecting the emphasis on long-term outcomes.
- About 58% of physicians preferred using Darunavir/Ritonavir (600/100 mg twice daily) for experienced HIV patients, indicating its strong position in managing advanced cases.
- Fatigue was reported as the most common side effect by 42% of physicians, with gastrointestinal symptoms and hypersensitivity reactions also noted, indicating areas for potential management improvements.

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