Indian pharmaceutical industry as a "pharmacy of the developing world"

- Clarification of the effect and problem of Indian generic Anti-retroviral Drugs (ARV) from the time-series changes in HIV prevalence and AIDS-related deaths -

Prepared by

Ikuo Kawauchi

Published by Vicharak Manch, Critical Thinkers of India. Web: vicharakmanch.com

Summary

Indian generic medicines that are cheap but ensure a certain level of quality play an important role for the poor people in LMICs from the viewpoint of SDGs & UHC. The aim of this study is understanding the role of Indian pharmaceutical industry as "pharmacy of the developing world".

[Method] This study based on review article about HIV infection and ARV's effect. This study summarizes the role of Indian generic ARV through previous studies about Indian pharmaceutical industry, HIV/AIDS, ARV, HIV prevalence and the case of India.

[Result] In India, HRGs(High Risk Group) are clusters of HIV prevalence during 2000s. West,South, Northeast Regions are high HIV prevalence areas in India. India took measures to halt and reverse the epidemic distributing free ARV and establishing ART centres focusing on HRGs. Complied with increasing people living with HIV accessing ART, number of AIDS-related deaths in West and South Regions in India decreased. Several challenging still remain. The future significant increase of funding and cost down can not be expected due to the major donnors' fisical conditions and limitation of ARV's cost structure. This might lead to ARV supply shortage and might be affect the future effects of HIV treatment. Another important point is adherence, one of the barriers to HIV treatment in India.

[Limitation] Since State-wise time-series data about HIV prevalence in India were available, detailed information about ARV supply are unavailable. Furthermore, this study can not clearly show the causal relationship between inter-State differences in India and State-wise HIV prevarence.

[Discussion] Several findings in this study could be extended to lead to studies about the other infectious diseases in India and more comprehensive studies about the role of Indian pharmaceutical industry as"pharmacy of the developing world".

Key words : Indian pharmaceutical industry, HIV, AIDS, ARV, Anti-retroviral Drug

Table of contents

Published by Vicharak Manch - Critical Thinkers of India.
Web: vicharakmanch.com

【Abbreviation】

1. Introduction

AIDS Acquired Immune Deficiency Syndrome

ART Anti-retroviral Therapy

ARV Anti-retroviral Drug

HIV Human Immunodeficiency Virus

HRGs High Risk Groups

2. The development history of Indian pharmaceutical industry

API Active Pharmaceutical Ingredient

CDRI Central Drug Research Institute

CSIR The Council of Scientific and Industrial Research

DMF Drug Master File

DPCO The Drug Price Control Order

EMR Exclusive Marketing Rights

FERA The Foreign Exchange Regulation Act

GVC Global Value Chain

HAL Hindustan Antibiotics Limited

IBEF Indian Brand Equity Foundation

IDPL Indian Drugs and Pharmaceuticals Limited

IICT Indian Institute of Chemical Technology

IPA Indian Pharmaceutical Alliance

NCL National Chemical Laboratory

NDP The New Drug Policy

PPPY per-person per-year

TRIPS Agreement on Trade-Related Aspects of Intellectual Property Rights

WTO World Trade Organization

3. HIV infection in the world and the role of the Indian generic drugs for treatment

ABC Abacavir

ATV/r Atazanavir /Ritonavir

AZT Azidothymidine

CHAI Clinton Health Access Initiative

DRV Darunavir

DTG Dolutegravir

d4T Stavudine

EFV Efavirenz

ERP Expert Review Panel

FDA Food and Drug Administration

FDC Fixed-Dose Combination

FTC Emtricitabine

HAART Highly Active Anti-retroviral Therapy

INSTI Integrase Strand Transfer Inhibitors

MPP Medicines Patent Pool

MSF Médecins Sans Frontières

NRTI Nucleoside Analogue Reverse Transcriptase Inhibitors

NNRTI Non-Nucleoside Reverse Transcriptase Inhibitors

NVP Nevirapine

LMICs Low and(to) Middle Income Countries

LPV/r Lopinavir/Ritonavir

PEPFAR The President's Emergency Plan for AIDS Relief

PI Protease Inhibitors

PLHIV People living with HIV

RAL Raltegravir

RTV Ritonavir

SOC Tenofovir/Lamivudine/Efavirenz(TDF/3TC/EFV)

TAF Tenofovir alafenamide

TDF Tenofovir

Published by Vicharak Manch - Critical Thinkers of India.
Web: vicharakmanch.com

TLD Tenofovir/Lamivudine/Dolutegravir(Tenofovir/3TC/DTG)

T-20 Enfuvirtide

UNAIDS Joint United Nations Programme on HIV/AIDS

ZDV Zidovudine

3TC Lamivudine

4. HIV infection in India

DAPCU District AIDS Prevention and Contorol Unit

DM Data Managers

FSW Female Sex Workers

ICER incremental cost-effectiveness ratio

IDA The International Development Association

IDU Injecting Drug User

LACs Link ART Centres

LPU lost to follow-up

LT Laboratory Technicians

MO Medical Officers

MTP Mid-Term Plan

MOHFW Ministry of Health and Family Welfare

MSM Men who have Sex with Men

NAC National AIDS Committee

NACO The National AIDS Control Organization

NACP The National AIDS Control Programme

OI Oppotunistic Infections

QALY Quality-adjustd life year

SMO Senior Medical Officer

TB Tuberculosis

UAS Unprotected Anal Sex

YLS Year of life saved

1 Introduction

(1) The aim of this study

In LMICs, access to the essential medicines is not adequate. Indian generic medicines that are cheap but ensure a certain level of quality play an important role for the poor people in LMICs from the viewpoint of SDGs & UHC.

This study aims understanding the role of Indian pharmaceutical industry as "pharmacy of the developing world".

For the aim, this study examines the effect of Anti-retroviral Drug(ARV) to treat HIV. Indian generic ARV is considered to be a symbolic example as Inidia's"pharmacy of the developing world".

(2) Method

This study bases on review article about HIV infection and ARV's effect and proceeds as follows.

First, this study summarizes the history & development process of Indian pharmaceutical industry.

Second, this study summarizes the situation of HIV infection and effect of ARV.

Third, this study focuses on the situation of HIV infection & the prevalence and effect of ARV in India.

Finally, this study shows several findings,

(3) Results

This study shows several findings.

In India, the Government took measures to halt and reverse HIV infection focusing on HRGs(High risk groups). Many HRGs live in West, South and Northeast Regions in India.

Complied with increasing people living with HIV accessing ART(Anti-retroviral Therapy), number of AIDS-related deaths decreaced especially in West and South Regions in India.

On the other hand, the future significant increase of funding for ARV and the future

large-scaled cost down of ARV cannot expected.

Adherence is one of the most important issues to HIV treatment. However, adherence is barrier to HIV treatment in India.

(4) Limitations

Since State-wise time-series data about HIV prevalence in India were available, detailed information about ARV supply are unavailable. Furthermore, this study can not clearly show the causal relationship between inter-State differences in India and State-wise HIV prevarence. They will be the issues in the future.

2. The development history of Indian pharmaceutical industry

Not all the countries succeeded in enhancing the capabilities in the pharmaceutical industry. Most often, development of Indian pharmaceutical industry is projected as the most successful case of import substituting industrization of developing countries.

In the post-independence period, Indian pharmaceutical industry exhibited several stages of growth as follows.

(1) 1947～1970: Dominance by foreign firms and advent of domestic public sector firms

After independence of India in 1947, foreign firms, enjoying a strong patent protection under the Patent and Design Act 1911, were unwilling to local production and mostly opted for imports from their home country as working of the patent. Given the inadequate capabilities of the domestic sector to start local production of bulk drugs and hesitation of foreign firms to do so, the Government of India decided to intervene through starting public sector firms. This lead to the establishment of two public sector firms: the Hindustan Antibiotics Limited(HAL) in 1954 and the Indian Drug and Pharmaceutical Limited(IDPL) in 1961. The starting of the public sector firms has been an important feature in the evolution of the pharmaceutical industry as it assumed initiative roles in producing bulk drugs indigenously and led to significant knowledge spillovers on the private domestic sector.(Jaya Prakash

Pradhan[2006][1])

The establishment of the two public sector firms marked the beginning of India's move toward self-reliance in essential drugs. It had the effect of reducing the country's technological dependence on foreign firms in the long run. The 2 companies met about 40 % of India's requirement for essential bulk drugs.(Sunil K. Sahu[2014][2])

The public sector research laboratories under the Council for Scientific and Industrial Research(CSIR), especially Central Drug Research Institute(CDRI), Indian Institute of Chemical Technology(IICT) and National Chemical Laboratory(NCL) also contributed considerably to the growth of the Indian pharmaceutical industry. They contributed to the development of laboratory level processes that were transferred to domestic private firms. And they lead to scale up the technologies at the industry level. The CSIR laboratories also developed the process technologies. Almost all the top pharmaceutical firms in India have used the services of the CSIR.(Reji K. Joseph[2011][3])

(2) 1970～1980: Enactment of Patent Act 1970 and growth of domestic firms

The second growth stage of the industry took place in the 1970s.

In 1949, a committee chaired by Justice Bakshi Tek Chand, a retired Judge of Lahore High Court, was constituted to review the patent law for suggesting suitable amendments in the patent system to protect national interest. The committee recommended that Patents Act should be amended to ensure that food, medicine, surgical and curative devices are made available to the public at the cheapest price by giving appropriate compensation to the patentee. Another committee chaired by Justice N. Rajagopala Ayyangar examined and reviewed the Patent law to protect the national interest. The Patent bill 1965 based mainly on his recommendations was passed by Parliament and then Patents Act 1970 came into force on April 1972 along with Patent Rules 1972.(Rupesh Rastogi and Virendra Kumar[2014][4])

The enactment of the Patent Act 1970 are important milestones in the history of the Indian pharmaceutical industry. The Act enabled Indian citizens to access the

cheapest drugs in the world and paved a way for the growth of Indian pharmaceutical industry. The Patent Act 1970 allowed only process patents and abolished product patents protection. Indian pharmaceutical firms required to invent new processes for manufacture of patented drugs. In doing so, Indian pharmaceutical firms could produce drugs patented by the foreign firms through reverse-engineering. (Rupesh Rastogi and Virendra Kumar[2014])

The act lowered the period of validity of patents in drugs from 16 years to 7 years.(Sunil K. Sahu[2014])

The Foreign Exchange Regulation Act (FERA) 1973 put restrictions on foreign equity holdings and helped the growth of domestic pharmaceutical industy. Foreign ownership were permitted and required to reduce their foreign holdings to 40%. Foreign ownership ware permitted up to 74% to only those firms producing high technology drugs. Foreign firms were required to produce formulations based on imported bulk drugs and to start local production from the basic stage within a 2 year period.(Jaya Prakash Pradhan[2006])

The growth of the domestic sector firms was further accelerated by the New Drug Policy(NDP) announced in 1978. The NDP was based primarily on the recommendations of the Hathi Committee Report in 1975. It divided drugs into 3 groups for purposes of reserving items for production by various sectors. Whereas the production of 17 essential drugs was reserved for the public sector and production of 27 items was reserved for the domestic public and private sector, public and private, 64 items were open for licensing to all sectors, including the foreign sector.(Jaya Prakash Pradhan[2006])

The Drug Price Control Order(DPCO) was first legislated in 1963. It was amended in 1979 to control drug prices and to ensure availability of essential drugs to the public at affordable prices. While the first DPCO covered all bulk drugs and their formulations, the 1979 Act reduced the number of drugs under price control to 347 bulk drugs, of which about 225 were domestically produced. DPCO has since been amended twice(in 1986 and 1995). The number of drugs listed under DPCO was

reduced to 142 in 1986, to 74(covered 40% of the formation market) in 1995.(Sunil K. Sahu[2014])

(3) 1980～1995: Internationalization of Indian pharmaceutical industry

The outcomes of the strategic government interventions affected a regime of discrimination against foreign firms and provided strong growth impetus to the domestic sector firms during 1980s. Domestic firms achieved near self-sufficiency in the technology and production of bulk drugs based on large-scale reverse engineering and process innovation. In 1991, domestic firms have emerged as the main players in the market with about 70% and 80% market shares in the case of bulk drugs and formulations respectively. The pharmaceutical industry turned out to be one of the most export-oriented sectors in Indian manufacturing with more than 30% of its production being exported to foreign markets. The trade deficits of the 1970s have been replaced by trade surpluses during 1980s.(Jaya Prakash Pradhan[2006])

The decade of 1980s witnessed technological upheaval and radical regulatory reform in western markets. Significant among these was the Hatch–Waxman Act passed in 1984 in the US to stimulate the market for generics, lower prices and enable greater accessibility to healthcare for its citizens.(Jaya Prakash Pradhan[2006])

The comparative advantage of the Indian firms in reverse engineering and process improvements enabled it to access the US and European markets for generics. The Indian firm's capabilities had been developed in the middle stages of the product life cycle but had been excluded from the new drug discovery and clinical trial stages.(Sumati Varma[2010][5])

Economic liberalization policy by the Government of India in 1991 aimed to establish stronger linkages with global economy and resulted in profound policy changes for Indian industry in general and the Indian pharmaceutical industry in particular. Liberalization of the economy was accompanied by delicensing of the pharmaceutical sector. India signed the General Agreement on Tariffs and Trade(now WTO) agreement on intellectual property in 1994, making it mandatory

to introduce product patents and provide legal protection to Trade Related Intellectual Property Rights(TRIPS) by 2005.(Sumati Varma[2010])

(4) 1995～Present: Further growth of Indian pharmaceutical industry after TRIPS

The year 1995 was another milestone for Indian pharmaceutical industry and TRIPS changed the competitive landscape of Indian pharmaceutical industry. This marked a dramatic strategic change for the Indian pharmaceutical industry and was the trigger for a change in its internationalization strategy.(Sumati Varma[2010])

TRIPS provided a 3-stage frame: ①From January 1995, introduction of a mail box facility to receive and hold product patent applixations. But Exclusive Marketing Rights(EMR) could be obtained for that application if a patent had been granted in some other WTO member countries. ②From January 1995, compliance with other obligations of TRIPS. ③From January 2005, introduction of full product patent protection in all fields. All the product patent applications held in the mail box were also required to be taken up for examination. To meet TRIPS obligations, India amended its patent law on March 2005, abolishing process patents and reintroduced product patents.(Madhur Mahit Mahajan[2011][6])

In spite of facing difficulties, Indian pharmaceutical industy overcomed it and is continuing to develop through change in business strategies(e.g. focusing to R&D, strengthening of partnership with foreign firms and participation in Global Value Chain(GVC)).

Table 1 summarized the history of the growth of Indian pharmaceutical industry.

(5) Previous studies on Indian pharmaceutical industry

There are plenty of previous studies on Indian pharmaceutical industry after TRIPS.

① Management and business strategies

The performance of the Indian pharmaceutical firms in the post TRIPS period has remained fairly good and they are likely to grow further.(Teg Alam and Rupesh Rastogi[2017][7])

Policy facter(changes in US regulations and liberalization of Indian economy)

played a key role in Indian phamaceuticals industy's internationalization strategies. The motive behind overseas expansion of Indian pharmaceutical firms is need to global competitiveness and acquisition of assets. Firm size mains a big factor in determination of modes of internationalization.(Amisha Gupta[2018][8])

For Indian pharmaceutical industry, India's radical regulatory changes served to open up new economic opportunities and constraints. Regulatory changes were catalyst for the creation of dynamic capabilities in Indian pharmaceutical firms in the absence of the introducation of radical innovations and appropriate for the new market environment.(Suma Athreye, et al[2008][9])

Indian pharmaceutical firms drew upon firms'own strengths, vision and managed risk in different ways and also showed considerable intreprenuerial behaviour in pursuing new opportunities.(Ravi Kiran and Sinita Mishra[2009][10])

According to the empirical evidence from firm-level investigations, each Indian pharmaceutical firm has a rich mixure of resources and has accordingly outlined a strategy for itself. And Indian pharmaceutical firms were evolving from reverse engineering outfits catering to domestic market to technologically advanced and sophisticated organisations capable of catering to diverse markets. (Kalpana Chaturvedi and Joanna Chataway[2015][11])

Indian multinationals are also upgrading their business models from pure generics and bulk drug manufacturing to new drug discovery. Both in-house and collaborations with foreign multinationals are actively sought by Indian multinationals. Further, acquisitions of business units of foreign multinationals in the western countries are also often undertaken as a strategy for chasing the global competition.(Surender Munjal[2015][12])

An increasing number of Indian pharmaceutical firms are observed to be using acquisition as a strategy to overcome their limited innovation strength by accessing new products and their technologies, skills and new markets.(Jaya Prakash Pradhan[2008][13]Jaya Prakash Pradhan[2010][14])

Indian pharmaceutical industry have used acquisition as well as alliances in the

spirit of co-opetition rather than competition, both in the domestic and international market as an important element of the industry's survival strategy.(Sumati Verma[2010])

Indian pharmaceutical firms has shifted their formulations exports from highly regulated market to unregulated markets after TRIPS.(Bishwanjit Singh[2017][15])

Acquisitions of foreign companies significantly create short-term wealth to the shareholders of acquiring companies as M&A activities in pharmaceutical industry do not creat short-term wealth.(Neelam Rani, et al[2011][16])

② R&D and innovation

Indian pharmaceutical firms have increased their R&D efforts, moved to the development of the capabilities and opeted for viguous DMF(Drug Master File) abroad reflecting qualitative modifications and adjustment in their R&D capabilities.(Madhur Mohit Mahajan[2011])

Increased R&D have a positive impact on the export performance and global expansion and to do it public-private R&D partnership directed to basic research is encouraged.(Shipi Tyagi, et al[2014][17])

The patent-law changes in Indian pharmaceutical industry provide opportunities to study changes of institutional and regulatory environments on innovation and social welfare in low income markets.(Georg T. Haley and Usha C.V. Haley[2012][18])

Indian pharmaceutical industry has shown the strongest performance in post-TRIPS period. Not only did the industry improve its production performance seen in the previous decades, the industry turned into a net foreign exchange earner during the decade.

