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Full Length Research Paper

Highly active antiretroviral therapy induced drug-drug interactions in Indian Human Immunodeficiency Virus positive patients

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One of the greatest challenges for the HIV clinician is the recognition and management of drug interactions. The HIV infected patient often receives numerous medications and has a great potential for adverse drug interactions. Although many of these interactions may be minor in nature, some are potentially serious, leading to severe toxicity or treatment failure. The aim of this study is to determine the incidence, pattern and to identify risk factors for possible drug-drug interactions (DDIs) in human immunodeficiency virus positive patients with antiretrovirals (ARVs) in an Indian tertiary care teaching hospital. A prospective case control study was performed for monitoring drug-drug interactions to antiretroviral therapy during hospitalization from August 2009 to March 2010. Possible DDIs found were classified according to Tatro. The prescription of each enrolled patient during hospitalization was reviewed and analyzed by a graduate trainee clinical pharmacist for possible drug to drug interactions based on Online Stockley's Drug Interactions (9th edition), Micromedex Online Drug Reference and Martindale, The Complete Drug Reference. The possible DDIs found were classified according to a clinical significance rating expressed as a number assigned to each DDI based on onset, severity and documentation. Multivariate logistic regressions were used to identify the risk factors for DDIs. The data consisted of 118 hospitalized HIV patients with ARV prescriptions. Out of which 175 DDIs were detected involving 77 patients. The overall incidence rate of DDIs was 65.2% and pharmacokinetic DDIs was the most commonly observed DDIs. 'Minor' and 'moderate' drug-drug interactions accounted for 50.8 and 26.9% respectively. A maximum of six DDIs was reported from a single patient. Most of the patients who developed DDIs were receiving more than nine to eleven drugs at the time of experiencing DDIs. Polypharmacy, tuberculosis and syphilis were observed as risk factors for DDIs. The increase in use of newer antiretrovirals in India increases the risk for drug interactions and complicates their management on HIV/AIDS. It is therefore recommended that clinicians must focus to detect potential DDIs at time of prescription of ARVs to ensure better patient care.

Key words: Drug interactions, antiretroviral therapy, highly active, India.

INTRODUCTION

Treatment of HIV infection commonly requires a combination of 3 to 4 anti-retrovirals, termed Highly Active Antiretroviral Therapy (HAART) (Josephson, 2010). In addition, some HIV-positive patients still require concomitant treatment with drugs for opportunistic infections; some require medication to treat unrelated medical conditions and/or the metabolic complications of ARV therapy (Fichtenbaum et al., 2002; Gerber et al., 2002) and others may self-medicate with herbal

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formulations and/or over the counter drugs. This markedly increases the risk of drug interactions and complicates their assessment. The chronic nature of HIV infection requires lifelong HAART (Negredo et al., 2006) to continuously suppress HIV viral replication, thus reducing morbidity and mortality. HAART is restricted by treatment barriers such as complex dosing, drug-drug interactions and toxicities, leading to patient non-adherence, with subsequent treatment failures and development of drug resistant. Therefore, the virtually limitless number of drug combinations that may be taken by patients undergoing treatment of HIV infection makes DDIs almost inevitable. This is one of the major challenges associated with the multidrug regimens used for HIV therapy. The Indian government has continued efforts to expand access to highly active antiretroviral therapy, Phase-III of the Indian National Aids Control Programme is estimated to spend INR 13, 340 million (US $266 million) for HAART (Esch, 2001). At the same time, the National AIDS Control Organization has established Antiretroviral Therapy (ART) centre's which offer free treatment for HIV and related opportunistic infections (Bachani, 2009). It is estimated that across India, free ART will be provided to 300 000 adults and 40 000 children by 2012 (NACO, 2009). Often DDIs go unnoticed or are not reported. Monitoring and reporting of DDIs to ARVs in the Indian population is very important. To our knowledge, there are no systematic studies conducted in India concerning DDIs in HIV patients receiving ART. Therefore, this study was conducted to determine the incidence and to identify risk factors for possible DDIs between ARVs and other drugs on prescriptions claimed for HIV positive patients receiving ART.

