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The dawn of precision medicine in HIV: State of the art of pharmacotherapy

Ying Mu¹, Sunitha Kodidela², Yujie Wang², Santosh Kumar², and Theodore J. Cory^{1,*}

¹Department of Clinical Pharmacy and Translational Science, University of Tennessee Health Science Center College of Pharmacy, Memphis, USA

²Department of Pharmaceutical Science, University of Tennessee Health Science Center College of Pharmacy, Memphis, USA

Abstract

Introduction: Combination antiretroviral therapy reduces viral load to under the limit of detection, successfully decreasing HIV-related morbidity and mortality. Due to viral mutations, complex drug combinations and different patient response, there is an increasing demand for individualized treatment options for patients.

Areas covered: This review first summarizes the pharmacokinetic and pharmacodynamic profile of clinical first-line drugs, which serves as guidance for antiretroviral precision medicine. Factors which have influential effects on the drug efficacy and thus precision medicine are discussed: patients' pharmacogenetic information, virus mutations, comorbidities and immune recovery. Furthermore, strategies to improve the application of precision medicine are discussed.

Expert opinion: Precision medicine for antiretroviral therapy requires comprehensive information on the drug, virus and clinical data from the patients. The clinically available genetic tests are a good starting point. To better apply precision medicine, deeper knowledge of drug concentrations, HIV reservoirs, and efficacy associated genes, such as polymorphisms of drug transporters and metabolizing enzymes, are required. With advanced computer-based prediction systems which integrate more comprehensive information on pharmacokinetics, pharmacodynamics, pharmacogenomics and the clinically relevant information of the patients, precision medicine will lead to better treatment choices and improved disease outcomes.

Keywords

Antiretroviral therapy; Pharmacokinetics; Pharmacodynamics; Pharmacogenetic; Precision medicine; Therapeutic monitoring

* Tcory1@uthsc.edu, Phone: 901-448-7216, Fax: 901-448-1741.

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1. Introduction:

33 million people are infected with HIV worldwide. [1] In the United States alone, more than 1.2 million people are living with HIV. Approximately 50,000 new infections occur in the United States each year. [2] Antiretroviral therapy (ART) largely reduces mortality and increases patient's quality of life by suppressing HIV-1 viremia to under the limit of detection. Since the Food and Drug Administration (FDA) approved the first antiretroviral zidovudine (AZT) in 1987, there are six classes of antiretroviral drugs have been approved: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor (FI), a CCR5 antagonist, and integrase strand transfer inhibitors (INSTIs). The treatment options started with a single-drug regimen. Due to the virus mutation which leads to drug resistance, combination therapy has become standard of care. Two NRTIs based treatment regimens are the backbone of therapy, with a third drug coming from the PI, NNRTI, or INSTI class is utilized in recommended treatment. [3]

Inter-patient variability in the outcome of combination therapy could be due to various factors: viral resistance, pharmacogenetics, medication adherence, drug distribution, and patient's comorbidities. Genetic variability exists among patients. Depending on patients' unique genetic risk factors, antiretroviral therapy may lead to an increased risk of side effects or a lack of therapeutic response. In individuals who have received antiretroviral therapy for an extended period of time, mutations in the viral genome can develop, resulting in the development of drug-resistant viruses. Drug resistance is one of the major factors to cause therapy failure.

Precision medicine refers to therapy selected based on the patient's genetic characteristics. [4] Precision medicine in ART is still relatively new, but becoming an emerging interest for researchers. A tailored treatment plan for each individual requires comprehensive knowledge including patients' characteristics, viral features, and drug properties. There is an increasing need for precise ART to provide efficient treatment while minimizing toxicity and decreasing the risk of viral resistance developing. HLA-B*5701 screening and genetic testing of viral tropism are good examples of utilizing precision medicine in the selection of HIV drugs. However, there's still a long road to be walked for precision medicine to be widely applied to ART in the clinical settings. It is imperative and helpful to summarize and analyze the status of today's ART precision medicine. In this paper, we reviewed the pharmacokinetics (PK) and pharmacodynamics (PD) of the first line clinical drugs. We also describe virus mutations and the polymorphisms in patients' genes which can cause a shift in efficacy. HIV associated comorbidities and ART caused immune recovery are examined as well. Finally, specific strategies and tools are discussed for precision ART.

2. PK, PD and pharmacogenetics

2.1. NRTIs

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) prevent HIV replication by inhibiting viral reverse transcriptase. NRTIs are administered as prodrugs and are phosphorylated into active triphosphorylated forms by intracellular kinases.