③ PPP(Public private partnership)

Indian pharmaceutical industry occupies an important position in the world, yet fails to give Indian people access to essential drugs. If the health policy objective of ensuring accessibility of drugs for all is to be satisfied, the state needs to play a much more active and pervasive role.(Sudip Chaudhuri[2007][19])

Path dependent systemic failures are observed to have impacted on the co-evolving

national system of innovation through the subcritical in-house product innovation capabilities, underdevelopment of local learning networks and lack of attention to domestic demand.(Dinesh Abrol, et al[2013][20])

Applied research at universities/public research labs and the culture of collaborating between academia/public labs and industry are insufficient. Adopting an innovation approach by the policymakers is an urgent need.(Bhawani Bhatnagar, et al[2015][21])

The link between domestic firms and public sector research organisations is weak. The government should rethink its strategies to get domestic firms to contribute to system-building activities.(Dinesh Abrol, et al[2019][22])

Appendix 1 shows the changes in the segment-wise annual turnover percentages based upon IBEF(Indian Brand Equity Foundation) data. Anti-infectives had the largest market share. Cardiac had also the large market share. Recently Anti-Diabetic is growing.(IBEF[2020][23][2015][24][2008][25])

Appendix 2 shows the top 15 pharmaceutical firms in India based on the overall revenue for 2018 financial year.

Indian Pharmaceutical Alliance(IPA)[2019][26] raises the 4 goals toward 2030: ①Accelerate the goal of universal health care across India and the world by providing access to high-quality affordable drugs, ②Emerge as an innovation leader to build a globally recognized position for India, ③Become the world's largest and most reliable drug supplier and reach US$120～130 billion by 2030, ④Contribute significantly to the growth of the Indian economy. Achieving these 4 goals will mean Indian pharmaceutical industry can improve its global market share to 7.0% by 2030 from current market share of 3.6% by value. It will also mean Indian pharmaceutical market will break into top 5 markets in the world from its current ranking of the 11th market by value.

So as to achieve Vision 2030, pursuing opportunities in newer product classes such as biosimilars, gene therapy and specialty drugs is important. In addition dependence on external markets for intermediates and API is critical problem for

Indian pharmaceutical industry as around 80% of India's requirements for API, by volume, are fulfilled by China.(IPA[2019])

3. HIV infection in the world and the role of the Indian generic drugs for treatment

(1) The history of the prevalence of ARV and the role of the Indian generic ARV

Human immunodeficiency virus(HIV) is an infection that attacks the body's immune system, specifically the white blood cells called CD4 cells. HIV destroys these CD4 cells, weakening a person's immunity against infections. If the person's CD4 cell count falls below 200, their immunity is severely compromised, leaving them more susceptible to infections. Someone with a CD4 count below 200 is described as having AIDS(acquired immunodeficiency syndrome).(WHO[27])

After its identification in 1981 as a novel distinct immuno deficiency syndrome, characterized by a depletion of CD4+T cells and an expansion of activated CD8+T cells, in 1983 AIDS was finally associated to HIV in a causative way.(Lucia Palmisano and Stefano Vella[2011][28])

The 1990s were years of pharmaceutical breakthrough in the prevention of HIV infection and the treatment of AIDS. 5 large multinational pharmaceutical firms developed a series of drugs that were effective in treating AIDS. In 1996, physicians in the US reported that patients treated with a combination of 3 of about 9 anti-HIV drugs, in a drug cocktail called HAART(Highly Active Antiretroviral Therapy) enjoyed near-miraculous improvements in health. These drugs are now referred to as "ARV(Anti-retroviral) drugs"because they have the potential to dramatically improve the health of people with AIDS.(Shyama V. Ramani and Vivekananda Mukherjee[2010][29])

However, with the costs of these drugs being well above US$10,000 PPPY(per-person per-year), it was out of reach for most patients in developing countries. Dr. Yousuf Hamied, the Chairman and Managing Director of Indian pharmaceutical firm Cipla, believes that providing essential drugs have a duty towards the poorest

in society for pharmaceutical firms and this belief motivated him to initiate research on ARV development. By 1997, Cipla became aware of HAART and started producing and marketing ARV. At last Cipla developed generic versions of ARV and announced a major price reduction for ARV. The cost of ARV required was US$350 PPPY for NGOs like MSF, US$600 PPPY for governments, and US$1,200 PPPY for retail distributers. The impact of Cipla's offer was immediate and significant.(Shyama V. Ramani and Vivekananda Mukherjee[2010])

South Africa wanted to the reasonably priced, good quality ARV and to stimulate production of ARV inside the country. A joint company called Cipla-Medpro, consisting of Cipla and a local firm, submitted an application of ARV in South Africa. In contrast, 39 pharmaceutical multinational firms accused the Government of South Africa to override its patents. The dispute developed to a global debate on fundamental priorities of patents and public health. In 2001 consequently the multinational pharmaceutical firms dropped their lawsuit. Cipla is about to get the first ARV registered in South Africa.(Von Richard Gerster[2002][30])

Cipla's dramatic price reduction widespread media attention. It also drew attention to the effects of generic competition in bringing drug prices down. Indian pharmaceutical industry was quickly becoming"pharmacy of the developing world".(Ellen Hoen, et al[2011][31])

In 2003, WHO and UNIAIDS(Joint United Nations Programme on HIV/AIDS) declared the lack of HIV/AIDS treatment to be a global public health emergency and announced the launch of a drive to get 3 million people on ART(Anti-retroviral Therapy) by 2005; this was the"3 by 5"campaign. The political momentum of the campaign, combined with newly available funding from governments, The Global Fund to Fight AIDS, Tuberculosis and Malaria(the Global Fund) and the US President's Emergency Plan for AIDS Relief(PEPFAR), allowed countries to begin purchasing ARV in significant volumes. By 2010, such purchases were predominantly generic ARV. The global donor-funded ARV market was comprised of generics, primarily from India.(Ellen Hoen, et al[2011])

There is indisputable evidence regarding the remarkable success over the past two decades in reducing HIV associated morbidity, mortality, transmission, stigma and improving the quality of life of people living with HIV. In 2014, UNAIDS and the partners launched the"90–90–90"targets; the aim was to diagnose 90% of all HIV-positive persons, provide ART for 90% of those diagnosed, and achieve viral suppression for 90% of those treated by 2020.(Luchuo Engelbert Bain, et al[2017][32])

UNAIDS shows the data as follows. In 2018, there were 37.9 million people living with HIV(PLHIV), 36.2 million adults and 1.7 million children(less than 15 years). In 2018, around 1.7 million were newly infected with HIV. As of end of June 2019, 24.5 million people were accessing ART. In 2018, around 770,000 people died from AIDS-related illnesses worldwide. AIDS-related deaths has declined by 33% since 2010(1.2 million) and have been reduced by more than 56% since the peak in 2004(1.7 million). In 2018, 79% of all people living with HIV knew their status, 62% were accessing treatment and 53% were virally suppressed in 2018.(UNAIDS[2019][33])

(2) Types and functions of ARV

ART consists of the use of a combination of at least three ARV from diferent classes to inhibit the replication of HIV. Continued suppression of viral replication leads to the restoration of immune response, reflected by an increase in the CD4 count. This increase leads to slowing of the disease progression, reduced frequency of Opportunistic infections, improvement in the quality of life and increased longevity. ARV cannot cure HIV infection, as the currently available ARV cannot eradicate the virus from the human body. The primary goals of ARV are maximal and sustained reduction of plasma viral levels and restoration of immunological functions. The reduction in the viral load also leads to reduced transmissibility and reduction in new infections.

The most commonly used drugs are as follows.

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors(NRTI) - NRTI act by incorporating themselves into the DNA of the virus, thereby stop the building process. The resulting DNA is incomplete and cannot create new virus. The

commonly used ARV of this class are Tenofovir(TDF), Zidovudine(ZDV, AZT), Lamivudine(3TC) and Abacavir(ABC).

Non-Nucleoside Reverse Transcriptase Inhibitors(NNRTI) - NNRTI stop HIV production by binding onto the reverse transcriptase and preventing the conversion of RNA to DNA. The commonly used ARV of this class are Efavirenz(EFV) and Nevirapine(NVP).

Protease Inhibitors(PI) - PI work at the last stage of the viral reproduction cycle. They prevent HIV from being successfully assembled and released from the infected CD4 cell. The commonly used ARV of this class are Atazanavir/ritonavir(ATV/r), Lopinavir/ritonavir(LPV/r), Darunavir(DRV) and Ritonavir(RTV).

Integrase Strand Tranfer Inhibitors(INSTI) - INSTI are a class of ARV designed to block the action of integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell. It can halt further spread of the virus. The commonly used ARV of this class are Raltegravir(RAL) and Dolutegravir(DTG).

Each ARV was approved by FDA as follows: AZT(ZDV) in 1987, d4T in 1994、3TC in 1995, NVP and RTV in 1996, EFV and ABC in 1998, LPV/r in 2000, TDF in 2001, FTC and ATV/r in T-20 in 2003, DRV in 2006, RAL in 2007, DTG in 2013, TAF in 2015.

Figure 1 shows the cycle of HIV infection and the types and functions of ARV.

UNAIDS Fast Track Report 2015(UNAIDS[2015][34]) estimated that 24.7 million person-years on ART in 2020 and 28.5 million person-years on ART in 2025(24.3 million on first-line treatment, 3.5 million on second-line treatment, and 0.6 million on third-line treatment).

Currently TDF is the most frequently used drug. Based on past data of WHO Survey on ARV Use, from 2009 to 2014, its market share increased consistently at the expense of the market share of AZT, to reach 69% of people on first-line treatment by 2014, and is forecasted to continue increasing. The introduction of TAF in 2019 will progressively erode the market share of TDF, leading to 31% patients on first-line using TAF by 2025. Whether TDF, AZT, or TAF is used, they will always be used

with either 3TC or FTC, most often as part of a FDC product. DTG is projected to be used by 57% on first-line treatment by 2025.(Aastha Gupta, et al[2016][35])

As far as the second-line treatment regimens, LPV/r was the most often used companion drug, with 81% of patients, and ATV/r was used by 17% in 2014. Use of ATV/r will reach to 66% market share by 2025. LPV/r will decline to 26% market share by 2025.(Aastha Gupta, et al[2016])

Clinton Health Access Initiative(CHAI)[2018] showed that TAF is a TDF pro-drug that could replace TDF in formulations such as TLD(TAF/3TC/DTG). Interest in TAF is largely based on potential cost savings relative to TDF-based regimens given a lower required dose(TAF 25mg vs TDF 300mg). The uptake of TAF-regimens is only forecasted to begin in 2021.

(3) Generic ARV manufacturing firms

Indian generic ARV dominate the ARV market, accounting for more than 80% of annual purchase volumes. Among paediatric ARV and adult nucleoside and non-nucleoside reverse transcriptase inhibitor markets, Indian-produced generics accounted for 91% and 89% of 2008 global purchase volumes, respectively. From 2003 to 2008, the number of Indian generic manufacturing firms supplying ARV increased from 4 to 10 while the number of Indian-manufactured generic products increased from 14 to 53. 96 of 100 countries purchased Indian generic ARV in 2008, including high HIV-burden sub-Saharan African countries. (a)Purchase ARV volumes supplied by Indian generic manufacturing firms (US$ million) and (b)% of Indian-manufactured generic ARV for countries with highest 2008 was as follows: 1 India (a)US$25.9 million (b)100%, 2 United Republic of Tanzania (a)US$27.3 million (b) 96%, 3 Nigeria (a)US$27.1 million (b)84%, 4 Ethiopia (a)US$27.6 million (b)96%, 5 Mozambique (a)US$15.3 million (b)99%, 6 Zambia (a)US$20.7 million (b)94%, 7 Namibia (a)US$15.3 million (b)99%, 8 Democratic Republic of the Congo (a)US$11.4 million (b)99%, 9 Kenya (a)US$10.2 million (b)82%, 10 Cameroon (a)US$15.0 million (b)93% (Brenda Waning, et al[2010][36])

(4) Cost calculations of ARV

Almost all API for ARV are prepared by chemical synthesis. Roughly 15 API account for essentially all of the ARV used in LMICs(Low and Middle Income Countries). Nearly all of the API purchased through the the Global Fund or PEPFAR are produced by generic firms. API are critical and the largest contribution to the overall cost of ARV, not the least because API account for about 60～80% of the cost of ARV. Efficient API production requires substantial investment in chemical manufacturing technologies and the ready availability of raw materials and energy at competitive prices. However, API price reductions for first-line ARV cannot continue indefinitely. Many of the API are reaching a point of diminishing returns for continued cost reduction.(Joseph M. Fortunak, et al[2014][37])

Since 2014, there have been 30% reduction in the price for generic ARV first-line treatment. TDF/FTC/EFV can be as low as US$100 PPPY, down from US$143 PPPY in 2014. Prices for first-line treatment are unlikely to decrease further, since they are now close to the minimum sustainable production price.(Médecins Sans Frontières, MSF)[2018][38])

According to CHAI HIV MARKET REPORT 2018, the annual costs of adult first-line were US$89, adult second-line costs were US$275 and pediatric treatment(first-line & second-line)were US$131 in 2017. The launch of TLD(TDF/3TC/DTG) put further price pressure. In the near-term, the price of TLD are expected to be further lower. In the longer-term, TAF-based ARV have the potential to help lower the cost of treatment further.(CHAI[2018])

Amy Zheng, et al[2018][39] compared the budget impact and HIV transmission effects of the 2 strategies for the estimated 444,000 and 916,000 patients likely to initiate ART in India over the next 2 and 5 years. Compared to SOC(TDF/3TC/EFV), DTG-based ARV improved 5-year survival from 76.7% to 83.0%, increased life expectancy from 22.0 years to 24.8 years, averted 13,000 transmitted HIV infection over 5 years, increased discounted lifetime care costs from $3,040 to US$3,240, and resulted in a lifetime ICER(incremental cost-effectiveness ratio) of US$130/YLS(year of life saved).

Appendix 3 shows the trends of major ARV FDC prices.

(5) Funding for HIV

Historically, the HIV response has been largely funded by international donors and governments, but LMICs are now beginning to lead on efforts to finance their HIV response. In 2015, domestic resources exceeded funds provided by donors and accounted for the majority of global HIV funding(57%), totalling US$10.9 billion. Although domestic investments increased by an average of 11% a year from 2006 to 2016, the rate of that increase slowed to 5% between 2015 and 2016. International HIV funding from donor governments is provided through both bilateral and multilateral channels. International investment in the HIV responses of these countries peaked in 2013 at nearly US$10 billion; it has since declined to around US$8.1 billion in 2016. The US accounted for the majority of bilateral and multilateral funding from donor governments in 2016(US$4.9 billion). Contributions by the US were followed by UK (US$645.6 million), France(US$242.4 million), the Netherlands(US$214.2 million) and Germany(US$182 million). Since 2006, these 5 countries have accounted for roughly 80% of all HIV funding from donor governments. This decline was due to a number of factors including the depreciation of donor currencies, delays in funding from the US, and the decision taken by many to front-load their contributions to the Global Fund. Founded in 2002, the Global Fund is an international financing organization that works in partnership between governments, civil society, the private sector and people affected by HIV, tuberculosis and malaria. It provides more than 20% of all international financing for HIV programmes. PEPFAR, initially started in 2003 as a five year, US$15 billion commitment by the US government to tackle the global HIV and AIDS epidemic PEPFAR has continued to this date and has spent more than US$70 billion on programmes globally to combat HIV/AIDS, tuberculosis, malaria and other Opportunistic infections since 2003. As well as providing funding for the global HIV response, many of the organisations provide other non-financial support such as price reductions for HIV treatment. The top 20 funders account for 87% of 2016

philanthropic resources, with the 2 largest funders — The Bill and Melinda Gates Foundation and Gilead Sciences representing over half of all philanthropic funding in 2016. Private philanthropic organizations provided US$680 million for global HIV and AIDS programmes in 2016. This is a 2% increase from 2015, the third consecutive year of growth, and US$8 million more than the previous record year of 2008. UNAIDS'ambitious Fast-Track approach, endorsed by the UN General Assembly in the 2016 Political Declaration on Ending AIDS, has committed to ending the global HIV epidemic as a public health threat by 2030. In order to achieve this, UNAIDS estimates that US$26.2 billion will be required for the HIV response in 2020, steadily decreasing to US$23.9 billion by 2030.(Figure 2) In order to reach the 2020 target, the world must increase the amount of resources available for the HIV response by around US$7 billion each year. As a result, there is a lot more emphasis on countries most affected by the HIV epidemic to finance their own responses and find more efficient and cost-effective ways to do so. Despite these rising financial commitments, the future outlook of global funding for the HIV response remains uncertain.(AVERT[2020][40])

(6) Medicines Patent Pool

In 2010, Unitaid created and invested in the Medicines Patent Pool(MPP), the world's first patent pooling initiative in public health, to address a need identified by WHO for a mechanism that could"examine the feasibility of voluntary patent pools for promoting the innovation of and access to health products and medical devices." MPP negotiates with patent holders for licences on life-saving medicines. These licences permit low-cost manufacturers to distribute patented medicines in LMICs. Licences also provide the freedom to develop new treatments needed in resource limited settings, such as paediatric formulations and FDCs. Competition amongst multiple manufacturers brings prices down, supporting treatment scale-up. As of December 2018, 11 MPP licensees were developing DTG 50mg, of which Cipla, Hetero and Mylan received WHO prequalification; Cipla and Mylan received US FDA approval; and Sun Pharma received approval from the Expert Review

Panel(ERP) coordinated by WHO. As of December 2018, 12 MPP licensees were developing TLD, of which Mylan received WHO prequalification; Hetero, Laurus Labs and Mylan received US FDA approval; and Cipla, Laurus Labs, Macleods and Sun Pharma received approval from the ERP. As of December 2018, 12 MPP licensees were developing TAF/FTC/DTG, of which Mylan received US FDA approval. As of December 2018, 4 companies were developing LPV/r, of which Aurobindo, Hetero and Mylan had US FDA approval, and Hetero and Mylan received WHO prequalification.(Medicines Patent Pool[2018][41])

(7) Changes in world-wide AIDS-related deaths after introducing ARV

Between 2005 and 2013, there has been a more than 50% decline in AIDS-related deaths in 9 countries(Ethiopia, Ghana, Haiti, Kenya, Malawi, Namibia, Thailand, Zambia and Zimbabwe) representing 19% of global AIDS-related deaths. Treatment in 3 countries increased from around 310,000 people on ART in 2005 to 3.2 million in 2013(46%) of people living with HIV. Significant decline in AIDS-related deaths was also seen in highest AIDS mortality burdened countries such as South Africa, India and Tanzania. On the other hand, 4 countries(Indonesia, Malaysia, Mozambique and South Sudan) representing 9% of global deaths have experienced a 42% increase in AIDS-related deaths between 2005 and 2013. In 2013, the number of people living with HIV on ART in these countries was 568,968(24%). South Africa and Nigeria could avert millions of deaths through the expansion of ART access, however, the number of AIDS-related deaths averted will directly depend on whether people living with HIV have earlier access to ART. These 2 examples illustrate the considerable potential impact of ART but also highlight that in many settings we have not realized the full benefits of ART access expansion.(Reuben Granlich, et al[2015][42])

Mari M. Kitahata, et al[2009][43] also examined that the early initiation of ART significantly improved survival, as compared with deferred therapy according to the analysis of 17,517 people living with HIV in the US and Canada who received medical care during the period from 1996 through 2005.