MATERIALS AND METHODS

A prospective case control study was done on ARV prescriptions in the medical wards of Kasturba Hospital, Manipal, India. The study was approved by the Institutional Ethics Committee of Kasturba Hospital, Manipal. Patients of either sex previously been diagnosed as HIV positive, already on HAART and admitted to hospital as in-patients were included in the study and HIV positive patients already on HAART, treated at out-patient basis and less than18 years of age were excluded from the study. Written informed consent was obtained from these patients. Between August 2009 and March 2010, these patients were intensively monitored on a daily basis by a graduate trainee clinical pharmacist for possible DDIs from the day of hospital admission to the day of discharge. All the necessary and relevant data were collected from in-patient case notes, treatment charts, laboratory data reports, including, demographic details of the patients, opportunistic infections, CD4 count, antiretroviral therapy, concomitant drugs the patient received, their respective dosage, route of administration with frequency and the patient's allergy status (to drugs and food). Use of oral contraceptives was also noted. In addition, the patient's medication history was taken and any co-morbidities was also noted and documented in a suitably designed 'Individual Case Record Form' (ICRF).

The prescription were reviewed and analyzed for possible drug-drug interactions using Online Stockley's Drug Interactions (9th edition), Micromedex Online Drug Reference, Martindale the complete drug reference. If DDIs was identified, and met the inclusion and exclusion criteria, data on those particular DDIs was documented in a suitably designed 'Drug interaction reporting and Documentation Form'. DDIs documented with necessary information were reviewed and assessed by a senior academic clinical pharmacist. Wherever appropriate, DDIs were discussed with the clinicians. The patients with DDIs were enrolled into the case group while the patients without DDIs were in the control group. In patients who had DDIs, antiretroviral (ARV) were considered as the index drugs while any other concomitant drugs as the interacting drug. Possible DDIs found were classified according to a clinical significant rating, and the formulae for the clinical significance rating of DDI are described in the form of three degree of severity, identified as major, moderate and minor, as described by Tatro (2005).

The major effects were potentially life threatening, capable of causing permanent damage, and necessitating additional treatment, hospitalisation or extension of hospital stay. Moderate effects were deterioration of a patient's clinical status, requiring additional treatment, hospitalization or extension of hospital stay. Minor effects are usually mild, having bothersome or unnoticeable consequences but not significantly affecting the therapeutic outcome. The documentation levels were distinguished, namely established, probable, suspected, possible and unlikely. The scale represents an evaluation of the quality and clinical relevance of the primary literature supporting the occurrence of an interaction (WHO, 2006). Data including age, gender, body mass index, number of drugs prescribed, comorbidities, commonly prescribed fixed dose of highly active antiretroviral therapy, CD4 count, detected DDI, and time of onset, degree of severity were entered in a Statistical Package for Social Science (SPSS). Multivariate logistic regressions were used to evaluate the influence of risk factors for DDIs to ART. All statistical calculations were performed using Statistical Package for Social Science (SPSS) Version 17.0. A p-value of < 0.05 was considered as statistically significant.

RESULTS

During the study period, 118 hospitalized HIV patients (90 males, 28 females) were included out of which 175 DDIs were detected, involving 77 patients. The majority of patients were in the age group of 41 to 59 years (49.1%) and patients aged 60 years and above were also included. The overall incidence of DDIs was 65.2%. Incidence of DDIs was higher in female population [67.8% (19/28)] compared to males [64.4% (58/90)]. There was a preponderance of male patients (71%). Pharmacokinetic DDIs were more common (89%) (Table 1). Of the 175 reported DDIs, 'minor' and 'moderate' drug-drug interactions accounted for 50.8% and 26.9% respectively. Only 22.3% of the drug-drug interactions were 'major'. Results are shown in Figure 1.

The time of onset of DDIs was delayed (79.4%) followed by not specified (13.8%) and rapid (6.8%). In the majority of DDIs, documentation was 'probable' (80%) and 'established' (14.2%) respectively. Possible DDIs with a clinical significance rating, Level-1 {(19.4%) [Major, n=34]} , significance Level- 2 {(24%) [moderate, n = 42]}, Level-3 {(51.4%) [Minor, n = 90]}, Level-5 {(5.2%)

Table 1. Demographic detail of the patients.