Lamivudine (3TC) has high oral bioavailability. Through passive diffusion, the drug is rapidly absorbed. The maximum concentration is achieved within 1.5 hours. [7] No significant difference in half-life was observed between 3TC 150mg twice a day and 300mg twice a day for 14 days. 70% of the drug is excreted as unchanged form through urine over 24 hours. [8] Renal impairment reduces drug clearance. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) suggest dose adjustment for patients with creatinine clearance lower than 50 ml/min.[9] Various enzymes and transporters are involved in 3TC metabolism and its efflux is mediated by the ABC family of transporters. However, very few studies have been reported on the influence of genetic variants on 3TC disposition in clinical settings. In a retrospective pilot study on 33 HIV-infected patients, Anderson et al. showed an association between the *MRP4*T4131 'G' variant and increased levels of circulating 3TC. [10]

The bioavailability of Abacavir (ABC) is 83%. Between 0.6 to 2.5 hours, the drug reaches maximum concentration, and the half-life is 20.5 hours. [11] The average intracellular half-life is 14.1 hours.[12] 83% of the dose is eliminated through urine and 16% through feces. Abacavir (ABC) is primarily metabolized by Alcohol Dehydrogenase (ADH) and Glucuronosyltransferase (UGT). The most common adverse event observed with the use of ABC is hypersensitivity reactions. [13]ABC binds to the HLA-B*5701 protein as a complex which can then be recognized as non-self by the immune system and activate CD8⁺ T cells. [14] Genetic variants in HLA have been associated with ABC-induced hypersensitivity reactions. Existing studies have provided strong evidence for ABC-induced hypersensitivity reactions that encouraged the FDA to implement a label warning in 2008 for the screening of the *HLA-B*5701* variant prior to starting ABC therapy.[13, 15, 16] Another study suggests that the prevalence of the *HLA-B*5701* allele is higher in the Caucasians than in African-Americans.[17] Therefore, testing for *HLA-B*5701* genotype is required before administration of ABC containing regimens.

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir which is hydrolyzed to tenofovir. Tenofovir alafenamide (TAF) is another prodrug of tenofovir approved by FDA. The active form of tenofovir (TFV) is a diphosphate, unlike other NRTIs whose active forms are triphosphates. The dosage for TDF is 300mg once daily with a greater than 60 hour intracellular half-life. Compared to TDF, TAF is administered 25mg once daily due to the higher intracellular concentration of the phosphorylated moiety tenofovir diphosphate and lower serum tenofovir. High circulating plasma level of TFV leads to renal and bone toxicity which is the case with TDF. [18] The major adverse effect reported with the use of tenofovir is renal dysfunction. Dose reduction is required for renal impaired patients. Inter-individual variability exists for the incidence and severity of tenofovir-induced kidney tubular toxicity. Tenofovir enters the kidney via SLC22A6 and SLC22A8 transporters and is exported by the transporter proteins ABCC10 and ABCC4. Variants in the genes coding these efflux transporters have been associated with altered tenofovir disposition and toxicity. [19–21]The *ABCC4*(rs1751034) 3463 'A' allele is associated with increased tenofovir renal clearance and decreased intracellular concentration of tenofovir diphosphate compared to 'G' allele carriers. [22]However, variants in the *SLC22A6* gene (453 G>A, 728 G>A) do not affect tenofovir PK. [19, 22] In a case-control study, Pushpakom et al. showed that the rs9349256 'G' variant allele in the *ABCC10* gene was significantly associated with kidney tubular

dysfunction in HIV-infected patients. Further, tenofovir levels were found to be higher in patients with renal tubular toxicity. However, there was no relationship between tenofovir levels and *ABCC10* rs9349256 'G' variant allele. The authors suggest that this could have been due to the relatively small sample size in their study. [21]

Emtricitabine (FTC) is 93% bioavailable for the capsule and 75% bioavailable for solution. FTC shows a linear PK. The time to reach maximum concentration is 1 to 2 hours. Co-administration of food does not have effects on the area under the plasma drug concentration-time curve (AUC) of FTC. [23] The half-life of FTC is 10 hours plasma half-life and 39 hours of intracellular half-life. [24, 25] Drug dose intervals are adjusted to 48–96 hours in patients with impaired renal function since FTC is excreted in the urine primarily. [23]

2.2 NNRTIs

Non-nucleoside/nucleotide reverse transcriptase inhibitor (NNRTI) reduce viral load by binding to a specific HIV-1 reverse transcriptase binding pocket in a noncompetitive manner. They are specific to HIV but not to human reverse transcriptase. Four NNRTIs have been approved by FDA: efavirenz (EFV), etravirine (ETR), nevirapine (NVP), rilpivirine (RPV), and doravirine (DOR). EFV or RPV combined with NRTIs tenofovir and FTC have been approved as initial treatment regimens for certain HIV patients.[9]

