Table 1. 1: Antiretroviral drugs used in the treatment of HIV infection, their mechanisms of action and mechanisms of resistance. Source: Adapted from François Clavel and Allan J. Hance 2004 (Clavel and Hance, 2004) and (Ammaranond and Sanguansittianan, 2012; Colin et al., 2013)

| **Drugs** | **Mechanism of Action** | **Mechanisms of Resistance** |
| --- | --- | --- |
| **Fusion and entry inhibitors** | | |
| Enfuvirtide (T-20) | 36 amino acid peptide derived from the HR2 domain of glycoprotein 41  Interferes with glycoprotein 41 dependent membrane fusion | Mutations affect HR1, a domain of glycoprotein 41 whose interaction with HR2 promotes membrane fusion |
| Maraviroc | Binds to CCR5 co receptor | Development of CXCR4 using HIV HIV-1 exploits CCR5 conformational heterogeneity |
| **Nucleoside reverse transcriptase inhibitors (NRTls)** | | |
| Zidovudine (AZT) | Analogues of normal nucleosides  Active as triphosphate derivatives  Incorporated into nascent viral DNA  Prematurely terminate HIV DNA synthesis | Thymidine analogue mutations promote ATP-mediated and pyrophosphate-mediated excision of the incorporated terminator |
| Didanosine (ddl) |
| Zalcitabine (ddC) |
| Stavudine (d4T) |
| Lamivudine (3TC) |
| Abacavir (ABC) |
| Tenofovir disoproxil (TVD) |
| Emtricitabine (FTC) |
| **Nucleotide reverse transcriptase inhibitors (NtRTls)** | | |
| Tenofovir | Same as nucleoside analogues | K65R impairs incorporation of tenofovir into DNA  Thymidine analogue mutations often associated with cross-resistance to tenofovir |
| **Non-nucleoside reverse transcriptase inhibitors (NNRTls)** | | |
| Nevirapine (NVP) | Bind a hydrophobic pocket of HIV type 1 reverse transcriptase  Block polymerization of viral DNA  Inactive against HIV type 2 | Mutations reduce affinity of the inhibitors for the enzyme  Single mutations generally sufficient to induce high level of resistance |
| Delavirdine (DLV) |
| Efavirenz (EFV) |
| Etravirine (ETR) |
| **Protease Inhibitors (PI)** | | |
| Saquinavir (SQV) | Structure derived from natural peptidic substrates of the HIV type 1 protease  Bind the active site of the protease | Mutations reduce affinity of the inhibitors for the enzyme  High-level resistance requires a accumulation of mutations |
| Ritonavir (RTV) |
| Indinavir (IDV) |
| Nelflnavir (NFV) |
| Amprenavir (APV) |
| Lopinavir + Ritonavir (LPV/r) |
| Fosamprenavir (FPV) |
| Tipranavir (TPV) |
| Darunavir (DRV) |
| Atazanavir (ATV) |
| **Integrase Inhibitors** | | |
| Raltegravir | Binds selectively to the enzyme complexes that results in inhibiting strand transfer of viral and host DNA | Mutations at conserved carboxylate residues (Asp64 and Asp116) |

Table 1. 2: Comparative analysis of different NGS systems. Source: adapted from Shokralla et al 2012 (Shokralla et al.), Niedringhaus et al 2011 (Niedringhaus et al.) and Glenn 2011 (Glenn, 2011)

| Platform | Read length (bp) | Reads/run | Sequencing output/run | Run time | Advantages | Primary applications |
| --- | --- | --- | --- | --- | --- | --- |
| Roche/454 GS FLX | 400–500 | 1 × 106 | ≤500 Mb | 10 h | Longest read lengths among 2nd generation, high throughput compared to 1st generation sequencing | 1\*, 2, 3\*, 4, 7, 8\* |
| Roche/454 GS FLX+ | 600–800 | 1 × 106 | ≤700 Mb | 23 h |
| Roche/454 GS Junior | 400–450 | 1 × 105 | ∼35 Mb | 10 h |
| Illumina HiSeq 2000 | 100–200 | 6 × 109 | ≤540–600 Gb | 11 d | Very high throughput | 1\*, 2, 3\*, 4, 5, 6, 7, 8 |
| Illumina HiSeq 1000 | 100–200 | 3 × 109 | ≤270–300 Gb | 8.5 d |
| Illumina GAIIx | 50–75 | 6.4 × 108 | ≤95 Gb | 7.5–14.5 d |
| Illumina MiSeq | 100–150 | 7 × 106 | ≤1–2 Gb | 19–27 h |
| AB SOLiD 5500 system | 35–75 | 2.4 × 109 | ∼100 Gb | 4 d | Very high throughput; lowest reagent cost needed to reassemble a human genome among the widely accepted 2nd generation platforms, lower error rate | 3\*, 5, 6, 8 |
| AB SOLiD 5500 xl system | 35–75 | 6 × 109 | ∼250 Gb | 7–8 d |
| Ion Torrent -314 chip | 100–200 | 1 × 106 | ≥10 Mb | 3.5 h | Direct measurement of nucleotide incorporation events; DNA synthesis reaction operates under natural conditions (no need for modified DNA bases) | 1, 2, 3, 4, 8 |
| Ion Torrent -316 chip | 100–200 | 6 × 106 | ≥100 Mb | 4.7 h |
| Ion Torrent -318 chip | 100–200 | 11 × 106 | ≥1 Gb | 5.5 h |

Bold indicates applications that are most often used, economical or growing

1 = de novo BACs, plastids, microbial genomes. 2 = transcriptome characterization.

3 = targeted re-sequencing. 4 = de novo plant and animal genomes.

5 = re-sequencing and transcript counting. 6 = mutation detection.

7 = metagenomics. 8 = other

\*Pooling multiple samples with sequence tags (i.e. MIDs) is required for efficient use of this application