Demographic characteristic	Total no. of patients {n=118 (%)}	No. of DDIs to HAART {n=175 (%)}	No. of patients with DDIs/ Total no. of patients × 100; Incidence (%)
Gender			
Male	90 (76.2)	125 (71.5)	58/90; (64.4)
Female	28 (23.8)	50 (28.5)	19/28; (67.8)
Overall incidence of DDIs (%)			77/118; (65.2)
Age (Years)			
18 - 40	52(44.2)	78(44.5)	29/52; (55.8)
41 - 59	58(49.1)	81(46.2)	41/58; (70.6)
≥ 60	8(6.7)	16(9.3)	7/8; (87.5)
Type of DDIs			
Pharmacokinetic		157 (89)	
Pharmacodynamic		18 (11)	
Body mass index (kg/m^2)			
<18.5	49(41.5)		
18.5 - 24.9	66 (55.9)		
>24.9	3 (2.6)		
CD4 count (cells/ µl)			
< 200	94 (80)		
≥ 200	24 (20)		
Antiretroviral therapy		**p-value**	**Incidence rate**
Zidovudine + Lamivudine + Nevirapine	33 (27.9)	< 0.001	25/33; (75.7)
Tenofovir + Emtricitabine+ Efavirenz	26 (22)	0.001	5/26; (19.2)
Lamivudine + Zidovudine+ Efavirenz	15(12.7)	0.348	13/15; (86.6)
Lamivudine + Tenofovir+ Efavirenz	14 (11.8)	0.338	8/14; (57.1)
Lamivudine + Stavudine+ Efavirenz	11(9.3)	0.001	9/11; (81.8)
Lamivudine + Stavudine+ Nevirapine	9 (7.6)	0.001	7/9; (77.7)
Tenofovir + Emtricitabine + Atazanavir + Ritonavir	5 (4.2)	0.001	5/5; (100)
Tenofovir + Emtricitabine + Lopinavir + Ritonavir	4 (3.3)	0.338	4/4; (100)
Atazanavir + Ritonavir	1 (1.2)		1/1; (100)

HAART, Highly active antiretroviral therapy; DDIs, drug to drug interactions; WHO, World Health Organization; HIV, Human Immunodeficiency Virus.

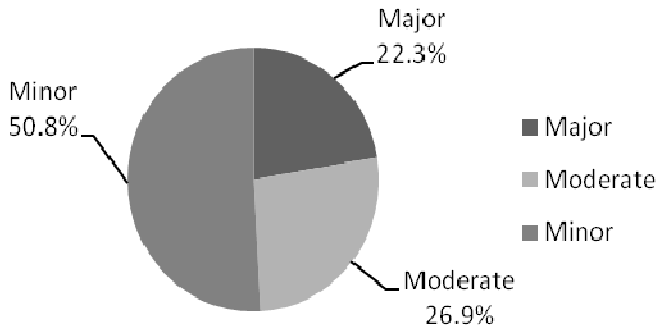

Figure 1. Level of severity of reported drug interactions.

Table 2. Clinical significance rating of the drug to drug interactions.

Characteristic			No. of DDIs to HAART {n = 175 (%)}
Time of onset			
Rapid			12 (6.8)
Delayed			139 (79.4)
Not specified			24 (13.8)
Documentation			
Established			25 (14.2)
Probable			140 (80)
Suspected			-
Possible			-
Unlikely			10 (5.8)
Significance rating	**Severity**	**Documentation**	
Level 1	Major	Suspected or greater	34 (19.4)
Level 2	Moderate	Suspected or greater	42 (24)
Level 3	Minor	Suspected or greater	90 (51.4)
Level 4	Major/Moderate	Possible	
Level 5	Minor/ Any	Possible/ Unlikely	9 (5.2)

HAART, highly active antiretroviral therapy; DDIs, drug to drug interactions.

Table 3. Characteristic of drug to drug interactions to highly active antiretroviral therapy.

Characteristic of drug to drug interactions	No. of patients with DDIs n = 77(%)
Maximum no. of drug to drug interactions	
1	26 (33.8)
2	25 (32.5)
3	14 (18.2)
4	4 (5.2)
5	7 (9)
6	1 (1.3)
CD4 count in patients with DDIs (cells/ µl)	
< 200	63 (81.9)
≥ 200	14 (18.1)
No. of co-morbidities associated with drug to drug interactions	
None	48 (62.4)
1	22 (28.6)
2 - >2	7 (9)

DDIs, drug to drug interactions.