About two-thirds of AIDS-related deaths occur to those who are not on ART. The number of AIDS-related deaths would also be reduced sharply from 1.6 million in 2010 to 340,000 by 2030, or a reduction of nearly 80%. The constant coverage will leads to approximately same downward trend of the past several years achieved. Furthermore the adoption of the Fast-Track approach would result in averting 11 million AIDS-related deaths and 18 million new HIV infections globally during the period 2016–2030; and 9.6 million and 15.1 million respectively in LMICs.(John Stover, et al[2016][44])

Figure 3 shows the world-wide time-series changes in number of people living with HIV, people living with HIV accessing ART and AIDS-related deaths.

In conclusion, as seen in Figure 3, world-wide number of AIDS-related deaths showed declining trends in parallel with number of people living with HIV accessing ART. However the future declining trends will be relatively stable as future outlook of global funding is uncertain and future continued reduction of ARV cost is indefinite.

4. HIV infection in India

India has a low HIV prevalence of 0.22% in 2017. The country's epidemic is concentrated among high-risk groups(HRGs) and is heterogeneously distributed with wide geographic variations in the vulnerabilities that drive the epidemic. Even with this low prevalence, in terms of absolute numbers, India has the third highest burden of HIV in the world with an estimated 2.14 million[1] people living with HIV, 87,000 estimated new infections and 69,000 AIDS-related deaths annually.(NACO[2018][45])

[1] UN has estimated the number of people with HIV in India as 5.7 million. In 2006, the Government of India revised the number to 2.5 million as India vastly increased its data sources and the number of routine facility-based HIV surveillance sites increased since 20054.(Mariam Claeson and Ashok Alexander[2008])

Therefore, this study examines the India case of HIV infection from the viewpoint of area study.

(1) History of HIV infection in India and the Indian policy

① Beginning of HIV prevalence in India

With the reporting of first AIDS case in Chennai, Tamil Nadu in 1986, the Government of India perceived the threat of the HIV epidemic and started discussions about containing the epidemic with increased involvements of health managers/policy makers. Ministry of Health and Family Welfare(MOHFW) constituted Indian Council of Medical Research and National AIDS Committee(NAC) chaired by Union Health Minister. In 1989, Mid-Term Plan(MTP) for HIV/AIDS Control was developed with US$10 million budget provided from external sources. The Government of India focused on high vulnerability 4 States - Tamil Nadu, Maharashtra, West Bengal and Manipur and 4 metropolitan cities - Chennai, Kolkata, Mumbai and Delhi under MTP.(AM Kadri[2012][46])

② Establishmet of NACO and launch of NACP(～1992)

In 1992, the Government of India organized NACO(The National AIDS Control Organization) for HIV/AIDS prevention and control under MOHFW. NACP-I(National AIDS Control Program Phase-I) was launched from September 1992 to September 1997, with an IDA(The International Development Association, part of the World Bank) Credit of US$84 million.(Akanksha Rathi[2018][47])

In November 1999, NACP-II was launched with World Bank credit of US$191 million. While in Phase-I central agencies were the main players, during Phase-II states were put in front seat. Aim of the NACP-II was to bring down the HIV prevalence below 5% of the adult population in high prevalence States, below 3% in States where the prevalence was moderate and below 1% in remaining States. Tamil Nadu, Andhra Pradesh, Maharashtra, Manipur and Nagaland were identified as high prevalence States, while Gujarat, Goa and Pondicherry were put in medium prevalence States and other all States were considered as vulnerable States.(AM Kadri[2012])

In the meantime in 2003, WHO and UNAIDS begun its "3 by 5 Initiative", under which the goal was to ensure 3 million people living with HIV would be receiving treatment by 2005. The Government of India declared the target to ensure 100,000 people on ART by the end of 2005 and begun distributing free ART initiative on April 2004.(Dlplka Jahn and Rachel Stephens[2008][48])

With a rich learning of about two decades, NACP-III was launched in 2007 with the goal to halt and reverse the epidemic in India in next 5 years. Funding for Phase-III increased to 3-to 4-folds from Phase II funding. NACP-III key strategies are 1.Prevention of new infection in HRGs and general population, 2.Greater care, support and treatment to larger number of people living with HIV, 3.Strengthening the infrastructure, systems and human resources at the district, state and national level and 4.Strengthening the nationwide Strategic Information Management System. NACP-III looks District as an implementing unit and a very important institutional mechanism. District AIDS Prevention and Control Unit(DAPCU) is newly created.(AM Kadri[2012])

③ Evaluation of NACO and ART centres

NACP is now in its fourth phase(NACP-IV(2013～)), which aims to accelerate the process of epidemic reversal and further strengthen the epidemic response in India through consolidating gains, focusing on HRGs, scaling up services, providing comprehensive care support and treatment services to all and accelerating quality assurance.(NACO[2015][49])

According to NACO, after the launch of free ART initiatives for eligible people living with HIV in 2004, 8 Government hospitals were located in 6 high prevalence States. The ART centres are established in the Medicine department of Medical colleges and District Hospitals mostly in the Government sector. However, some ART centres are functioning in the sub-district and area hospitals, also, mainly in high prevalence States. The ART centres are set up based on prevalence of HIV in the District, volume of people living with HIV detected and capacity of the institution to deliver ART related services.(NACO[2018])

Till March 2019, 544 ART centres and 1,108 Link ART centres(LACs) are functioning. (NACO[2018][50])

Appendix 4-1 is ART centre distribution map drawn on India map.

Prevention services for HRGs and bridge populations(e.g. migrants and truck drivers) were scaled up nationwide through targeted-intervention projects.(Akanksha Rathi[2018])

The program of NACP has started from centrally controlled and moved down to Districts over the period of time very rapidly.(AM Kadri, et al[2012])

NACO evaluated the quality of ART centres and showed the result in 2015. The 357 facilities attained a combined average score 5 for the attribute of infrastructure, out of a maximum possible score of 7. Over 40.6%(145) ART centres achieved Excellent/Good score, 41.5%(148) centres received Average scores, whereas 17.9%(64) centres were graded as Poor.(NACO[2015])

Overall the ART centres were found to be performing satisfactory under this attribute. Overall, 80% of the facilities were found to be clean and well maintained. However the pharmacies in 40% of the ART centres will need space, storage and shelving as the space allotted to the pharmacy was inadequate or there was excessive humidity, which can lead to reduced shelf life and increased wastage of the ART. Over all 80% of the ART staff positions were filled. The recruitment status for most positions such as Counsellors, Pharmacists, Data Managers(DM), Care Coordinators and Laboratory Technicians(LT) was close to or more than 90%. While 74% of the Medical Officers(MO) were in position against the requirement, 47% of the SMO(Senior Medical Officer) positions were vacant and nearly on the nurse positions were vacant. Centre-wise analysis revealed that the SMO position was completely vacant in 169, MO positions in 85 Centres and staff nurse in 52.(NACO[2015])

④ Summary

Appendix 4-2 shows State-wise and Region-wise number of ART centres, people living with HIV accessing ART and the caluculations of the accessibility rate.

Appendix 4-3 shows the time-series changes in State-wise and Region-wise number of people living with HIV accessing ART. And Appendix 4-4 shows graphically the changes in number of people living with HIV accessing ART and number of AIDS-related deaths.

Evidences show that HIV epidemic in India is of concentrated type and characterized by the heterogeneity, following the patterns, where the epidemic shifts from the most vulnerable populations(such as FSW(female sex workers), MSM(men who have sex with men), IDU(injecting drug users) to bridge populations(clients of sex workers, sexually transmitted infection patients, partners of drug users, long route truck drivers, short stay cyclical single male migrants), then to the general population and from urban centers to rural areas(ruralization of epidemic) with increasing involvement of youth and women(feminization of epidemic).(AM Kadri, et al[2012])

In 2015 NACO evaluated that more than 0.88 million patients are receiving free ART at ART centres, which is the second highest number in the world. Wider access to ART has led to 29% reduction in estimated annual AIDS-related deaths between 2007 and 2011. It is estimated that the scale up of free ART since 2004 has averted over 150,000 AIDS-related deaths. It is further estimated that with the current pace of scale up of ART services will further avert approximately 50,000～60,000 deaths annually in the next 5 years. (NACO[2015])

The total number of people living with HIV remains stable at around 2.1 million, largely probably due to the increased life expectancy following ART.(Akanksha Rathi[2018])

(2) India's State-wise and Region-wise HIV infection

This section shows India's State-wise and Region-wise HIV epidemiological fact mainly based on NACO[2017a][51], NACO[2017b][52] and NACO[2017c][53]. Appendix 5-2 summarized changes in State-wise and Region-wise number of people living with HIV from 2007 to 2015. Appendix 5-3 summarized changes in State-wise and Region-wise number of people of new HIV infection from 2007 to 2015. Appendix 5-4

summarized changes in State-wise and Region-wise number of people of AIDS-related deaths from 2007 to 2015. Appedix 5-1 shows changes in State-wise and Region-wise population from 2006, 2011 to 2017.

① Northeast

A.L. Sharma, et al[2018][54] noted that in Northeast India the prime cause of the HIV is due to the uses of heroin smuggled from the"South Asia Golden Triangle" and complex patterns of cross-border movement for trade and commerce.

In Manipur, there was a steady decline in the total burden of the epidemic since 2007, from 30,399 in 2007 to 24,457 in 2015 – around 20% decline in total HIV/AIDS cases during last 8 years. During the same time period, AIDS-related deaths declined by 22%, from a total of 1,470 in 2007 to 1,146 in 2015. The estimated adult HIV prevalence continued to be high with an estimated adult prevalence of 1.15% in 2015. HIV prevalence rate among key populations in 2014-2015 were 12.1% among IDU and 5.9% among FSW.

A.L. Sharma, et al[2018] examined that in Manipur the drug abuse, social stigma, geographical location and resource limitation and socio-political problem of the region have contributed strongly on spreading and failure of preventively programme of HIV/AIDS.

In Mizorom, there has been an increase in the total burden of the epidemic since 2007, from 4,725 in 2007 to 5,762 in 2015 – a 22% increase in total estimated HIV/AIDS cases during last 8 years. During the same time period, AIDS-related deaths declined by 69%, from a total of 258 in 2007 to 79 in 2015. The estimated adult HIV prevalence has remained unchanged during last eight years at 0.80%. HIV prevalence rate among key populations in 2014-2015 were 10.0% among IDU and 5.9% among FSW.

In Nagaland, there was a margical decline in the total burden of the epidemic since 2007, from 12,005 in 2007 to 11,050 in 2015 – about 8% decline in total estimated HIV/AIDS cases during last 8 years. During the same time period, AIDS-related deaths declined by 60%, from a total of 724 in 2007 to 287 in 2015. The estimated

adult HIV prevalence has been high during last 8 years at 0.78%. Nagaland was the only State in country that recorded a prevalence of more than 1% among pregnant women. HIV prevalence rate among key populations in 2014-2015 were 5.9% among FSW, 3.2% among IDU and 1.8% among MSM.

② North

In Haryana, there was an increase in the total burden of the epidemic since 2007, from 15,380 in 2007 to 22,596 in 2015 – a 47% increase in total estimated HIV/AIDS cases during last 8 years. During the same time period, AIDS-related deaths declined by 32%, from 536 in 2007 to 364 in 2015. The estimated adult HIV prevalence among the general population appears to have an increasing trend during the last decade. HIV prevalence rate among key populations in 2014-15 were 7.3% among IDU, 1.7% among MSM and 1.5% among FSW.

In Punjab, there was a steady increase in the total burden of the epidemic since 2007, from 23,258 in 2007 to 36,794 in 2015 – a 58% increase in total estimated HIV/AIDS cases during last 8 years. During the same time, AIDS-related deaths declined by 47%, from a total of 978 in 2007 to 523 in 2015. The estimated adult HIV prevalence increased from 0.15% in 2007 to 0.19% in 2015. HIV prevalence rate among key populations in 2014-15 were 9.7% among IDU, 2.0% among MSM and 1.5% among FSW.

In Chandigarh[2], the total burden of the epidemic has nearly doubled during the last 8 years, from 1,414 in 2007 to 2,933 in 2015. While the estimated HIV prevalence among the adult population appears to be rising, wide uncertainty bounds indicates that trend need to be interpreted cautiously and shall be corroborated with findings of other data sources. During the same period, AIDS-related deaths also increased, from a total of 31 in 2007 to 87 in 2015. HIV prevalence rate among key populations in 2014-15 were 9.7% among IDU, 2.0% among MSM and 1.5% among FSW.

In Delhi, there was a steady increase in the total burden of the epidemic since 2007, from 17,799 in 2007 to 30,216 in 2015 – a 70% increase in the total HIV/AIDS cases

[2] Chandigarh is a city, district and union territory in India that serves as the capital of the two neighbouring states of Punjab and Haryana.

during last 8 years. During the same reference period, AIDS-related deaths remained stable, from a total of 345 in 2007 to 331 in 2015. HIV prevalence rate among key populations in 2014-15 were 21.8% among IDU, 2.4% among MSM and 1.5% among FSW.

In Rajasthan, there was a steady increase in the total burden of the epidemic since 2007, from 78,596 in 2007 to 103,148 in 2015 – around 31% increase in the total HIV/AIDS cases during last 8 years. During the same reference period, AIDS-related deaths increased by 40%, from a total of 2,930 in 2007 to 4,105 in 2015. The estimated adult HIV prevalence remained constant around 0.22～0.23%. HIV prevalence rate among key populations in 2014-15 were 21.8% among IDU, 2.4% among MSM and 1.5% among FSW.

③ Central

In Uttar Pradesh, there was a steady increase in the total burden of the epidemic since 2007, from 130,898 in 2007 to 150,361 in 2015 – a 15% increase in total estimated HIV/AIDS cases during last 8 years. During the same time, AIDS-related deaths declined by 32%, from a total of 7,677 in 2007 to 5,195 in 2015. The estimated adult HIV prevalence remained stable around 0.12%. HIV prevalence rate among key populations in 2014-15 were 27.2% among IDU, 2.9% among MSM and 0.8% among FSW.

In Madhya Pradesh, there was a decline in the total burden of the epidemic since 2007, from 44,664 in 2007 to 44,409 in 2015 – about 1% decline in total estimated HIV/AIDS cases during last 8 years. During the same time, AIDS-related deaths declined by 30%, from a total of 2,553 in 2007 to 1,799 in 2015. The estimated adult HIV prevalence came down slightly from 0.12% in 2007 to 0.09% in 2015. HIV prevalence rate among key populations in 2014-15 were 13.6% among IDU, 1.9% among MSM and 0.8% among FSW.

In Chhattisgarh, there was an increase in the total burden of the epidemic since 2007, from 27,237 in 2007 to 30,838 in 2015 – about 13% increase in total estimated HIV/AIDS cases during last 8 years. During the same time, AIDS-related deaths

declined by 41%, from a total of 1,788 in 2007 to 1,062 in 2015. The estimated adult HIV prevalence remained unchanged during the last 8 years at 0.19～0.20%. HIV prevalence rate among key populations in 2014-15 were 13.6% among IDU, 1.9% among MSM and 0.8% among FSW.

④ East

In West Bengal, there was a steady decline in the total burden of the epidemic since 2007, from 156,791 in 2007 to 128,757 in 2015 – an 18% decline in total estimated HIV/AIDS cases during last 8 years. During the same time, AIDS-related deaths declined by 23%, from a total of 10,509 in 2007 to 8,127 in 2015. The estimated adult HIV prevalence came down from 0.29% in 2007 to 0.21% in 2015. HIV prevalence rate among key populations in 2014-15 were 9.7% among IDU, 7.5% among Transgender people, 6.7% among MSM and 1.2% among FSW.

In Odisha, there was a steady increasing trend in total estimated HIV/AIDS cases until 2012, but since 2013 a declining trend is noted, from 67,591 in 2007 to 71,730 in 2012, to 67,654 in 2015. During the same time, AIDS-related deaths increased by 44%, from a total of 2,756 in 2007 to 3,965 in 2015. The estimated HIV prevalence among adult population declined from 0.30% in 2007 to 0.25% in 2015. HIV prevalence rate among key populations in 2014-15 were 9.7% among IDU, 6.7% among MSM and 1.2% among FSW.

In Bihar, there was an increase in the total burden of the epidemic since 2007, from 122,573 in 2007 to 150,689 in 2015 – a 23% increase in total estimated HIV/AIDS cases during last 8 years. During the same time, AIDS-related deaths increased by 59%, from a total of 4,722 in 2007 to 7,514 in 2015. The estimated adult HIV prevalence remained stable around 0.25%. HIV prevalence rate among key populations in 2014-15 were 27.2% among IDU.