The oral bioavailability of EFV is between 40%–45%. [26] The half-life of EFV is between 36 to 100 hours. The drug is highly plasma protein bound. In a study of 35 HIV infected patients, the steady state C_{max} and C_{min} were $12.9 \pm 3.7 \mu M$ and $5.6 \pm 3.2 \mu M$, respectively with a treatment of 600mg once daily. [27] No dosage adjustment is required in patients with impaired renal function as EFV is eliminated as an unchanged form through urine. EFV is an inhibitor of UGT1A1, BSEP, MRP2, MRP3, CYP2B6, CYP2C8, CYP2C9 and CYP2C19. EFV is also an inducer for CYP3A4 and CYP2B6. [28]. EFV cannot be used as a single regiment due to its low genetic barrier to the resistance and some level of intraclass cross-resistance. [29] EFV is primarily metabolized by CYP2B6, also by CYP2A6, CYP1A2, CYP3A4, and CYP3A5. CYP2B6 is also expressed in the brain, thus may play a role in the neurological side effects of EFV. [30] The *CYP2B6* gene is highly polymorphic, and genetic variants that affect its function are likely to contribute to inter-individual variability in EFV treatment outcomes. Different polymorphisms in *CYP2B6* (rs3745274, rs2279345) have been shown to affect the dosage, PK, and toxicity of EFV in clinical studies. Of those, the rs3745274 516 G>T variant, which has been widely studied, decreases CYP2B6 activity, leading to increased levels of circulating EFV in different ethnicities. [31] In a clinical study on 456 HIV-infected patients, 16 patients who had 516 TT genotypes, including *6/*6 and *6/*26, had extremely high blood concentrations of EFV (>6000 ng/mL) compared to patients with 516 GG genotypes with standard EFV 600mg treatment. A novel *CYP2B6* haplotype, *26, containing 499 G, 516 T, and 785 G variants was identified in this study. Similarly, high EFV concentrations were also observed in EFV-naïve 516 TT patients with a reduced dose of 400 mg EFV and even 200 mg treatments. The plasma viral load was consistently undetectable. Moreover, the CNS symptoms were improved after dose reduction from 600 mg to 400 or 200 mg. [32] To support these findings,

Lam et al. conducted a population PK/PD simulation study and predicted that the optimal doses of EFV for *CYP2B6* 516 GG, GT, and TT genotype carriers were 500 mg, 350 mg, and 100 mg daily, respectively, to achieve therapeutic concentrations of EFV between 1–4 mg/L. [33] Similarly, Bienczak et al. conducted simulation studies, predicted EFV metabolic subgroups, and adjusted doses accordingly in African children with HIV based on *CYP2B6* rs3745274 516 G>T and rs28399499 T>C genotypes. [34] Recently Atwine et al., in a systematic review, suggest that *CYP2B6* 516 G>T mutation is associated with increased plasma levels of EFV, irrespective of ethnicity. [35] Thus, growing evidence supports modulation of EFV dose based on *CYP2B6* variant genotypes, primarily *CYP2B6* 516 G>T.

RPV is highly plasma protein binding (99%). The drug is administered once daily due to its half-life of 38 hours. Bioavailability increases with an acidic environment. [36] C_{max} and AUC decrease by 46% and 43% when administered without food. [37] RPV has a non-competitive inhibition of HIV-1 reverse transcriptase but does not inhibit human cellular DNA polymerases α , β , γ . [38] Rilpivirine (RPV) is mainly metabolized by CYP3A4 and to a lesser extent by CYP2C19 and UGTs 1A1 and 1A4. Aouri et al. conducted a POPPK and POPPG analyses of RPV using 325 plasma RPV concentrations from 249 HIV-infected patients. The demographic covariates and studied variants in RPV-metabolizing enzymes couldn't account for the inter-individual variability in RPV PK. [39]

Doravirine (DOR), which is an investigational drug, is under clinical trial for safety and efficacy as both single-drug tablet and fixed-dose combinational tablet with 3TC and TDF. DOR is metabolized through CYP3A4 mostly. It is a PGP substrate. The range of mean half-life of DOR in patients in fed state was from 11.75 hours to 13.1 hours, in fasted states ranged from 14.2 to 14.35 hours when administered as 100mg of a single-agent tablet and fixed-dose combination. [40] Viral mutants which are resistant to DOR are susceptible to RPV and EFV, the virus which is resistant to RPV and EFV are susceptible to DOR. [41, 42] This made DOR a very promising alternative drug for RPV and EFV. Adverse effects of DOR in the central nervous system was less common than patients who received EFV in a clinical phase IIb trial. For the fixed-dose tablet clinical trials, the overall adverse effects were compatible except for the effects on LDL and non-HDL with DOR reducing and DOR +RTV increasing the level of two lipid parameters between DOR only and DOR+RTV groups. [43–45] Adverse effects such as dizziness, sleep disorders/disturbances, and altered sensorium were significantly less common in the DOR/3TC/TDF group compared with Atripla (EFV/FTC/TDF) group. [46] [47]