[Possible/unlikely, n = 9]}, was the total number of identified interactions (Table 2). In our study, a maximum of six DDIs were reported from a single patient (1.3%). A maximum of 9% patients with DDIs were associated with two or more than two comorbidities as presented in Table 3. Among 118 patients, 46 (39%) of the patients were receiving nine to eleven drugs followed by 40 (33.9%) of the patients receiving ≥12 drugs and 32 (27.1%) of the patients ≤ 8 drugs. Majority (45.5%) of the patients who developed DDIs were receiving more than nine to eleven drugs at the time of experiencing DDIs. The frequencies of Levels 1 to 5 interaction were: Level 3, n = 90; 51.4%; Level 2, n = 42; 24%; Level 1, n = 34, 19.4%; and Level 5, n = 90, 5.2%. The majority of Level 3 interactions were

Table 4. Antiretrovirals most commonly associated with drug to drug interactions.

Index drug	Interacting drug	No. of DDIs n = 175 (%)	Significance rating of DDIs	No. of DDIs n = 175 (%)
Lamivudine	Cotrimoxazole	51 (29.1)	Level-3 interactions	90 (51.4)
Zidovudine	Cotrimoxazole	31 (18)	Level-3 interactions	
Nevirapine	Fluconazole	7 (4)	Level-3 interactions	
Efavirenz	Carbamazepine	1 (0.5)	Level-3 interactions	
Zidovudine	Acetaminophen	18 (10.3)	Level-2 interactions	42 (24)
Efavirenz	Rifampin	16 (9.1)	Level-2 interactions	
Nevirapine	Rifampin	6 (3.5)	Level-2 interactions	
Efavirenz	Diltiazem	2 (1.1)	Level-2 interactions	
Atazanavir	Tenofovir	6 (3.5)	Level-1 interactions	34 (19.4)
Zidovudine	Fluconazole	5 (2.9)	Level-1 interactions	
Zidovudine	Rifampin	5 (2.9)	Level-1 interactions	
Ritonavir	Tenofovir	4 (2.2)	Level-1 interactions	
Efavirenz	Phenytoin	3 (1.7)	Level-1 interactions	
Efavirenz	Phenobarbitone	1 (0.5)	Level-1 interactions	
Atazanavir	Rifampin	1 (0.5)	Level-1 interactions	
Atazanavir	Amlodipine	1 (0.5)	Level-1 interactions	
Atazanavir	Phenytoin	1 (0.5)	Level-1 interactions	
Atazanavir	Amitryptaline	1 (0.5)	Level-1 interactions	
Atazanavir	Venlafexine	1 (0.5)	Level-1 interactions	
Ritonavir	Venlafexine	1 (0.5)	Level-1 interactions	
Ritonavir	Phenytoin	1 (0.5)	Level-1 interactions	
Ritonavir	Efavirenz	1 (0.5)	Level-1 interactions	
Ritonavir	Amitryptaline	1 (0.5)	Level-1 interactions	
Tenofovir	Acyclovir	1 (0.5)	Level-1 interactions	
Zidovudine	Pyrazinamide	9 (5.2)	Level-5 interactions	9 (5.2)

DDIs, drug to drug interactions.

between: (i) lamivudine and cotrimoxazole (n=51; 29.1%), (ii) Zidovudine and Cotrimoxazole (n=31; 18%), (iii) Nevirapine and Fluconazole (n=7; 4%). Level 2 interactions were between: (i) Zidovudine and Acetaminophen (n = 18; 10.3%), (ii) Efavirenz and Rifampin (n = 16; 9.1%), (iii) nevirapine and rifampin (n = 6; 3.5%). Level 1 interactions were between: (i) Atazanavir and Tenofovir (n = 6; 3.5%), (ii) Zidovudine and Fluconazole (n = 5; 2.9%), (iii) Zidovudine and Rifampin (n = 5; 2.9%). Level-5 interactions were between: (i) Zidovudine and Pyrazinamide (n = 9; 5.2%), as set out in (Table 4).