⑤ West

In Gujarat, there was an increase in the total burden of the epidemic since 2007, from 142,206 in 2007 to 166,333 in 2015 – a 17% increase in total estimated HIV/AIDS cases during last 8 years. During the same time, AIDS-related deaths declined by

45%, from a total of 11,012 in 2007 to 6,067 in 2015. The estimated adult HIV prevalence has not declined during the last one decade, from 0.41% in 2007 to 0.42% in 2015. HIV prevalence rate among key populations in 2014-15 were 6.8% among MSM, 1.5% IDU and 1.1% among FSW.

In Maharashtra, there was a steady decline in the total burden of the epidemic since 2007, from 391,464 in 2007 to 301,453 in 2015 – a 23% decline in total estimated HIV/AIDS cases during last 8 years. During the same time, AIDS-related deaths declined by 81%, from a total of 34,927 in 2007 to 6,766 in 2015. Similarly, the estimated HIV prevalence among the adult population came down from 0.60% in 2007 to 0.37% in 2015. HIV prevalence rate among key populations in 2014-15 were 18.8% among Hijra/Transgender people, 7.4% among FSW, 4.9% among MSM, and 1.5% among IDU.

In Goa, there was a steady decline in the total burden of the epidemic since 2007, from 5,520 in 2007 to 4,619 in 2015 – a 16% decline in total estimated HIV/AIDS cases during last 8 years. During the same time, AIDS-related deaths declined by 81%, from a total of 393 in 2007 to 122 in 2015. The estimated HIV prevalence among adult population declined from 0.6% to 0.4% during last 8 years. HIV prevalence rate among key populations in 2014-15 were 6.8% among MSM, 1.5% among IDU and 1.1% among FSW.

⑥ South

In Andhra Pradesh & Telangana[3], there was a steady decline in the total burden of the epidemic since 2007, from 472,753 in 2007 to 394,661 in 2015 – a 17% decline in total HIV/AIDS cases during last 8 years. AIDS-related deaths also declined by 69%, from a total of 29,397 in 2007 to 9,249 in 2015. The estimated HIV prevalence among the adult population came down from 0.94% in 2007 to 0.66% in 2015. HIV prevalence rate among key populations in 2014-15 were 10.1% among MSM, 6.3% among FSW and 0.8% among IDU.

[3] In 2014, Ten districts of Andhra Pradesh State were carved out and Telangana State was officially formed.

In Karnataka, there was a steady decline in the total burden of the epidemic since 2007, from 244,500 in 2007 to 199,060 in 2015 – a 19% decline in total HIV/AIDS cases during last 8 years. AIDS-related deaths also declined by 80%, from a total of 18,370 in 2007 to 3,744 in 2015. The estimated HIV prevalence among the adult population came down from 0.68% in 2007 to 0.45% in 2015. HIV prevalence rate among key populations in 2014-15 were 5.8% among FSW, 4.1% among MSM, and 0.8% among IDU.

In Tamil Nadu, there was a steady decline in the total burden of the epidemic since 2007, from 161,743 in 2007 to 142,982 in 2015 – a 12% decline in total HIV/AIDS cases during last 8 years. AIDS-related deaths also declined by 73%, from a total of 13,886 in 2007 to 3,763 in 2015. The estimated HIV prevalence among the adult population came down from 0.34% in 2007 to 0.26% in 2015. HIV prevalence rate among key populations in 2014-15 were 3.8% among Hijra/Transgender people, 2.9% among MSM and 1.0% among FSW.

In Kerala, there was a steady decline in the total burden of the epidemic since 2007, from 27,945 in 2007 to 23,376 in 2015 – a 16% decline in total HIV/AIDS cases during last 8 years. AIDS-related deaths also declined by 23%, from a total of 1,342 in 2007 to 1,030 in 2015. The estimated HIV prevalence among the adult population came down from 0.15% in 2007 to 0.11% in 2015. HIV prevalence rate among key populations in 2014-15 were 2.9% among MSM, 1.0% among FSW and 0.8% among IDU.

⑦ Summary - Findings

Figure 4 shows the high HIV prevalence areas in 2007 on India map. The high prevalence areas identified as Karnataka, Andra Pradesh/Telangana and Tamil Nadu States in South, Maharastra State in West and Manipur, Mizorum and Nagaland States in Northeast in 2007. HRGs are concentrated in these areas, like IDU in Northeast and FSW and MSM in West and South.

Figure 5 shows Region-wise changes in the rate of number of people living with HIV per population. In West and South more rapid decreasing of the rate compared

to the others is confirmed.

Figure 6 shows Region-wise changes in the rate of number of AIDS-related deaths per number of people living with HIV. In West and South, more rapid decreasing of the rate compared to the others is confirmed.

Figure 7 shows time-series and Region-wise changes in (a)the rate of number of AIDS-related deaths per number of people living with HIV and (b)the rate of number of people living with HIV per population. The vertical line is (a)the rate of number of AIDS-related deaths per number of people living with HIV. The horizontal line is (b)the rate of number of people living with HIV per population. In West and South, very sharp curbs compared to the others is confirmed. The curves length became shorten from 2007-2011 to 2011-2015. This indicates the effect of ARV may be weaken after 2011.

Figure 8 shows time-series and Region-wise changes in (a)the number of AIDS-related deaths and (b)the number of people living with HIV accessing ART. The vertical line is (a)the number of AIDS-related deaths. The horizontal line is (b) the number of people living with HIV accessing ART. In West and South, very sharp curbs compared to the others is confirmed. This indicates the effect of ART in West and South.

According to Manoj V. Maddalli, et al[2015], 831,000 new people living with HIV and 482,000 AIDS-related deaths would occur in India over two decades if current ART initiation practices were maintained. Early ART initiation in this idealized care would result in 517,000 new people living with HIV(38% reduction) and 411,000 AIDS-related deaths(15% reduction) over two decades, at a cost-effectiveness of US$442/QALY-gained and incremental healthcare expenditures of US$329 million.

According to Rajneeth Kumar Joshi and Sanjay M. Mehendale[2019][55], 63 Districts with consistently high HIV prevalence were found clustered in the South and the Northeast. Population size, density and urbanisation were found to be positively associated with consistently high HIV prevalence in these Districts. Higher levels of literacy, better socio-economic status, higher proportion of population in

reproductive age group and late marriages were positively associated with consistently high HIV prevalence in almost all areas of India. Higher levels of knowledge about the role of condom in HIV prevention and condom use were associated with low HIV prevalence at the District level.

Increasing awareness about HIV alone is not sufficient for controlling the HIV epidemic and there is a need to raise knowledge levels about preventive measures against HIV and promote the use of condoms amongst population.

Estimated adult HIV prevalence retained a declining trend in India, following its peak in 2002 at a level of 0.41%. By 2010 and 2011, it levelled at estimates of 0.28% and 0.27%, respectively. Estimated number of people living with HIV reduced by 8% between 2007(2.10 million) and 2011(1.94 million). While children accounted for approximately 6.3% of the total HIV infections in 2007, this proportion increased to about 7% in 2011.(Yujwal Raj, et al[2015][56])

(3) Characteristics of HIV infection in India – from previous studies

① Importance of starting ART

According to the survey in 2011 conducted on 142 people living with HIV registered ART centres between 2005 and 2008, the probability of being alive at the end of 5 years was 85%. It was significant in patients with more than 95% adherence. The first line treatment was effective in patients attending the programme clinic. The adherence level influenced immunological and virological outcomes of patients.(Manisha Ghate, et al[2011][57])

According to the survey in Surat, Gujarat in 2011 conducted on 5,422 people living with HIV registered ART centres since 2006 until 2010, the 4 years survival probability was 88% after the start of ART. The crude mortality rate was 8.6%. The mortality density was 10.8 per 1000 person years.(Sridhar P Ryavanki, et al[2013][58])

According to the survey in Karnataka in 2011 conducted on 55,801 people living with HIV registered ART centres since 2006 until 2011, Those who were on ART had a higher likelihood of survival(788 per 1000) compared to those not on ART(690 per 1000) post 10 years since tested HIV-positive.(Prakash Javalkar, et al[2016][59])

② Importance of early treatment

Early ART initiation resulted in 1,050,000 new HIV infections and 883,000 AIDS-related deaths or 18% and 9% reductions, respectively compared to current numbers. (Manoj V. Maddalli, et al[2015][60])

According to the survey conducted on 972 people living with HIV, 71% were alive after 2 years of treatment. Over 2 years, 124 patients(13%) died; the majority of deaths(68%) occurred within the first 6 months of treatment. Over the 2-year period, 323 patients(35%) missed picking up their monthly drugs at least once and 147 patients(16%) were lost to follow-up.(Damodar Bachani, et al[2010][61])

According to the survey conducted in Andhra Pradesh on 992 people living with HIV, registered ART centres since 2005 until 2009, more than 50% of people living with HIV were died within the 6 months. The overall mortality density was estimated as 28 per 1,000 person-years at registration. Survival was significantly associated with age, sex, education, occupation, delay in ART registration and mode of transmission.(Ram Bajpal, et al[2014][62])

According to the survey conducted in 2013 on 139,679 people living with HIV, registered ART centres since 2007 until 2011, approximately 13.2% of those newly initiated on ART died during follow-up. Of those deaths, 56% occurred in the first 3 months. The crude mortality rate was 80.9 per 1,000 person-years at risk. The study findings revealed that high mortality was observed within the first 3 months of ART initiation. Patients with poor baseline clinical characteristics had a higher risk of mortality.(Ram Bajpal, et al[2016])[63]

According to the survey conducted in Uttar Pradesh on 1,689 people living with HIV, registered ART centres since 2009 until 2010, 272(16.10%) died, 205(12.13%) were lost to follow-up, 526(31.14%) were transferred out to other facilities and 686(40.63%) were alive at the end of 2 years. 92% of the deaths occurred in the first 6 months of therapy. The study findings revealed poor survival in the first 6 months of therapy especially in those with severe immunosuppression. This emphasizes the need for early enrollment into the programme.(Jaya Chakravarty, et al[2013][64])

According to the survey conducted in Pune, Maharastra on 270 people living with HIV, registered ART centres since 2009 until 2010, 17 patients(12%) died after ART initiation and 6 of them died within first 6 months. The probability of being alive at the end of one year was 94%, 92% at the end of 2 years, 91% at the end of 3 years, 87% at the end of 4 years and 85% at the end of 5 years. The first line treatment was effective in patients attending the programme clinic. The adherence level influenced immunological and virological outcomes of patients.(Nanisha Ghate, et al[2011][65])

③ Barriers to treatment

Lost to follow-up and low adherence remains the major challenge in the success of ART treatment. Lost to follow-up patients develop drug resistance virus resulting in failure to treatment and increasing the risk of AIDS-related deaths. One needs to do thorough investigation into the reasons of loss to follow-up and discontinuation of ART.(Seema Patrikar, et al[2018][66])

According to the survey conducted in Gujarat and Maharastra on 2,079 people living with HIV, registered ART centres since 2014 until 2015, 339(16%) were not started on ART within 2 months of registration, 115(34%) died, 152(45%) were lost to follow-up and 72(21%) were still in pre-ART care at 2 months of enrollment. The factors as key barriers to ART initiation(the reasons of not starting ART) were as follows. Government health system-related reasons are (a)long queues and increased waiting times for laboratory investigations, (b)overburdened staff in centres with high patient loads, inadequate remuneration, delays in salary payment, (c)frequently changing programme guidelines on ART eligibility, (d)occasional shortages in supplies of ARV, (e)the cost of patients'travel to the ART centre. Patient-related challenges reasons are (a)some patients perceived themselves as being healthy and were in denial about the existence of the HIV infection or the need for ART, (b)fears related to HIV, disclosure to family members and resulting stigma and discrimination, (c)adverse effects of ART and other medicines for co-infections, (d)preference for the traditional Indian system of medicine(traditional faith healers or ayurvedic healers), (e)tending to avoid government health facilities due to the

long queues, fear of disclosure and unfriendly staff behavior.(S. Chawlar, et al[2017][67])

④ Importance of adherence

One of the major important issues related to ART is a lifelong treatment to adhere to daily medication dosing schedules and scheduled visits to the ART center.

According to the survey conducted in 2009 in Maharashtra on 32 people living with HIV, multiple barriers to ART adherence and follow up were: (a)Financial barriers where the contributing factors were unemployment, economic dependency and debt, (b)Social norm of attending family rituals, and fulfilling social obligations emerged as socio-cultural barriers, (c)patients'belief, attitude and behaviour towards medication and self-perceived stigma were the reasons for suboptimal adherence, and (d)long waiting period, doctor-patient relationship and less time devoted in counselling at the center contributed to missed visits(N Joglekar, et al[2010][68])

According to the survey conducted in in West India on 755 people living with HIV, registered ART centres since 2014 until 2015, 534(70.7%) were alive on ART, 433(57.3%) were adherent, 61(8%) were transferred out, 68(9%) died, and 92(17%) were lost to follow-up. There is a need to emphasize on increasing drug adherence rate.(Kedar G. Mehta, et al[2016][69])

According to the survey conducted in in Allahabad, Uttar Pradesh on 152 people living with HIV, 94(61.8%) participants reported the occurrence of at least one adherence. The most common reason of non-adherence was forgetting to take the medicine(21.8%).(Arkapal Bandyopadhy, et al[2019][70])

According to the survey conducted in Bangalore, Karnakata on 60 people living with HIV, 60% were fully adherent. 100% adherence trends were seen in older people, male, those from larger families, those who had a previous AIDS defining illness, those taking fewer tablets, and without food restrictions. Commonest side-effects causing non-adherence were metabolic reasons(66%)(Jean Ann Saunders, et al[2009][71])

According to the survey conducted in 2007 in Jharkhand on 239 people living with

HIV, About 57% were adherent. The mortality rate was higher among patients who were non-adherent to ART(64.5%) than who were adherent(15.4%). Adherence to ART is associated with a higher chance of survival of HIV infected patients.(Sandeep Rai, et al[2013][72])

According to the survey conducted in South India on 536 people living with HIV, Nearly two third of the participants(359, 67.0%) reported more than 95% adherence. Common reasons for less adherence were personal commitments(51, 28.8%) and working time inconvenience(42, 23.7%). Demographic factors such as marital status, residing in rural area, and other personal factors like having good knowledge about ART, without side effects to drugs, and having support of friends and family members were found to show a high level of adherence to ART.(Vendan Hiregoudar, et al[2019][73])

According to the survey conducted in 2008 in South India on 198 people living with HIV, 49% were less than 95% adherence, People with alcohol use and sexually active were likely to be non-adherent.(Kartik K. Venkatesh, et al[2010][74])

According to the survey conducted in Mumbai, Maharastra on 152 people living with HIV, 57% were adherent. Knowledge of drugs, mode of transportation, side-effects, distance from clinic, cost of treatment, concurrent drug/alcohol abuse, and clinic satisfaction were reasons of non-adherence. 75% of patients reported cost of treatment to be the single greatest obstacle to adherence. Those claiming knowledge about their drugs were 2.3 times more likely to be adherent less than those who abused drugs or alcohol.(Eknath Naik, et al[2009][75])

According to the survey conducted in Karnataka on 242 people living with HIV, 31.6% were 100% adherent. The reason of non-adherence were Forgetfulness(44.9%), Depression(22.8%), Fear of disclosure(21.5%), Loss of interest in treatment(12%).(Bharatesh D. Basti, et al[2017][76])

⑤ Treatment challenges for HRGs

HIV prevalence among all adults has been declining steadily from 0.38% in 2001 to 0.26% in 2015, while among FSW, MSM and IDU it remains at 2.2%, 4.3%, and 9.9%,

respectively.(Sukurma Tanwar, et al[2016])

According to the survey conducted in 2007 in Chennai, the primary individual-level barrier for kothis(men who have sex with men whose gender expression is feminine) and aravanis(transgender women, also known as hijras) were integrally linked to the family/social and healthcare levels: many kothis and aravanis feared serious adverse consequences if their HIV-positive status were revealed to others. Consequences of disclosure, including rejection by family, eviction from home, social isolation, loss of subsistence income, and maltreatment within the healthcare system, presented powerful disincentives to accessing ART.(Venkatesan Chakrapani, et al[2011][77])

According to the survey conducted in 2009 in Chennai, Maharastra on 210 MSM, 39% were experienced a high-level of stigma in their lifetime. More than one fifth of the MSM reported unprotected anal sex(UAS) in the past three months.(Beena Thomas, et al[2012][78])

According to the survey conducted in 2009 in Visakhapatnam(Andhra Pradesh), Hyderabad (Telangana), Chennai and Madurai(Tamil Nadu), Bengalore(Karnataka) on 47 wives of MSM, wives of MSM were at risk for HIV from their husbands'sexual practices, which are often hidden to avoid the potential consequences of stigmatisation, and from gender-based inequities that make husbands the primary decision-makers about sex and condom use.(Celillia Tomori, et al[2018][79])

According to the survey conducted with available program data year-wise from 2008–2009 to 2014–2015 in West Bengal, trucker group showed a significant increase in HIV positivity over the past 3 years,since FSW, MSM, IDU and migrant did not undergo significant changes.(Suman Gamguly, et al[2018][80])

According to the survey conducted in Chennai, migrants and partners of migrants faced a complex series of obstacles to accessing HIV diagnosing and treatment. Employment insecurity, lack of entitlement to sick pay or subsidised healthcare at destination are their obstacles, delay in disclosure of husband's HIV status led to delays in their treatment.(Tanvi Rai, et al [2015][81])

According to the survey conducted in 2013 in 7 Northeast and 8 North/Central

cities on 14,481 IDU, the median estimated HIV prevalence was 18.1%. HIV prevalence was higher in Northeast while HIV incidence was higher in North/Central. In Kanpur, Uttar Pradesh had an HIV prevalence of 31%. The odds of prevalent HIV were over 3-fold higher in women than men.(Gregory M. Licus, et al[2015][82])

According to the survey conducted in the 4 high HIV prevalence States on 5,498 FSW, F SW with greater degree of mobility were more vulnerable against HIV than the FSW with lesser degree of mobility. They experienced physical violence, consumed alcohol prior to sex, and did inconsistent condom use in sex with clients.For FSW, mobility and socio-economic vulnerabilities are important factors.(Niranjan Saggurti, et al[2011][83])

⑥ Opportunistic infections

India has the highest tuberculosis(TB) burden in the world with an estimated 2.8 million new cases in 2016. Of these cases, 87,000(3%) were estimated to also have HIV co-infection, which is the second highest TB-HIV burden in the world after South Africa.(Chandravali Madan, et al[2018][84])

According to the survey conducted between 2002 and 2004 in Pune, Maharastra, TB was the most common Opportunistic infections(OI) with an incidence of 15.4 per 100 person-years, followed by oral candidiasis 11.3 per 100 person-years, herpeszoster 10.1 per 100 person-years, and cryptococcal meningitis 1.7 per 100 person-years.(Manisha Ghate, et al[2007][85])

According to the survey conducted between 2006 and 2012 in Assam on 5,612 people living with HIV, 370 deaths have occurred. TB(28%) was the most common Opportunistic infections, followed by AIDS-related complex(11%), wasting syndrome(9%) and multiple infections(9%). TB has remained the leading cause of death among people living with HIV. Strengthening the linkages and referral between the HIV and TB program will be crucial to reduce the AIDS-related deaths attributed to TB.(Chiraneev Bhattacharya, et al[2018][86])

⑦ Funding, cost and procurement

According to the survey conducted in Andhra Pradesh(high-HIV burden State) and Rajasthan(low-HIV burden State) from fiscal year 2007–2008 to 2012–2013, the average cost per patient alive and on ART in 2015–2016 was US$162 in undivided in Andhra Pradesh and US$186 in Rajasthan, which was 51.4% and 35.8% lower than in 2007–2008, respectively. Average ARV cost declined by 27.2% from fiscal year 2007–2008 to 2012–2013.(G.Anil Kumar, et al[2018][87])

The cost for ART services from April 2013 to March 2014 was US$133.89 PPPY, of which US$88.66(66%) is for ARV, US$45.23(34%) is for non-ART recurrent expenditure, while the cost for pre-ART care is US$33.05 PPPY.(Reshu Agarwal, et al[2017][88])

According to a MSF activist, some Indian ARV suppliers stopped participating in the government's tender process over the past year because of delays in getting paid. Cipla had stopped bidding in the tender process. According to another activist, Cipla is making drugs for Tuberculosis, leprosy and cancer, etc, but for HIV they are not bidding because they are getting more margins from exporting the drugs," "Individually we cannot pursue companies."[89]

5. Conclusion

(1) Findings

① Trends of HIV prevalence(India's case)

・As shown in Chapter 4, HRGs(High Risk Group) are clusters of HIV prevalence in India, during 2000s.

