Chapter 1
Computational Analysis of Reverse Transcriptase Resistance to Inhibitors in HIV-1

Ameeruddin Nusrath Unissa
National Institute for Research in Tuberculosis (NIRT), India

Luke Elizabeth Hanna
National Institute for Research in Tuberculosis (NIRT), India

ABSTRACT

Reverse transcriptase (RT) is a vital enzyme in the process of transcription of HIV-1. The nucleoside analogues of RT inhibitors (NRTIs) act by substrate competition and chain termination as they resemble a nucleotide. To understand the basis of RT resistance in HIV-1, in this chapter, one of the clinically essential mutants Q151M of RT which exhibits multi-resistance to many NRTIs was modeled and docked with NRTIs in comparison to wild type (WT). The results of docking indicate that the WT showed high affinity with all inhibitors compared to the mutant (MT). It can be suggested that the high affinity in WT could be attributed to the favorable interactions with all inhibitors that lacks in MT due to amino acid substitution that leads to structural changes in MT protein, which alters the favorable network of interaction and eventually imparts resistance to all inhibitors.

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INTRODUCTION

Human immunodeficiency virus (HIV) continues to be a major global public health issue. In 2015, globally 1.1 million people died, 36.7 million people living with HIV and 2.1 million people newly infected from HIV-related diseases. Sub-Saharan Africa is the most affected region, which accounts for two-thirds of the global total of new HIV infections. HIV infection is often diagnosed through rapid diagnostic tests, which detect the presence or absence of HIV antibodies. Although, there is no cure for HIV infection, however, effective antiretroviral (ARV) drugs can control the virus and help prevent transmission so that people with HIV, and those at substantial risk, can live healthy, long and productive lives. Expanding ART prevention choices to all people living with HIV can help avert 21 million AIDS-related deaths and 28 million new infections by 2030 (World Health Organization, 2016).

Reverse transcriptase (RT) is an important enzyme in the transcription process of the type-1 HIV (HIV-1). The RT enzyme functions as RNA-dependent DNA polymerization and DNA-dependent DNA polymerization. The enzyme RT is a heterodimer comprises of p66 and p51 subunits. The first 440 amino acids of p66 and p51 are identical, and both subunits appear to contain a polymerase function. The C-terminal portion of p66 contains the RNase H domain. The p66 subunit contains the DNA-binding groove and the active site; the p51 subunit displays no enzymatic activity and functions as a scaffold for the enzymatically active p66 subunit. The p66 subunit has five subdomains namely fingers, palm, thumb, connection and RNase H subdomains (Shafer et al., 2001; Erickson & Burt, 1996).

The nucleoside RT inhibitors (NRTIs) are prodrugs that are triphosphorylated by host cellular enzymes. The triphosphorylated NRTIs then compete with natural deoxynucleoside triphosphates (dNTPs) for incorporation into the newly synthesized DNA chains where they cause chain termination. There are two biochemical mechanisms of NRTI drug resistance. The first mechanism is mediated by mutations that allow the RT enzyme to discriminate against NRTI during synthesis, thereby preventing their addition to the growing DNA chain relative to the natural dNTP substrates (Larder & Stammers, 1999; Sarafianos et al., 1999; Huang et al., 1998). The second mechanism is mediated by mutations in RT that increase the rate of hydrolytic removal of the chain terminating NRTI and thus enable continued DNA synthesis (Arion et al., 1998; Boyer et al., 2001; Meyer et al., 1998). This mechanism of resistance has also been referred to as pyrophosphorolysis, nucleotide excision, and primer unblocking. The hydrolytic removal requires a pyrophosphate donor, which in most cells is usually ATP (Meyer et al, 1999).

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