Higher prevalence of DDIs was noted with Zidovudine+ Lamivudine + Nevirapine fixed dose combination [n = 25 (75.7%)] while the prevalence was lowest with Tenofovir+ Emtricitabine+ Efavirenz combination [n = 5 (19.2%)] (Table 1). In the majority of DDIs, PI based regimens Tenofovir + Emtricitabine + Atazanavir + Ritonavir (n=5), Tenofovir + Emtricitabine + Lopinavir + Ritonavir (n = 4) and Atazanavir + Ritonavir (n = 1) was found to have at least one DDIs. The incidence rate of DDIs was highest with Lamivudine + Zidovudine + Efavirenz fixed dose combination and lowest with the Tenofovir + Emtricitabine + Efavirenz fixed dose combination (Table 1). Statistical analysis identified concurrent tuberculosis (p-value = 0.025) and syphilis (p-value = 0.049) was the influential risk factor for DDIs (Table 5).

DISCUSSION

DDIs can have detrimental effects on a patient's well being and the overall health care system. A comprehensive ongoing DDIs program in a hospital can help to complement organization risk management activities, assess the safety of drug therapies, measure DDIs incidence rates over time, and educate health care

Table 5. Risk factors associated for the occurrence of DDIs to antiretroviral in intensively monitored patients.

Characteristic		Control {n = 41(%)}	Case {n = 77 (%)}	p-value
Gender				
Male		32 (78)	58 (75.3)	0.740
Female		9 (22)	19 (24.7)	
Age (years)				
18 - 40		23 (56.1)	29 (38)	
41 - 59		17 (41.5)	41 (53)	0.110
≥60		1 (2.4)	7 (9)	
Body mass index (kg/m^2)				
<18.5		14 (34.2)	35 (45.5)	
18.5 - 24.9		25 (60.9)	41 (53.2)	0.256
>24.9		2 (4.9)	1 (1.3)	
CD4 count (cells/µl)				
<200		31 (75.6)	63 (81.8)	0.425
>200		10 (24.4)	14 (18.2)	
Opportunistic infections				
Tuberculosis	No	30 (73.1)	40 (52)	
	Yes	11 (26.9)	37 (48)	< 0.001
Candidiasis	No	27 (65.9)	48 (62.3)	0.706
	Yes	14 (34.1)	29 (37.7)	
Pneumocystis pneumonia	No	38 (92.7)	64 (83.1)	0.171
	Yes	3 (7.3)	13 (16.9)	
Herpes zoster	No	35 (85.3)	70 (91)	0.360
	Yes	6 (14.7)	7 (9)	
Syphilis	No	37 (90.2)	76 (98.7)	
	Yes	4 (9.8)	1 (1.3)	< 0.001
Cytomegalovirus infection	No	41 (100)	75 (97.4)	0.543
	Yes	0	2 (2.6)	
Toxoplasmosis	No	41 (100)	73 (94.9)	0.297
	Yes	0	4 (5.1)	
Tubercular meningitis	No	41 (100)	76 (98.7)	1.00
	Yes	0	1 (1.3)	
Cryptococcal meningitis	No	41 (100)	75 (97.4)	
	Yes	0	2 (2.6)	0.543
Cryptosporidiosis	No	41 (100)	76 (98.7)	
	Yes	0	1 (1.3)	1.00

Total no. of patients n=118

professionals about drug interactions and increase their level of awareness regarding DDIs. The overall incidence of DDIs reported in our study was 65.2%. The reason for a higher incidence in our study could be due to the inclusion of inpatients from internal medicine wards where usually chronically ill patients with multiple complications are hospitalized. Currently, data on the incidence of potential drug interactions in HIV positive patients are lacking in India. However, the incidence obtained from our study suggests that patients with HIV

who are receiving antiretroviral (ARV) therapy along with polypharmacy are at high risk for drug–drug interactions (DDIs). The demographic reports of various drug to drug interactions studies (Barry et al., 1999) cited a predominance of the male population. This study also revealed a male predominance over female but comparatively, the percentage of incidence to DDIs was slightly higher in females (67.8%) compared to males (64.4%). This is because female patients being treated for opportunistic infections experience DDIs at a much higher rate. Antibiotics and drugs used for treatment of opportunistic infections are implicated in two thirds of hospital-acquired DDIs. We also observed the probability of occurrence of DDIs to antiretroviral in HIV patients with tuberculosis. In this study, we found that the majority of the DDIs were pharmacokinetic (89%) compared to pharmacodynamics (11%). This could be because highly active antiretroviral therapies are extensively metabolized by the cytochrome P450 isoenzyme system, particularly by CYP3A415. They also have the potential to interact with other drugs mebolished by CYP3A4. However, other studies (Pau et al., 2002; Johnson et al., 1999) that were carried out reported pharmacodynamic interactions as the most commonly associated interactions encountered in clinical practice.