・As shown in Figure 4, West(like Maharastra State), South(like Karnataka, Andra Pradesh/Telangana and Tamil Nadu States), Northeast(Manipur, Mizorom and Nagaland States) Regions are high risk(high HIV prevalence) areas in India.

・It implies that many FSW(Female Sex Workers) and MSM(Men who have Sex with Men) live in West and South Regions and many IDU(Injecting Drug User) live in Northeast Region.

・Since recognized this situation, the Government of India took measures to halt and

reverse HIV prevalence through NACP(The National AIDS Control Program), distributing free ARV and establishing ART centres focusing on HRGs.

・As shown in Figure 5, 6, 7 and 8, complied with increasing people living with HIV accesing ART, number of AIDS-related deaths in West and South decreaced.

・The findings offer the implications that distributing ARV affected AIDS-related deaths in India.

・Since the confounding factors are not measured and considered, this study can not conclude the effects or the degree of these effects.

② Future prospect of HIV prevalence

・As shown the previous study of AM Kadri, et al[2012], now, the epidemic is shifting HRGs to bridge populations(like long route truck drivers, migarants and so on), urban centers to rural areas in India. India's measures also shifted by Central Government to by District. It implies that the main targets are shifting large clusters in West and South Regions in India to small clusters all over India.

③ Funding for ARV and cost of ARV

・In 2000s, funding of ARV increased gradually and cost of ARV were dropped year by year. However, since the future significant increase of funding amount and cost down can not be expected due to the major donnors' fisical conditions and limitation of ARV's cost structure, the future funding increase and large-scaled cost down are indefinited. This might lead to ARV supply shortage and might be affect the future effects of HIV treatment to people living with HIV.

④ ARV Adherence

・Adherence is one of the important isssues to HIV treatment since ARV can restrict the HIV functions but can not cure HIV infection. The daily dosing of ARV is indispensable.

・However as many previous studies indicated, adherence is barrier and challenging to HIV treatment in India. Adherence is vital problem except for ARV supply shotage.

・As shown by many previous studies, adherence is both patient side problem and

medical staff side problem.

(2) Limitations

・Since State-wise time-series data about HIV prevalence in India were available, detailed information about ARV supply both in volume and in value(e.g. State-waise, District-wise and ART centre-wise) is unavailable.

・In addition, since adherence is vital problem in India, inclusive(all over India level and State-wise level) fact data can not find out.

・Furthermore, this study can not clearly show the causal relationship between inter-State differences in India and State-wise HIV prevarence.

(3) Discussion

・One implication of this study is that prevalence of infectious diseases in India might be related to the role of the government, world organizations, generic pharmaceutical firms and inter-State differences in India.

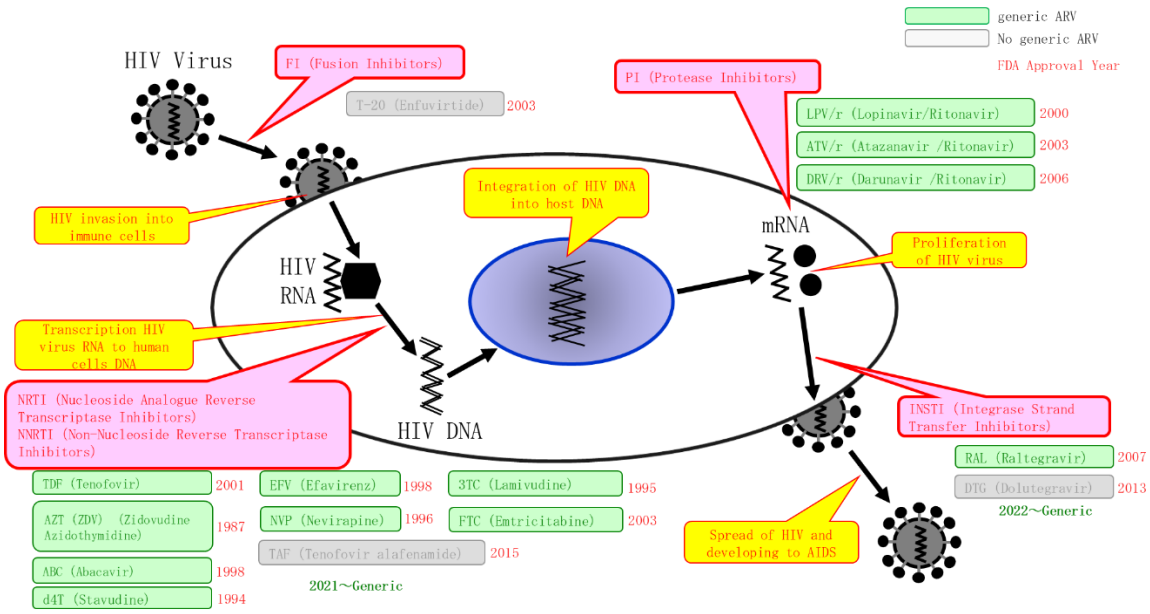
・Several findings(made use of previoous studies) in this study could be extended to lead to studies about the other infectious diseases in India and more comprehensive studies about the role of Indian pharmaceutical industry as“pharmacy of the developing world”.

Table 1　History of Indian Pharmaceutical Industry

History of Indian phrmaceutical industry

	Domestic law and system related to phrmaceutical industry	Domestic business circumstances & Government policy	International affairs related to phrmaceutical industry
1947		Independence	
1950			
		MNCs' dominance of domestic market	
	The Drug Price Control Order, DPCO	Establishment of public-sector companies & laboratories	
1970	The Patents Act, 1970 Drug Price Control Order, 1970	(HAL, IDPL % CDRI)	
	The Foreign Exchange Regulation Act (FERA)	Industyial Policy, 1973	
1975		Domestic companies development	
		The New Drug Policy (NDP), 1978	
	The Drug Price Control Order, 1970		
1980			
			Hatch-Waxman Act
1985		Domestic companies dominated domestic market	
	The Drug Price Control Order, 1986	Modifications in Drug Policy	
		Tranfer to an excess of xxport over import	
1990		Beginning of Internationalization	
		Policy change to economic liberalization	
1995	The Drug Price Control Order, 1995		Agreement on Trade-Related Aspects of Intellectual Property Rights, TRIPS
2000			
		Phrmaceutical Policy, 2002	Cipla introduced generic ARV to South Africa
2005	The Patents (Amendment) Act		Achieving complete TRIPS compliance
2010			Patent Cliff

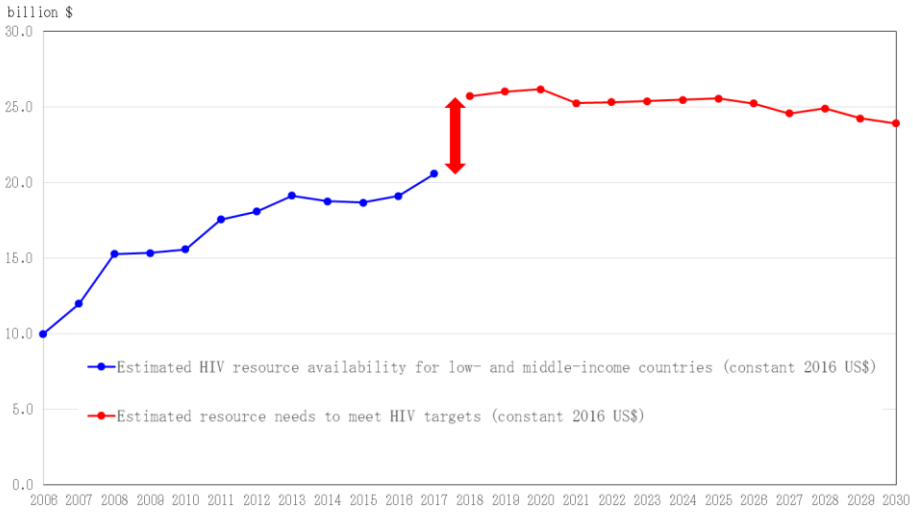
Figure 1



HIV Cycle & Functions of major ARV

【Data source】Created based upon data from National AIDS Control Organization(NACO) "National Technical Guidelines on ART October 2018"

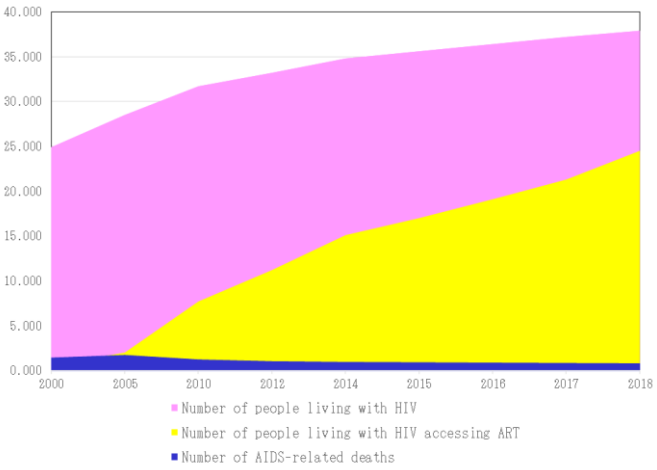
Figure 2



Estimated HIV resource availability for LMICs and Needs to meet HIV targets

【Data source】Created based upon data from AVERT Website"Funding for HIV and AIDS"(https://www.avert.org/professionals/hiv-around-world/global-response/funding)

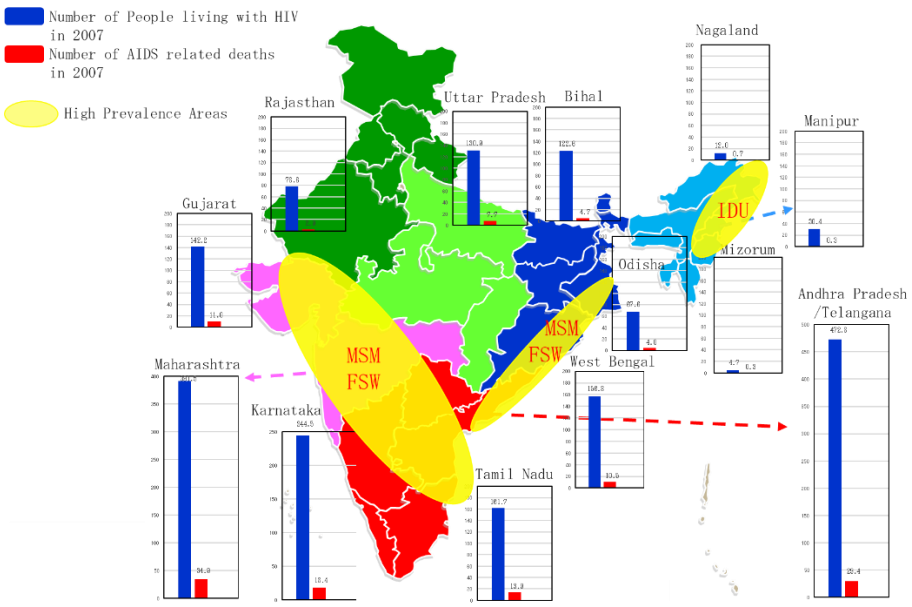
Figure 3



Time-series changes in world-wide Number of people living with HIV, Number of people living with HIV accessing ART and Number of AIDS-related deaths

【Data source】Created based upon data from UNAIDS[2019]"Fact Sheet - World AIDS Day 2019"

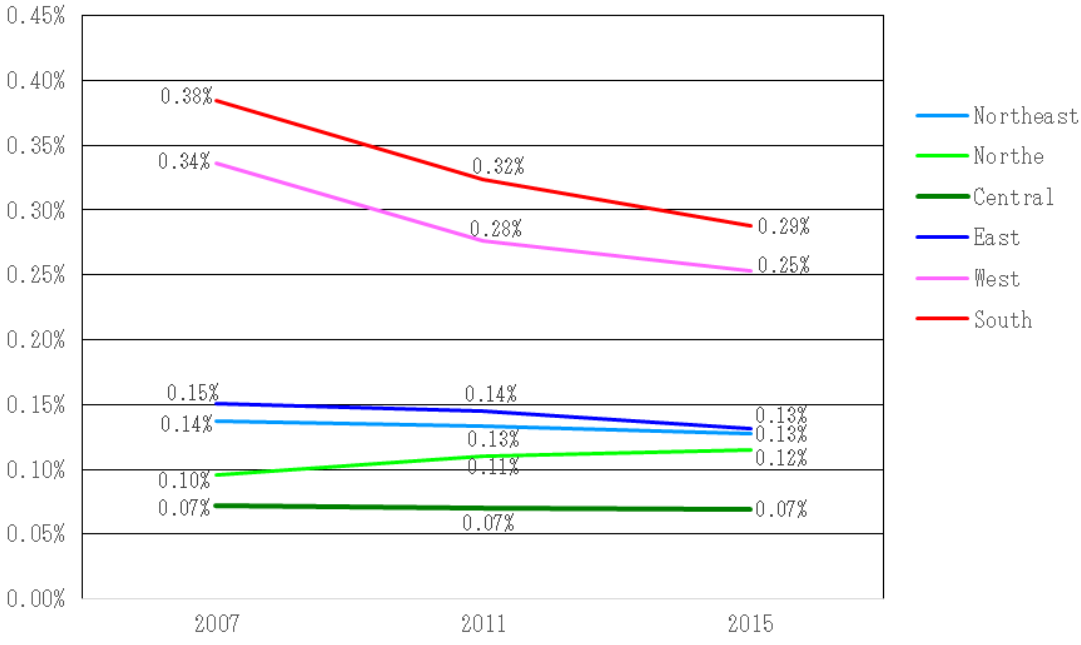
Figure 4



HIV high prevalence area in India in 2007

【Data sources】Created based upon data from National AIDS Control Organization(NACO)

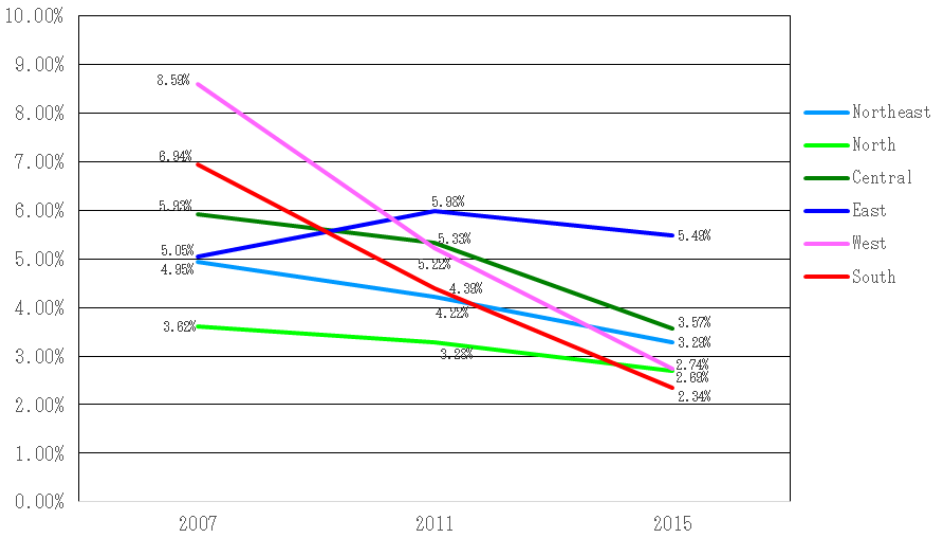
Figure 5



Region-wise changes in rate of number of people living with HIV per population

【Data sources】Created based upon data from National AIDS Control Organization(NACO) and Office of the Registrar General & Census Commissioner, India

