Chapter 5
Human Immunodeficiency Virus Reverse Transcriptase (HIV-RT): Structural Implications for Drug Development

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ABSTRACT

Reverse transcriptase (RT) is a multifunctional enzyme in the life cycle of human immunodeficiency virus and represents a primary target for drug discovery against HIV-1 infection. Two classes of RT inhibitors, the nucleoside and the non-nucleoside RT inhibitors, are prominently used in the highly active antiretroviral therapy in combination with other anti-HIV drugs. This chapter deals with the salient features of HIV-RT that make it an attractive target for rational drug design and chemotherapeutic intervention in the management of acquired immunodeficiency syndrome. Further, the role of RT in the viral life cycle, the ways the drugs act to inhibit the normal functions of RT, and the mechanisms that the virus adapts to evade the available drugs have been discussed. Computational strategies used in rational drug design accompanied by a better understanding of RT, its mechanism of inhibition and drug resistance, discussed in this chapter, shall provide a better platform to develop effective RT inhibitors.

INTRODUCTION

Human immunodeficiency virus (HIV), a lentivirus belonging to the *Retroviridae* family, has been identified as an etiological agent of Acquired Immune Deficiency Syndrome (AIDS). In 1983, Luc Montagnier's group of Pasteur Institute, France, investigated Lymphadenopathy-associated virus (LAV). In 1984, Robert Gallo's group from National Institute of Health (NIH), USA, investigated a retrovirus, HTLV-III, first reported in 1981 in Los Angeles, New York and San Francisco, USA. In 1985, Jay Levy's group

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from California University, San Francisco, USA, identified this virus as AIDS-Related Virus (ARV). In 1986, these three retroviruses (LAV, HTLV-III, ARV) were re-named as Human Immunodeficiency Virus (HIV) by an International Committee. In the same year, antigenic variants of HIV were designated as HIV-1 and HIV-2. For the discovery of HIV, Francoise Barre-Sinoussi and Luc Antoine Montagnier were awarded Nobel prize for physiology in 2008 (Gallo & Montagnier, 2003, Barre-Sinoussi, Chermann, Rey, Nugeyre, & Chamaret, 1983, Kumari & Singh, 2012).

Global HIV/AIDS Statistics

AIDS has been defined as the development of an immunocompromised state (Gottlieb et al., 1981) which continues to be a dreaded killer till date. It has caused a great burden to global wealth and health as 76.1 million [65.2 million–88.0 million] people have become infected with HIV since the start of the epidemic and 35.0 million [28.9 million–41.5 million] people have died so far because of AIDS-related illnesses. A global statistics have been shown in Table 1 (UNAIDS, 2016).

HIV/AIDS Status in India

According to a United Nations (UN) report, India has the third highest number of people living with HIV in the world with 2.1 million Indians, accounting for about four out of 10 people infected with the deadly virus in the Asia—Pacific region (Figure 1). As per the recently released data from National AIDS Control Organisation (NACO), HIV prevalence in Indian adult (15–49 years) is estimated at 0.26% (0.22% – 0.32%) in 2015 (0.30% among males and at 0.22% among females).

Among the States/ Union territories (UTs), in 2015, Manipur has shown the highest estimated adult HIV prevalence (1.15%), followed by Mizoram (0.80%), Nagaland (0.78%), Andhra Pradesh and Telangana (0.66%), Karnataka (0.45%), Gujarat (0.42%) and Goa (0.40%). Besides these States, Maharashtra, Chandigarh, Tripura and Tamil Nadu have shown estimated adult HIV prevalence greater than the national prevalence (0.26%), while Odisha, Bihar, Sikkim, Delhi, Rajasthan and West Bengal have shown an estimated adult HIV prevalence in the range of 0.21– 0.25%. All other States/UTs have levels of adult HIV prevalence below 0.20%. The adult HIV prevalence at national level has continued its steady decline from an estimated peak of 0.38% in 2001-03 through 0.34% in 2007 and 0.28% in 2012 to 0.26% in 2015 (NACO, 2015-2016).

Table 1. Global fact sheet 2016 (UNAIDS)

1. People living with HIV
In 2016, there were 36.7 million [30.8 million–42.9 million] people living with HIV.
34.5 million [28.8 million–40.2 million] adults
17.8 million [15.4 million–20.3 million] women (15+ years)
2.1 million [1.7 million–2.6 million] children (<15 years)
2. New HIV infections
Worldwide, 1.8 million [1.6 million–2.1 million] people became newly infected with HIV in 2016.
Since 2010, new HIV infections among adults declined by an estimated 11%, from 1.9 million [1.6 million–2.1million] to 1.7 million [1.4 million–1.9 million] in 2016.
New HIV infections among children declined by 47% since 2010, from 300 000 [230 000–370 000] in 2010 to 160 000 [100 000–220 000] in 2016.
3. AIDS-related deaths
AIDS-related deaths have fallen by 48% since the peak in 2005.
In 2016, 1 million [830 000–1.2 million] people died from AIDS-related illnesses worldwide, compared to 1.9 million [1.7 million–2.2 million] in 2005 and 1.5 million [1.3 million–1.7 million] in 2010.