In our hospital setup, patients were initiated on a zidovudine-containing regimen only if the haemoglobin level was more than 8 g/dl at baseline, thereby avoiding the occurrence of anaemia. In comparison to other ARV regimens, Protease inhibitors (PI) based regimens were found to be the least prescribed (8.7%). We also found that most of the patients on PI based regimens have at least one DDI. This could be attributed to the pharmacokinetic characteristics of the PIs as they are potent inhibitors of CYP3A4 and thereby decrease the hepatic clearance of CYP3A4 substrates and increasing their plasma levels. However, we observed that Tenofovir + Emtricitabine + Efavirenz (22%) were found to be the regimen least implicated with drug interactions. Major DDIs (22.3%) required intensive medical care, caused a permanent harm to the patient or, either directly or indirectly led to the death of the patient. These reactions demanded greater expenditure from the patients. Most of the moderate DDIs (26.9%) in our study lead to the deterioration of patient's status. Most of the potential DDIs in our study had a ‘probable’ documentation status (80%) thus with the sound knowledge and information of DDIs, these DDIs can be predicted and hence prevented. In this study, we found that the majority of the interactions (51.4%) were categorized as Level 3 according to the significance rating scale. Our finding differed from (Katende et al., 2008) where Levels 1 and 2 represented 8% of the total number of identified interactions, Level 3 represented 6.7%, Level 4 represented 37% while Level 5 represented 48.3%. This difference could be due to a relatively shorter duration of intensive monitoring of DDIs and less sample size in our study.

Various studies (CDCP, 2007; Piscitelli et al., 2001) have reported that HIV positive patient receive an average of five to six medications throughout their disease course, and this number may be as high as nine. However, the present study revealed (9 to 11 drugs) predominance. This finding is consistent with Sanderson et al. (2005) where they found that the risk of DDIs increased from 13% in patients taking two drugs and 82% in patients taking seven or more drugs. This may be due to the fact that most of our patients had polypharmacy and multiple drug interactions which might have become increasingly complex. Since antiretroviral therapy is life long, the nature of these interactions requires delineation to provide an optimal pharmacologic strategy for the use of these agents in combination (CDCP, 2004). Our study results observed a significant association between DDIs and opportunistic infections such as tuberculosis ($p = 0.025$) and syphilis ($p = 0.049$). This may be due to the fact that combination ARV is frequently initiated when patients are being treated for tuberculosis (Boulle et al., 2004; Lawn et al., 2006). Although ARV reduces tuberculosis incidence, tuberculosis continues to occur at considerably higher rates than in individuals who are not infected with Human Immunodeficiency Virus (HIV) (Brinkh et al., 2007; Corbett et al., 2006). Co-administration of ARV and anti-tubercular therapy may be complicated by shared toxicity, notably hepatotoxicity, 32 or by drug interactions. Rifampicin is a potent inducer of cytochrome P450 enzymes, which metabolize many drugs including non-nucleoside reverse transcriptase inhibitor. Rifampicin-based antitubercular therapy reduces the plasma concentrations of Nevirapine and Efavirenz. However, the virological consequences of these drug interactions are not well described.

LIMITATIONS

The clinical relevance of the identified DDIs was evaluated according to criteria stated in the literature. No clinical evaluation of the real effects of these interactions was possible. However, the results emphasized the possibility of DDIs that could have led to severe problems.

Conclusion

This is the first observational study that is designed to evaluate the antiretroviral-induced DDIs in Indian HIV positive patients. DDIs are largely unavoidable in HIV management, and the problem is likely to worsen. They can significantly impact on patient care and lead to morbidity, if not appropriately managed. We also propose that clinicians should in their daily practice, look for web systems updating DDIs such as www.hiv-druginteractions.org and monitor DDIs to antiretroviral

whilst simultaneously improving access to newer ARV for the Indian population to ensure better patient care.

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