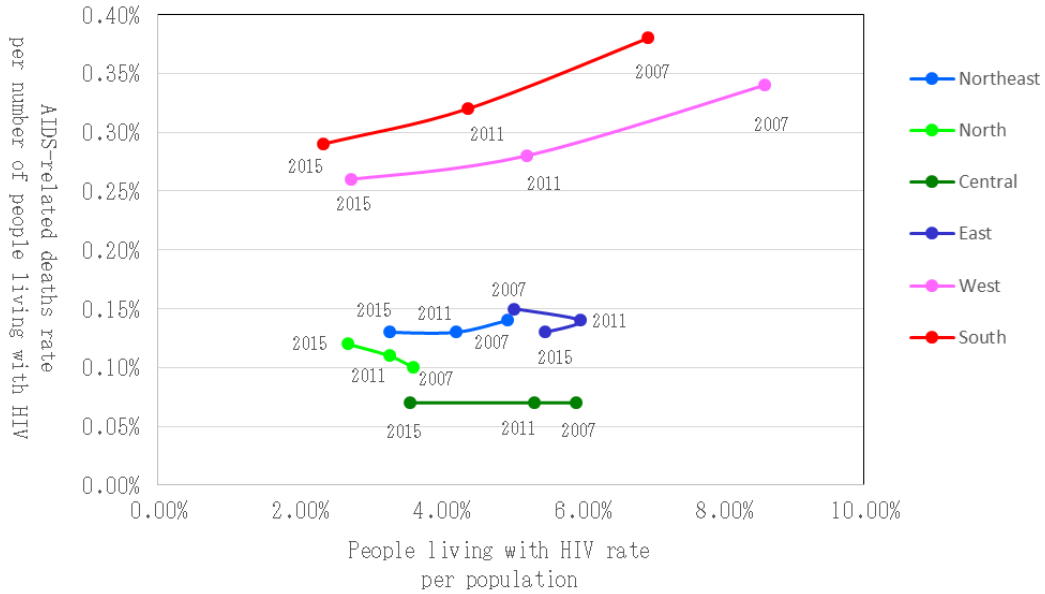
Figure 6



Time-series Region-wise changes in rate of AIDS-related deaths per number of people living with HIV

【Data sources】Created based upon data from National AIDS Control Organization(NACO)

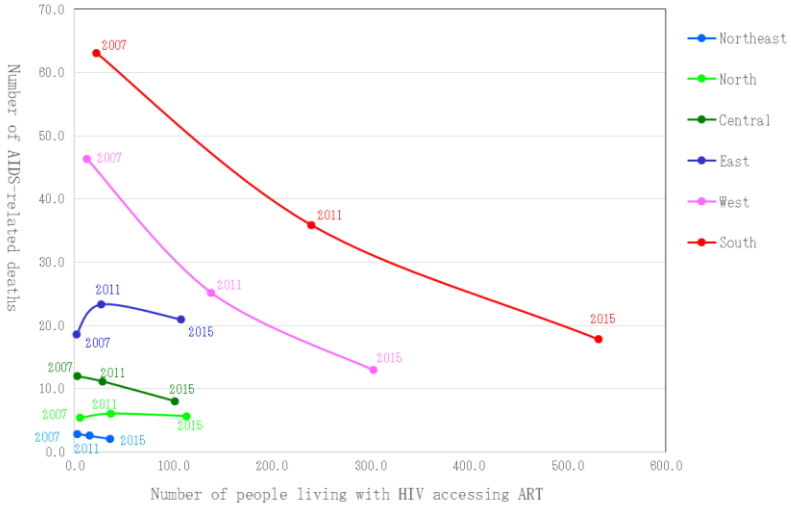
Figure 7



Time-series & Region-wise changes in People living with HIV rate per population and AIDS-related deaths rate per number of people living with HIV

【Data sources】Created based upon data from National AIDS Control Organization(NACO)

Figure 8



Time-series Region-wise changes in numbers of people leving with HIV accessing ART and numbers of AIDS-related deaths

【Data sources】Created based upon data from National AIDS Control Organization(NACO)

[References]

2. The development history of Indian pharmaceutical industry

[1] Jaya Prakash Pradhan[2006]"Global Competitiveness of Indian Pharmaceutical Industry: Trends and Strategy"Institute for Studies an Industrial Development(ISID), Working Paper 2006/05

[2] Sunil K. Sahu[2014]"Globalization, WTO, and the Indian Pharmaceutical Industry"Asian Affairs: An American Review

[3] Reji K. Joseph[2011]"The R&D Scenario in Indian Pharmaceutical Industry"Research and Information System for Development Countries(RIS)Discussion Paper #176, December 2011

[4] Rupesh Rastogi and Virendra Kumar[2014]"The Influence of TRIPS Compliant Patent Laws on Indian Pharmaceutical Industry"School of Management Sciences（SMS） Lucknow A Journal of Management Sciences, Vol. 4, No. 1, June, 2014

[5] Sumati Varma[2010]"Strategic Alliances in A Changing Global Order - A Study OF The Indian Pharmaceutical Industry"International Conference on Strategy and Organisation, 14-15 May 2010

[6] Madhur Mahit Mahajan[2011]"The Emergence of New R&D Paradigms in the Indian Pharmaceutical Industry: Post TRIPS Period"Journal of Intellectual Property Rights

, Vol 16, July 2011

[7] Teg Alam and Rupesh Rastogi[2017]"Agreement on trade-related aspects of intellectual property and the pharmaceutical industry: An empirical study" International Journal of Mechanical Engineering and Technology(IJMET). Volume 8, Issue 9, September 2017, pp369-377

[8] Amisha Gupata[2018]"Internationalization of Indian Pharmaceutical Industry" Global Journal of HUMAN-SOCIAL SCIENCE: Economics, Volume 18, Issue 2, Version 1.0, 2018

[9] Suma Athreye, et al[2008]"Experimentation with strategy and evolution of dynamic capability in the Indian Pharmaceutical Sector"United Nations University Working Paper Series #2008-041

[10] Ravi Kiran and Sinita Mishra[2009]"Performance of the Indian Pharmaceutical Industry in Post-TRIPS Period: A Firm Level Analysis"International Review of Business Research Papers, Vol. 5 No. 6 November 2009, pp148-160

[11] Kalpana Chaturvedi and Joanna Chataway[2006]"Strategic integration of knowledge in Indian pharmaceutical firms: creating competencies for innovation"Journal of Business Innovation and Research, Vol. 1, Nos 1/2, 2006

[12] Surender Munjal[2015]"Internationalization of Indian Pharmaceutical Multinationals"International Business and Strategy: Theory and Practise

[13] Jaya Prakash Pradhan[2008]"Overcoming Innovation Limits through Outward FDI: The Overseas Acquisition Strategy of Indian Pharmaceutical Firms" Munich University Personal PePEc Archive(MPRA) Paper No.2. 12362

[14] Jaya Prakash Pradhan[2010]"Strategic Asset-seeking Activities of Emerging Multinationals Perspectives on Foreign Acquisitions by Indian Pharmaceutical MNEs" Organizations and Markets in Emerging Economies, 2010, Vol.1 No.2(2)

[15] Bishwanjit Singh[2017]"Impact of TRIPS and RTAs on the Indian Pharmaceutical Product Exports"International Journal of Research in Economics & Social Sciences

[16] Neelam Rami, et al[2008]"Impact of Mergers and Acquisitions on Shareholders' Wealth in Short-Run: An Empirical study of Indian Pharmaceutical Industry"International Journal of Global Business and Competitiveness, 2011, Vol. 6, No. 1, pp40-52

[17] Shipi Tyagi, et al[2014]"Innovations in Indian Drug and Pharmaceutical Industry: Have they Impacted Export?" Journal of Intellectual Property Rights, Vol19, July 2014, pp243-252

[18] Georg T. Haley and Usha C.V. Haley[2012]"The effects of patent-law changes on innovation: The case of Indian pharmaceutical industry" Technological Forecasting & Social Change 79(2012) pp607-619

[19] Sudip Chaudhuri[2007]"The Gap Between Successful Innovation and Access to its Benefits: Indian Pharmaceuticals" The European Journal of Development Research, v. 19, pp49-65

[20] Dinesh Abrol, et al[2013]"Innovation patterns limits to learning and the pathway of neoliberal globalization evidence from Indian pharmaceutical multinationals" International Journal of Technological Learning, Technological Learning, Innovation and Development, Vol,6 Nos,1/2, 2013

[21] Bhawani Bhatnagar, et al[2015]"Open Innovation Networks in Indian Pharmaceutical Sector" British Academy of Management(BAM) 2015 Conference Proceedings

[22] Dinesh Abrol, et al[2019]"India's Domestic Pharmaceutical Firms and Their Contribution to National Innovation System-building" Economic and political weekly, Vol. 54, Issue No. 35, 31 Aug, 2019

[23] India Brand Equity Foundation (IBEF)[2020]"Pharmaceuticals February 2020"

[24] India Brand Equity Foundation (IBEF)[2015]"Pharmaceuticals March 2015"

[25] India Brand Equity Foundation (IBEF)[2008]"Pharmaceuticals December 2008"

[26] Indian Pharmaceutical Alliance(IPA)[2019]"The Indian pharmaceutical industry the way forward"

[27] World Health Organization Website (https://www.who.int/health-topics/hiv-aids/) . (Accessed June 13, 2020)

[28] Lucia Palmisano and Stefano Vella[2011]"A brief history of antiretroviral therapy of HIV infection: success and challenges" Annali dell'Istituto superiore di sanita, 2011, Vol. 47, No. 1: pp44-48

[29] Shyama V. Ramani and Vivekananda Mukherjee[2010]"CSR and market changing product innovations: Indian case studies"United Nations University Working Paper Series #2010-026, p13-14

[30] Von Richard Gerster[2002]"The success story of the Indian pharmaceutical industry" Medicus Mundi Schweiz, #84 April 2002

[31] Ellen Hoen, et al[2011]"Driving a decade of change: HIV/AIDS, patents and access to medicines for all"Journal of the International AIDS Society, 2011, 14:15

[32] Luchuo Engelbert Bain, et al[2017]"UNAIDS 90–90–90 targets to end the AIDS epidemic by 2020 are not realistic: comment on "Can the UNAIDS 90–90–90 target be achieved? A systematic analysis of national HIV treatment cascades"BMJ Global Health 2017, 2:e000227

[33] UNAIDS[2019]"Fact Sheet – World AIDS Day 2019 Global HIV Statistics"

[34] UNAIDS[2016]"How many people living with HIV access treatment?

[35] Aastha Gupta, et al[2016]"Projected Uptake of New Antiretroviral (ARV) Medicines in Adults in Low- and Middle-Income Countries: A Forecast Analysis 2015-2025"PLoS One 11(10), e0164619

[36] Brenda Waning, et al[2010]"A lifeline to treatment the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries"Journal of the International AIDS Society, 2010, 13:35

[37] Joseph Fortunak, et al[2014]"Active pharmaceutical ingredients for antiretroviral treatment in low- and middle-income countries: a survey"National Institutes of Health(NIH) Public Access Author Management

[38] Médecins Sans Frontières(MSF)[2016]"Untangling the web of antiretroviral price reductions"18th edition – June 2016

[39] Amy Zheng, et al[2018]"The cost-effectiveness and budgetary impact of a dolutegravir-based regimen as first-line treatment of HIV infection in India" Journal of the International AIDS Society 2018, 21:e25085

[40] AVERT Website"Funding for HIV and AIDS"(https://www.avert.org/professionals/hiv-around-world/global-response/funding) (Accessed June 13, 2020)

[41] Medicine Patent Pool[2018]"MPP 2018 Annual Report: EXPANDING ACCESS to public health"

[42] Reuben Granich, et al[2015]"Trends in AIDS Deaths, New Infections and ART Coverage in the Top 30 Countries with the Highest AIDS Mortality Burden; 1990-2013"PLOS ONE,10(7), e0131353

[43] Mari M. Kitahata, et al[2009]"Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival"The New England Journal of Medicine, Vol.360 No.18, April 2009

[44] John Stover, et al[2016]"What Is Required to End the AIDS Epidemic as a Public Health Threat by 2030? The Cost and Impact of the Fast-Track Approach" PLOS ONE, 11(5), e0154893

4. HIV infection in India

[45] National AIDS Control Organization(NACO), Ministry of Health and Family Welfare, Government of India[2018]"Technnical Guidelines on Anti Retroviral Treatment"

[46] AM Kadri, et al[2018]"Insititutionalization of the NACP and Way Ahead"Indian Journal of Community Medicine, 2012 Volume 37 Issue 2, pp83-88

[47] Akanksha Rathi[2018]"The Evolution of NACP: India's attempt at Controlling the HIV/AIDS Epidemic"International Journal of Scientific Research, Volume-7 Issue-1, January 2018

[48] Dlplka Jahn and Rachel Stephens[2008]"The Struggle for Access to Treatment for HIV/AIDS in

India"Human Rights Law Network(HRLN) A division of Socio Legal Information Centre
[49] National AIDS Control Organization(NACO), Ministry of Health and Family Welfare, Government of India[2015]"Assessment of ART Centres in India National Report 2015"
[50] National AIDS Control Organization(NACO), Ministry of Health and Family Welfare, Government of India[2018]"Annual Report NACO 2018-19"
[51] National AIDS Control Organization(NACO), Ministry of Health and Family Welfare, Government of India[2017]"State Epidemiological Fact Sheets (Volume I-North East Region)
[52] National AIDS Control Organization(NACO), Ministry of Health and Family Welfare, Government of India[2017]"State Epidemiological Fact Sheets (Volume III-Northern, Central & Eastern Region)
[53] National AIDS Control Organization(NACO), Ministry of Health and Family Welfare, Government of India[2017]"State Epidemiological Fact Sheets (Volume II-West & South Regions)
[54] A.L. Sharma, et al[2018]"Understanding of HIV/AIDS in the international border area, Manipur: Northeast India"Epidemiology and Infection(Cambridge University Press), 2018, 147, e113
[55] Rajneeth Kumar Joshi and Sanjay M. Mehendale[2019]"Determinants of consistently high HIV prevalence in Indian Districts: A multi-level analysis" PLoS One 14(5), e0216321
[56] Yujwal Raj, et al[2015]"Modelling and estimation of HIV prevalence and number of people living with HIV in India, 2010-2011"International Journal of STD & AIDS, October 2015, Volume 27 No.14
[57] Manisha Ghate, et al[2011]"Use of first line antiretroviral therapy from a free ART programme clinic in Pune, India – preliminary report"The Indian Journal of Medical Research, 137, May 2013, pp942-949
[58] Sridhar P Ryavanki, et al[2013]"General Profile and Survival Probabilities of HIV Patients Registered at Anti Retroviral Therapy Centre, New Civil Hospital, Surat, Gujarat"National Journal of Community Medicine, Volume 4 Issue 2, April-June 2013
[59] Prakash Javalkar, et al[2016]"An Estimation of Mortality Risks among People Living with HIV in Karnataka State, India: Learnings from an Intensive HIV/AIDS Care and Suport Programme" PLoS One 11(6), e0156611
[60] Manoj V. Maddalli, et al[2015]"Economic and epidemiological impact of early antiretroviral therapy initiation in India"Journal of the International AIDS Society 2015,18: 20217
[61] Damodar Bachani[2010]"Two-year treatment outcomes of patients enrolled in India's national first-line antiretroviral therapy programme" The National Medical Journal of India, Vol.23 No.1 2010
[62] Ram Bajpal, et al[2014]"Dmographic Correlates of Survival in Adult HIV Patients Registered at ART Centers in Andhra Pradesh, India: A Retrospective Cohort Study" Public Health Research, 2014, 4(1), pp31-38
[63] Ram Bajpal, et al[2016]"Effects of Antiretroviral Therapy on the Survival of Human Immunodeficiency Virus-positive Adult Patients in Andhra Pradesh, India: A Retrospective Cohort Study, 2007-2013"Journal of Preventive Medicine & Public Health, 2016, 49; pp394-405
[64] Jaya Chakravarty, et al[2013]"Determinants of survival in adult HIV patients on antiretroviral therapy in Eastrn Uttar Pradesh: A prospective study"The Indian Journal of Medical Research, 140, October 2014, pp491-500
[65] Nanisha Ghate, et al[2011]"Mortality in HIV infected individuals in Pune, India" The Indian Journal of Medical Research, April 2011, pp414-420
[66] Seema Patrikar, et al[2018]"A systematic review and cost-effectiveness anaslyses of the new World Health Organization guidelines for the treatment of HIV-positive adults in India"Medical Journal Armed Forces India, 75(2019), pp31-40

[67] S. Chawlar, et al[2017]"Why are HIV-infected people not started on antiretroviral therapy? A mixed-methods study from Gujarat, India" Public Health Action, 2017 September, 21; 7(3):pp183–192

[68] N. Joglekar, et al[2010]"Barries to ART adherence & follow ups among patients attending ART centres in Maharashtra, India"The Indian Journal of Medical Research, 134, December 2011, pp954-959

[69] Kedar G. Mehta, et al[2016]"Drug adherence rate and loss to follow-up among people living with HIV/AIDS attending an ART Centre in a Tertiary Government Hospital in Western India"Journal of Family Medicine and Primary Care, 2016 Apr-Jun; 5(2): pp266–269

[70] Arkapal Bandyopadhy, et al[2019]"A study of adherence to antiretroviral therapy in a tertiary care hospital at Allahabad, India"Indian Journal of Sexually Transmitted Diseases and AIDS, 2019 Jan-Jun, 40(1): pp46-50

[71] Jean Ann Saunders, et al[2009]"Adherence to anti-retroviral therapy among HIV patients in Bangalore, India"AIDS Research and Therapy, May 2009

[72] Sandeep Rai, et al[2013]"Adherence to Antiretroviral Therapy and its Effect on Survival of HIV-Infected Individuals in Jharkhand, India"PLoS One 8(6), e66860

[73] Vendan Hiregoudar, et al[2019]"Proportion and Determinants of Adherence to Antiretroviral Therapy among HIV Positive People Registered Under ART Centerin South India"International ournal of Preventive Medicine, 2019, 10:206

[74] Kartik K. Venkatesh, et al[2010]"Predictors of Nonadherence to Highly Active Antiretroviral Therapy Among HIV-Infected South Indians in Clicical Care: Implications for Developing Adherence Interventions in Resource-Limited Settings"AIDS PATIENT CARE and STDs, Volume 24, November 12, 2010, pp795-803

[75] Eknath Naik, et al[2009]"Cost of treatment: The single biggest obstacle to HIV/AIDS treatment dherence in lower-middle class patients in Mumbai, India"Indian Journal of Sexually Transmitted Diseases and AIDS, 2009 January-June, 30(1)

[76] Bharatesh D. Basti, et al[2017]"Factors affecting antiretroviral treatment adherence among people living with human immunodeficiency virus/acquired immunodeficiency syndrome: A prospective study"Journal of Family Medicine and Primary Care, Volume6 Issue3, July-September 2017, pp482-486

[77] Venkatesan Chakrapani, et al[2011]"Barriers to free antiretroviral treatment access among kothi-identified men who have sex with men and aravanis (transgender women) in Chennai, India"AIDS Care 2011, Volume 23 Issue 12, pp1687–1694

[78] Beena Thomas, et al[2012]"The influence of stigma on HIV risk behavior among men who have sex with men in Chennei, India"AIDS Care 2012, Volume 24 Issue 11, pp1401–1406

[79] Celillia Tomori, et al[2018]"High-risks among women who are married to men who have sex with men in India: A qualitative investigation"Cult Health Sex 2018 August; 20(8): pp873-887

[80] Suman Ganguly, et al[2018]"HIV/AIDS epidemic in West Bengal: An overview"Journal of Family Medicine and Primary Care, 2018, Volume7 Issue5, pp898-902

[81] Tanvi Rai, et al[2015]"Complex routes into HIV care for migrant workers: a qualitative study from north India"AIDS Care, 2015, Volume 27 No.11, pp1418-1423

[82] Gregory M. Lucas, et al[2015]"High HIV burden among people who inject drugs in 15 Indian cities"National Institute of Health(NIH) Public Access AIDS 2015, March 13; 29(5): pp619-628

[83] Niranjan Saggurti, et al[2011]"Indicators of Mobility, Social-Economic Vulnerabilities and HIV Risk Behaviours Among Mobile Female Sex Workers in India" AIDS Behavier. 2012 May; 16(4): pp952–959

[84] Chandravali Madan, et al[2018]"Developing a model to predict unfavorable treatment outcomes in patients with tuberculosis and human immunodeficiency virus co-infection in Delhi, India"PLoS One, 13(10), e0204982

[85] Manisha Ghate, et al[2007]"Incidence of common opportunistic infections in HIV-infected individuals in Pune, India: analysis by stages of immunosuppression represented by CD4 counts" International Journal of Infectious Diseases, 2009, 13

[86] Chiraneev Bhattacharya, et al[2018]"Cause of Death among HIV-Infected Adults Registed in Selected Anti-Retroviral Therapy Centers in North-Eastern India"World Journal of AIDS, 2015, 5, pp90-99

[87] G.Anil Kumar, et al[2018]"Decreasing cost of public sector first-line ART services in India from 2007-2008 to 2015-2016"PLoS One 13(11), e02006988

[88] Reshu Agarwal, et al[2017]"Delivery of antiretroviral treatment services in India estimated costs incurred under the National AIDS Control Programme"WHO South-East Asia Journal of Public Health, April 2017, 6(1)

[89] Zeba Siddiqui and Aditya Kalra[2014]"Poor patients in India facing HIV/AIDS drug shortages"Reuters, September 14, 2014

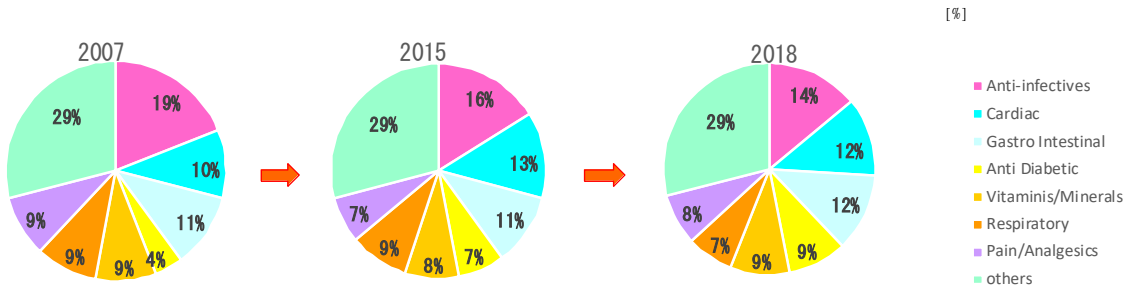
Appendix 1 TOP 15 Pharmaceutical firms overall Revenue for FY2018

[2019 avarage rate 1 ?=0.14203US$]

	Firm name	Head office	2019 Overall revenue (billion ?)	2019 Overall revenue (billion US$)
1	Sun Pharmaceutical Industries	Mumbai, Maharashtra	273.28	3.88
2	Aurobindo Pharma	Hyderabad, Telangana	164.99	2.34
3	Lupin	Mumbai, Maharashtra	159.55	2.27
4	Cipla	Mumbai, Maharashtra	155.77	2.21
5	Dr. Reddy?s Laboratories	Hyderabad, Telangana	144.36	2.05
6	Cadila Healthcare	Ahmedabad, Gujarat	120.50	1.71
7	Intas Pharmaceuticals	Ahmedabad, Gujarat	108.86	1.55
8	Glenmark Pharma	Mumbai, Maharashtra	91.86	1.30
9	Torrent Pharmaceuticals	Ahmedabad, Gujarat	63.01	0.89
10	ManKind Pharma	Delhi, Delhi	52.00	0.74
11	Biocon	Bangalore, Karnataka	43.36	0.62
12	Piramal Enterprises	Mumbai, Maharashtra	43.22	0.61
13	Wockhardt	Mumbai, Maharashtra	40.57	0.58
14	Divis Laboratories	Hyderabad, Telangana	40.26	0.57
15	Abbott India	Mumbai, Maharashtra	34.24	0.49

【Data source】Market Research Report[2019] "Indian Pharmaceuticals Industry Analysis and Trends 2023"

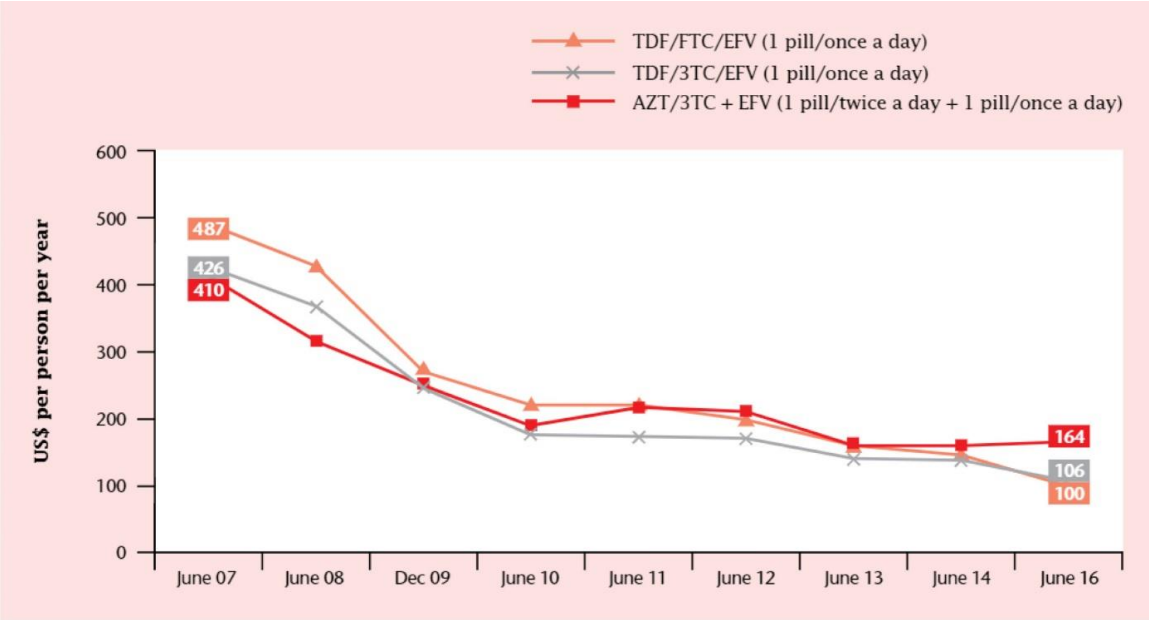
Appendix 2



Segment-wise Annual Turnover Trends

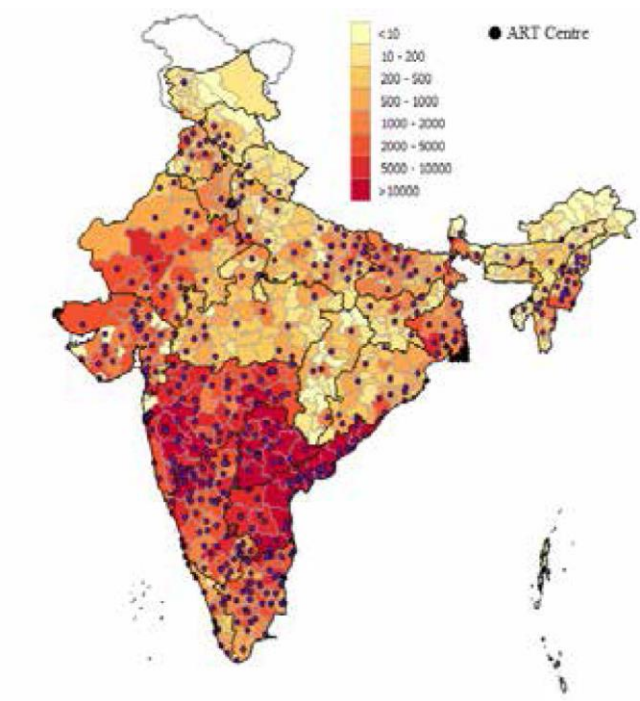
【Data Source】Created based upon data from IBEF (India Brand Equity Foundation)

Appendix 3



【Source of Figure】Médecins Sans Frontières[2016] "Untangling The Web of Antiretroviral Price Reductions"

Appendix 4-1



【Source of Figure】National AIDS Control Organization(NACO)[2018] "Annual Report NACO-2017-18"

Appendix 4-2 State-wise & Region-wise Number of people living with HIV accessing ART and number of ART centre in India

State-wise number of people living with HIV accessing ART and Number of ART cntre in India

States	Number of people living with HIV accessing ART	Number of people living with HIV	Percentage(%)	Number of ART centre(2016)
Arunachal Pradesh	96	588	16.3%	1
Assam	5,846	13,539	43.2%	6
Nagaland	7,290	17,029	42.8%	8
Manipur	12,483	31,549	39.6%	13
Mizoram	7,412	16,773	44.2%	6
Tripura	1,186	2,678	44.3%	3
Meghalaya	1,777	2,141	83.0%	1
Sikkim	170	230	73.9%	1
Jammu and Kashmir	2,350	2,984	78.8%	2
Himachal Pradesh	2,991	3,148	95.0%	6
Uttarakhand	3,575	8,021	44.6%	3
Punjab	27,697	40,632	68.2%	12
Chandigarh	1,988	2,093	95.0%	1
Haryana	11,059	36,286	30.5%	1
Delhi	27,250	45,726	59.6%	11
Rajasthan	37,092	54,682	67.8%	23
Uttar Pradesh	67,855	134,020	50.6%	38
Madhya Pradesh	22,133	51,223	43.2%	18
Chhattisgarh	12,235	26,206	46.7%	5
Bihar	46,047	115,448	39.9%	16
Jharkhand	9,471	33,367	28.4%	8
West Bengal	35,685	143,904	24.8%	19
Odisha	17,142	41,357	41.4%	15
Gujarat	62,752	91,766	68.4%	30
Maharashtra	237,796	329,744	72.1%	87
Goa	2,884	5,944	48.5%	2
Andhra Pradesh/Telangana	249,517	473,696	52.7%	62
Karnataka	155,411	247,413	62.8%	64
Kerala	12,919	22,755	56.8%	10
Tamil Nadu	112,778	141,895	79.5%	55
Puducherry	1,193	1,821	65.5%	1
others	106	1,389	7.6%	1
Total	1,196,186	2,140,047	55.9%	529

Region-wise number of people living with HIV accessing ART and Number of ART cntre in India

Regions	Number of people living with HIV accessing ART	Number of people living with HIV	Percentage(%)	Number of ART centre(2016)
Northeast	36,260	84,527	42.9%	39
North	114,002	193,572	58.9%	59
Central	102,223	211,449	48.3%	61
East	108,345	334,076	32.4%	58
West	303,432	427,454	71.0%	119
South	531,818	887,580	59.9%	192

【Data source】Created based upon data from NACO(The National AIDS Control Organisation)

※Difinition of Region-wise classification

Northeast—Arunachal Pradesh、Assam、Nagaland、Manipur、Mizoram、Tripura、Meghalaya、Sikkim

North—Jammu and Kashmir、Himachal Pradesh、Uttarakhand、Punjab、Chandigarh、Haryana、Delhi、Rajasthan

Central—Uttar Pradesh、Madhya Pradesh、Chhattisgarh

East—Bihar、Jharkhand、West Bengal、Odisha

Westn—Gujarat、Maharashtra、Goa

South—Andhra Pradesh/Telangana、Karnataka、Kerala、Tamil Nadu、Puducherry

Appendix 4-3 State-wise & Region-wise time-series changes in Number of people living with HIV accessing ART

State-wise number of people living with HIV accessing ART

States	2007	2011	2015
Arunachal Pradesh	0	26	96
Assam	140	1,648	5,846
Nagaland	323	3,432	7,290
Manipur	2,473	7,158	12,483
Mizoram	34	1,429	7,412
Tripura	0	1,216	1,186
Meghalaya	0	212	1,777
Sikkim	2	60	170
Jammu and Kashmir	51	833	2,350
Himachal Pradesh	101	1,447	2,991
Uttarakhand	30	1,000	3,575
Punjab	318	8,226	27,697
Chandigarh	961	2,167	1,988
Haryana	178	2,612	11,059
Delhi	3,175	9,956	27,250
Rajasthan	1,227	10,761	37,092
Uttar Pradesh	2,038	18,845	67,855
Madhya Pradesh	755	6,861	22,133
Chhattisgarh	0	2,727	12,235
Bihar	800	10,121	46,047
Jharkhand	141	2,854	9,471
West Bengal	1,313	10,230	35,685
Odisha	21	4,224	17,142
Gujarat	1,352	25,885	62,752
Maharashtra	11,213	111,663	237,796
Goa	348	1,439	2,884
Andhra Pradesh/Telangana	4,303	103,396	249,517
Karnataka	4,983	71,019	155,411
Kerala	1,437	6,374	12,919
Tamil Nadu	11,807	58,532	112,778
Puducherry	60	820	1,193
others	0	0	106
Total	49,584	487,173	1,196,186

Regin-wise number of people living with HIV accessing ART

Regin	2007	2011	2015
Northeast	2,972	15,181	36,260
North	6,041	37,002	114,002
Central	2,793	28,433	102,223
East	2,275	27,429	108,345
West	12,913	138,987	303,432
South	22,590	240,141	531,818

【Data source】Created based upon data from NACO(The National AIDS Control Organisation)

※Difinition of Region-wise classification

Northeast—Arunachal Pradesh、Assam、Nagaland、Manipur、Mizoram、Tripura、Meghalaya、Sikkim

North—Jammu and Kashmir、Himachal Pradesh、Uttarakhand、Punjab、Chandigarh、Haryana、Delhi、Rajasthan

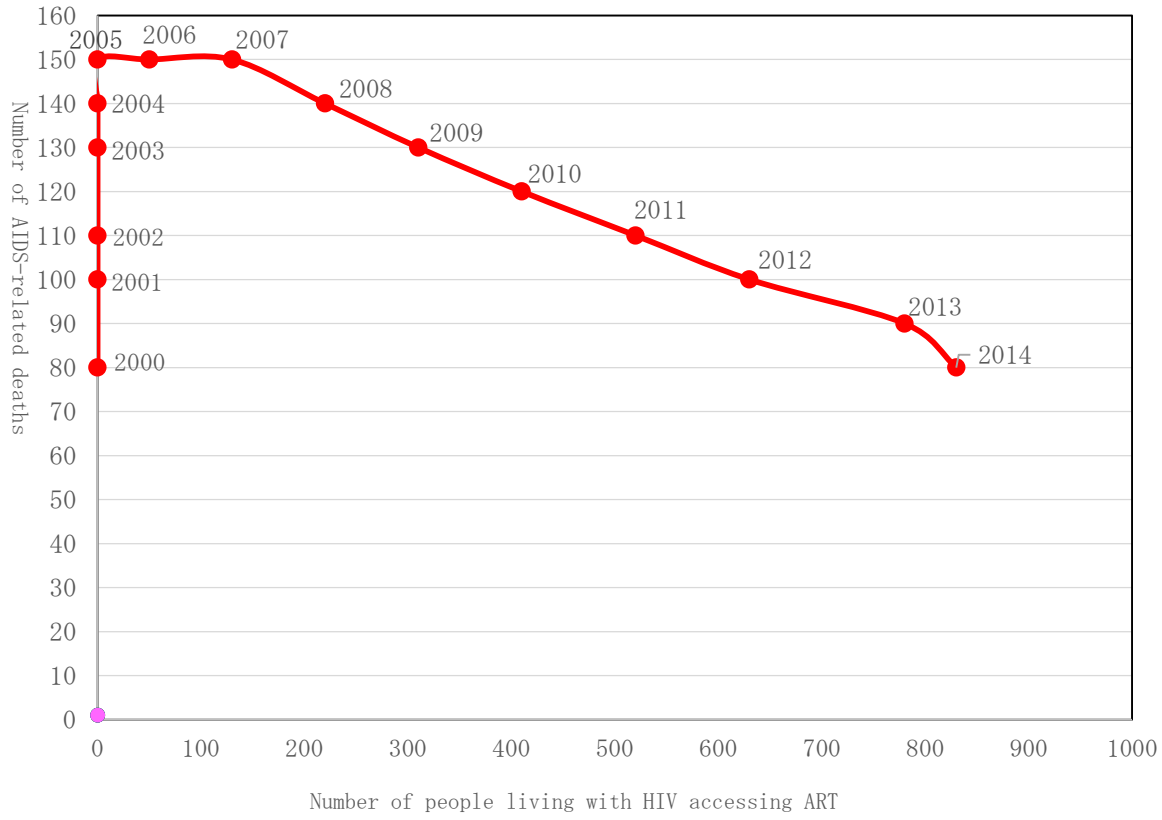
Central—Uttar Pradesh、Madhya Pradesh、Chhattisgarh

East—Bihar、Jharkhand、West Bengal、Odisha

Westn—Gujarat、Maharashtra、Goa

South—Andhra Pradesh/Telangana、Karnataka、Kerala、Tamil Nadu、Puducherry

Apendix 4-4



Time-series changes in Number of people living with HIV accessing ART and Number of people of AIDS-related deaths in India

【Data source】Created based upon data from NACO(The National AIDS Control Organisation)

Appendix 5-1 Changes in State-wise & Region-wise population in India

Changes in State-wise population in India

States	2006	2011	2017
Arunachal Pradesh	1,173,000	1,383,927	1,550,000
Assam	29,009,000	31,205,576	33,530,000
Nagaland	2,113,200	1,978,502	2,100,000
Manipur	2,561,000	2,855,794	3,220,000
Mizoram	955,000	1,097,206	1,210,000
Tripura	3,421,000	3,673,917	3,930,000
Meghalaya	2,473,000	2,966,889	3,340,000
Sikkim	580,000	610,577	650,000
Jammu and Kashmir	11,603,000	12,258,433	13,650,000
Himachal Pradesh	6,425,000	6,864,602	7,220,000
Uttarakhand	9,215,000	10,086,292	10,870,000
Punjab	25,976,000	27,743,338	29,830,000
Chandigarh	1,013,000	1,055,450	1,140,000
Haryana	23,041,000	25,351,402	27,420,000
Delhi	16,065,000	16,787,941	18,660,000
Rajasthan	62,431,000	68,548,437	74,260,000
Uttar Pradesh	183,856,000	199,810,341	217,510,000
Madhya Pradesh	66,801,000	72,626,809	78,780,000
Chhattisgarh	29,859,000	25,545,198	27,930,000
Bihar	90,174,000	104,099,452	113,640,000
Jharkhand	29,174,000	32,988,134	36,120,000
West Bengal	85,780,000	91,276,115	96,490,000
Odisha	39,053,000	41,974,218	44,410,000
Gujarat	54,814,000	60,439,692	65,050,000
Maharashtra	104,104,000	112,374,333	120,060,000
Goa	1,536,000	1,978,502	1,520,000
Andhra Pradesh/Telangana	80,430,000	84,580,777	88,250,000
Karnataka	56,137,000	61,095,297	64,900,000
Kerala	33,569,000	33,406,061	34,320,000
Tamil Nadu	65,261,000	72,147,030	75,970,000
Puducherry	1,041,000	1,247,953	1,450,000
others	887,000	1,322,502	1,376,000
Total	1,120,530,200	1,211,380,697	1,300,356,000

Changes in Region-wise population in India

Regions	2006	2011	2017
Northeast	42,285,200	45,772,388	49,530,000
North	155,769,000	168,695,895	183,050,000
Central	280,516,000	297,982,348	324,220,000
East	244,181,000	270,337,919	290,660,000
West	160,454,000	174,792,527	186,630,000
South	236,438,000	252,477,118	264,890,000

【Data source】Created based upon data from Office of the Registrar General & Census Commissioner, India

※Difinition of Region-wise classification

Northeast—Arunachal Pradesh、Assam、Nagaland、Manipur、Mizoram、Tripura、Meghalaya、Sikkim

North—Jammu and Kashmir、Himachal Pradesh、Uttarakhand、Punjab、Chandigarh、Haryana、Delhi、Rajasthan

Central—Uttar Pradesh、Madhya Pradesh、Chhattisgarh

East—Bihar、Jharkhand、West Bengal、Odisha

West—Gujarat、Maharashtra、Goa

South—Andhra Pradesh/Telangana、Karnataka、Kerala、Tamil Nadu、Puducherry

Appendix 5-2 Changes in State-wise & Region-wise number of people living with HIV in India

Changes in State-wise number of people living with HIV in India

States	2007	2008	2009	2010	2011	2012	2013	2014	2015
Arunachal Pradesh	419	463	500	533	560	582	591	599	606
Assam	6,221	6,916	7,635	8,388	9,188	9,996	10,721	11,417	12,090
Nagaland	12,005	11,817	11,589	11,384	11,228	11,111	11,066	11,052	11,050
Manipur	30,399	30,152	29,718	29,019	28,252	27,404	26,349	25,397	24,457
Mizoram	4,725	4,827	4,940	5,087	5,259	5,443	5,559	5,670	5,762
Tripura	3,069	3,429	3,843	4,305	4,821	5,388	5,958	6,564	7,238
Meghalaya	874	912	949	988	1,030	1,070	1,090	1,108	1,122
Sikkim	340	388	444	508	580	661	744	837	939
Jammu and Kashmir	2,164	2,320	2,440	2,539	2,623	2,700	2,732	2,752	2,777
Himachal Pradesh	5,666	5,567	5,485	5,438	5,458	5,541	5,589	5,655	5,723
Uttarakhand	4,243	4,782	5,261	5,693	6,094	6,442	6,674	6,871	7,059
Punjab	23,258	25,036	26,825	28,683	30,598	32,488	34,017	35,495	36,794
Chandigarh	1,414	1,563	1,715	1,861	2,009	2,167	2,403	2,643	2,933
Haryana	15,380	16,471	17,478	18,458	19,416	20,346	21,076	21,826	22,596
Delhi	17,799	19,359	20,937	22,509	24,041	25,507	27,092	26,652	30,216
Rajasthan	78,596	84,086	88,469	92,102	95,006	97,520	99,599	101,361	103,148
Uttar Pradesh	130,898	131,731	132,920	134,650	137,042	140,093	142,934	146,419	150,361
Madhya Pradesh	44,664	44,735	44,617	44,420	44,340	44,412	44,247	44,246	44,409
Chhattisgarh	27,237	27,379	27,634	27,931	28,376	28,914	29,299	29,937	30,838
Bihar	122,573	130,821	136,979	141,827	145,806	148,849	149,522	150,026	150,689
Jharkhand	21,642	24,424	26,895	29,020	30,870	32,470	33,299	33,835	34,386
West Bengal	156,791	153,517	149,706	145,776	142,116	138,741	134,667	131,207	128,757
Odisha	67,591	70,050	71,304	71,824	71,730	71,236	70,019	68,750	67,654
Gujarat	142,206	142,551	144,004	146,655	150,325	154,793	158,418	162,245	166,333
Maharashtra	391,464	369,793	351,924	337,686	327,235	319,119	311,619	306,927	301,453
Goa	5,520	5,253	5,025	4,857	4,734	4,635	4,607	4,594	4,619
Andhra Pradesh/Telangana	472,753	460,908	448,502	438,475	428,656	420,162	409,354	400,876	394,661
Karnataka	244,500	234,191	223,665	218,944	214,506	211,519	206,826	202,622	199,060
Kerala	27,945	27,325	26,580	25,853	25,189	24,600	24,156	23,758	23,376
Tamil Nadu	161,743	155,906	151,680	149,046	147,680	147,378	145,471	144,168	142,982
Puducherry	1,344	1,352	1,372	1,393	1,422	1,452	1,491	1,526	1,560
others	497	525	559	600	649	707	773	846	933
Total	2,225,940	2,198,549	2,171,594	2,156,452	2,146,839	2,143,446	2,127,962	2,117,881	2,116,581

Changes in Region-wise number of people living with HIV in India

Regions	2007	2008	2009	2010	2011	2012	2013	2014	2015
Northeast	58,052	58,904	59,618	60,212	60,918	61,655	62,078	62,644	63,264
North	148,520	159,184	168,610	177,283	185,245	192,711	199,182	203,255	211,246
Central	202,799	203,845	205,171	207,001	209,758	213,419	216,480	220,602	225,608
East	368,597	378,812	384,884	388,447	390,522	391,296	387,507	383,818	381,486
West	539,190	517,597	500,953	489,198	482,294	478,547	474,644	473,766	472,405
South	908,285	879,682	851,799	833,711	817,453	805,111	787,298	772,950	761,639

【Data source】Created based upon data from NACO(The National AIDS Control Organisation[2017] "State Epidemiological Fact Sheets"

※Difinition of Region-wise classification

Northeast—Arunachal Pradesh、Assam、Nagaland、Manipur、Mizoram、Tripura、Meghalaya、Sikkim

North—Jammu and Kashmir、Himachal Pradesh、Uttarakhand、Punjab、Chandigarh、Haryana、Delhi、Rajasthan

Central—Uttar Pradesh、Madhya Pradesh、Chhattisgarh

East—Bihar、Jharkhand、West Bengal、Odisha

West—Gujarat、Maharashtra、Goa

South—Andhra Pradesh/Telangana、Karnataka、Kerala、Tamil Nadu、Puducherry

Appendix 5-3 Changes in State-wise & Region-wise number of people of new HIV infections in

India

Changes in State-wise number of people of new HIV infections in India

States	2007	2008	2009	2010	2011	2012	2013	2014	2015
Arunachal Pradesh	62	58	55	53	51	50	49	49	49
Assam	901	930	946	990	1,029	1,055	1,070	1,053	1,036
Nagaland	943	817	731	653	598	567	552	529	539
Manipur	1,506	1,288	1,133	967	829	724	645	568	539
Mizoram	388	377	363	353	344	331	317	277	255
Tripura	471	528	594	649	720	781	854	909	994
Meghalaya	91	88	83	81	78	73	68	54	49
Sikkim	57	64	73	82	91	102	115	127	141
Jammu and Kashmir	249	200	161	146	136	125	119	94	101
Himachal Pradesh	303	278	261	255	248	246	241	238	233
Uttarakhand	702	666	614	574	541	500	467	429	393
Punjab	2,736	2,626	2,510	2,526	2,528	2,547	2,469	2,369	2,225
Chandigarh	181	189	204	212	225	238	256	264	305
Haryana	1,712	1,663	1,639	1,637	1,618	1,582	1,541	1,468	1,390
Delhi	1,908	1,928	1,926	1,897	1,874	1,853	1,823	1,741	1,702
Rajasthan	9,885	9,182	8,416	7,930	7,391	7,172	6,913	6,626	6,274
Uttar Pradesh	9,329	9,410	9,472	9,730	10,061	10,341	10,630	10,837	10,868
Madhya Pradesh	3,151	2,897	2,755	2,666	2,640	2,580	2,535	2,456	2,382
Chhattisgarh	1,738	1,831	1,926	2,008	2,109	2,161	2,199	2,229	2,251
Bihar	15,811	14,052	12,526	11,772	11,366	10,980	10,640	10,291	10,035
Jharkhand	3,739	3,544	3,336	3,115	2,901	2,804	2,486	2,312	2,309
West Bengal	7,126	5,974	5,126	4,667	4,324	4,074	3,878	3,682	3,548
Odisha	8,928	8,324	7,994	7,696	7,530	7,352	7,178	7,051	6,914
Gujarat	158	147	131	125	118	113	110	99	98
Maharashtra	10,813	11,063	11,320	11,554	11,815	11,930	12,005	11,787	11,595
Goa	11,236	9,382	7,867	7,046	6,585	5,976	5,338	4,303	3,984
Andhra Pradesh/Telangana	18,759	15,463	13,450	12,382	11,537	10,669	9,782	8,886	8,331
Karnataka	7,508	6,338	5,038	4,524	4,075	3,641	3,264	3,011	2,703
Kerala	1,252	1,059	931	865	813	782	751	733	698
Tamil Nadu	5,836	5,185	4,925	4,968	4,687	4,742	4,689	4,605	4,207
Puducherry	47	40	32	32	31	32	33	32	34
others	50	57	63	71	81	90	102	113	127
Total	127,576	115,648	106,601	102,226	98,974	96,213	93,119	89,222	86,309

Changes in Region-wise number of people of new HIV infections in India

Regions	2007	2008	2009	2010	2011	2012	2013	2014	2015
Northeast	4,419	4,150	3,978	3,828	3,740	3,683	3,670	3,566	3,602
North	17,676	16,732	15,731	15,177	14,561	14,263	13,829	13,229	12,623
Central	14,218	14,138	14,153	14,404	14,810	15,082	15,364	15,522	15,501
East	35,604	31,894	28,982	27,250	26,121	25,210	24,182	23,336	22,806
West	22,207	20,592	19,318	18,725	18,518	18,019	17,453	16,189	15,677
South	33,402	28,085	24,376	22,771	21,143	19,866	18,519	17,267	15,973

【Data source】Created based upon data from NACO(The National AIDS Control Organisation[2017] "State Epidemiological Fact Sheets"

※Difinition of Region-wise classification

Northeast—Arunachal Pradesh、Assam、Nagaland、Manipur、Mizoram、Tripura、Meghalaya、Sikkim

North—Jammu and Kashmir、Himachal Pradesh、Uttarakhand、Punjab、Chandigarh、Haryana、Delhi、Rajasthan

Central—Uttar Pradesh、Madhya Pradesh、Chhattisgarh

East—Bihar、Jharkhand、West Bengal、Odisha

West—Gujarat、Maharashtra、Goa

South—Andhra Pradesh/Telangana、Karnataka、Kerala、Tamil Nadu、Puducherry

Appendix 5-4 Changes in State-wise & Region-wise number of AIDS-related deaths in India

Changes in State-wise number of AIDS-related deaths in India

States	2007	2008	2009	2010	2011	2012	2013	2014	2015
Arunachal Pradesh	13	15	18	20	24	28	30	31	32
Assam	199	194	197	206	198	215	234	235	229
Nagaland	724	698	663	571	470	404	359	300	287
Manipur	1,470	1,416	1,439	1,521	1,461	1,453	1,369	1,209	1,146
Mizoram	258	260	239	201	167	146	133	93	79
Tripura	148	161	174	184	202	218	239	254	266
Meghalaya	46	46	42	37	31	28	26	17	14
Sikkim	14	14	14	16	16	19	22	25	27
Jammu and Kashmir	46	43	43	50	55	52	53	43	39
Himachal Pradesh	399	373	348	308	239	189	167	143	124
Uttarakhand	110	106	115	125	124	137	151	148	120
Punjab	978	756	651	609	558	612	601	531	523
Chandigarh	31	33	44	59	70	73	78	86	87
Haryana	536	512	579	612	626	632	591	488	364
Delhi	345	368	360	357	360	398	420	374	331
Rajasthan	2,930	3,263	3,601	3,866	4,053	4,231	4,415	4,458	4,105
Uttar Pradesh	2,553	2,631	2,706	2,716	2,601	2,438	2,271	2,020	1,799
Madhya Pradesh	7,677	7,698	7,451	7,206	6,870	6,481	6,090	5,648	5,195
Chhattisgarh	1,788	1,753	1,744	1,769	1,712	1,681	1,532	1,309	1,062
Bihar	4,722	5,441	6,102	6,756	7,296	7,852	8,030	7,924	7,514
Jharkhand	624	685	790	925	999	1,129	1,243	1,366	1,355
West Bengal	10,509	10,997	11,297	11,207	10,861	10,478	9,901	9,202	8,127
Odisha	2,758	3,166	3,583	3,887	4,184	4,366	4,360	4,235	3,965
Gujarat	11,012	10,412	9,648	8,751	8,066	7,460	7,070	6,552	6,067
Maharashtra	34,927	30,604	25,492	21,049	16,889	14,154	10,879	7,056	6,766
Goa	393	372	328	274	232	210	199	169	122
Andhra Pradesh/Telangana	29,397	25,258	22,956	21,391	19,293	17,215	15,372	12,075	9,249
Karnataka	18,370	16,621	13,668	11,317	8,645	6,920	5,802	4,972	3,744
Kerala	1,342	1,385	1,414	1,386	1,326	1,270	1,170	1,098	1,030
Tamil Nadu	13,886	11,616	9,748	8,164	6,636	5,634	5,066	4,358	3,763
Puducherry	75	52	33	31	24	25	29	30	32
others	29	32	35	37	39	41	44	45	49
Total	148,309	136,981	125,522	115,608	104,327	96,189	87,946	76,494	67,612

Changes in Region-wise number of AIDS-related deaths in India

Regions	2007	2008	2009	2010	2011	2012	2013	2014	2015
Northeast	2,872	2,804	2,786	2,756	2,569	2,511	2,412	2,164	2,080
North	5,375	5,454	5,741	5,986	6,085	6,324	6,476	6,271	5,693
Central	12,018	12,082	11,901	11,691	11,183	10,600	9,893	8,977	8,056
East	18,613	20,289	21,772	22,775	23,340	23,825	23,534	22,727	20,961
West	46,332	41,388	35,468	30,074	25,187	21,824	18,148	13,777	12,955
South	63,070	54,932	47,819	42,289	35,924	31,064	27,439	22,533	17,818

【Data source】Created based upon data from NACO(The National AIDS Control Organisation[2017] "State Epidemiological Fact Sheets"

※Difinition of Region-wise classification

Northeast—Arunachal Pradesh、Assam、Nagaland、Manipur、Mizoram、Tripura、Meghalaya、Sikkim

North—Jammu and Kashmir、Himachal Pradesh、Uttarakhand、Punjab、Chandigarh、Haryana、Delhi、Rajasthan

Central—Uttar Pradesh、Madhya Pradesh、Chhattisgarh

East—Bihar、Jharkhand、West Bengal、Odisha

West—Gujarat、Maharashtra、Goa

South—Andhra Pradesh/Telangana、Karnataka、Kerala、Tamil Nadu、Puducherry