2.3 Integrase inhibitors

HIV integrase inhibits integration of viral genome into chromosomal DNA. Raltegravir (RAL), dolutegravir (DTG) and elvitegravir (EVG) have been approved by FDA. RAL is administered 400mg twice daily and the half-life is 7–12 hours. [48] After 12 hours, the plasma RAL concentration is 63 ng/ml. Except for patients over 60 years old and younger who has reduced creatinine clearance of RAL, there is no need to adjust RAL dosage based on sex, gender, body weight, hepatic or renal function impairment. [9] A new once-daily RAL (2 × 600 mg once-daily) plus FTC/TDF was proven non-inferior than the original version (400 mg twice daily) plus FTC/TDF. [49] Raltegravir (RAL) is metabolized

by UGT1A1. The polymorphisms in *UGT1A1* may not be clinically relevant in dose adjustment of RAL. [50, 51] Similarly, Calcagno et al also reported that variants in genes encoding RAL transporters (ABCB1 3435, SLCO1A2, ABCC2 and SLC22A6) and hepatocyte nuclear factor 4 α (HNF4 α) did not account for high inter-patient variability of RAL CSF concentrations in HIV-infected subjects. [52]

DTG is prescribed as part of a single-tablet regimen containing ABV and 3TC without pharmacologic enhancement.[53] DTG has a much longer half-life 71 hours, compared to RAL (8.8 hours) and EVG (2.7 hours). It is predominately metabolized by UGT1A1 and also metabolized by CYP3A4.[54] . A slight but not significant difference in DTG exposure was observed in UGT1A1 variants carrier and no dosage adjustment is recommended in a meta-analysis study. [54] Though the FDA-approved drug label states that there is a decreased clearance of DTG in individuals with UGT1A1 variants, specific genetic testing of *UGT1A1* for initiating therapy with DTG is not required. The other polymorphisms explored in DTG disposition were in genes encoding for transporters; *ABCB1* and *ABCG2*. Tsuchiya et al. reported a lack of association between *ABCB1* variants (1236 C>T, 2677 G>T/A, 3435 C>T, 4036 A>G) with DTG concentration. However, the authors found that *ABCG2* 421 'AA' homozygous mutant genotype carriers had high peak plasma concentrations of DTG compared with heterozygous (CA) and homozygous wild-type genotype carriers (CC). However, limitations apply to the finding: the DTG metabolism by UGT1A1 and CYP3A4 is unknown. Further studies are needed to implicate the contribution of ABCG2 in DTG drug concentration.[55]

EVG is highly plasma protein bound (>99%). Food intake with EVG increases oral bioavailability: 34 and 24% of increases in AUC and C_{max} are observed respectively.[56] No dose adjustment is required for patients with moderate impaired hepatic and renal function (eGFR <30 ml/min, not on dialysis).[57] EVG is primarily metabolized by CYP3A4, and also an inducer of CYP3A4. Co-administration with COBI increases AUC of EVG 20 times higher, and the median half-life was increased from 3.5 hours to 9.5 hours.[57] A Mild but not significant reduction of CL in patients with homozygosity for the allele UGT1A1*28 was observed in an EVG PK modeling study. [58]

2.4 Protease Inhibitors

By preventing the cleavage of the HIV pol-polypeptide precursors into mature enzymes, protease inhibitor interferes with multiple steps of HIV life cycle.[9, 59] Protease inhibitors (PIs) are metabolized by cytochrome P450 and are characterized by a short half-life. Atazanavir (ATV) exhibits potent anti-HIV activity and good oral bioavailability. Compared to other protease inhibitors, fewer side effects are associated with atazanavir. [60] Food intake with ATV decreases its PKC variability. It is highly plasma bound, and shows non-linear PK. [61] ATV is metabolized by CYP3A and is an inhibitor of CYP3A and UGT1A. ATV increases the risk of hyperbilirubinemia by inhibiting UGT1A1. [62] A C_{trough} of ATV at 150 μ g/l is defined as the threshold of effective ATV, while a concentration of 750 μ g/l has been found to lead to grade III/IV hyperbilirubinemia. [62, 63] In a study identifying genetic variants associated with ATV pharmacokinetics and hyperbilirubinemia in HIV patients, including the *UGT1A1-364 TT*(rs887829) genotype to a model with non-genetic factors

increased the predictability percentage of inter-individual variability in peak on-treatment bilirubin concentration (>3.0 mg/dL) from 33.4% to 41.3%. [64] Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for pharmacogenomic prescribing of ATV recommends counseling on the likelihood of developing hyperbilirubinemia in *UGT1A1**28/*28, *28/*37, *37/*37, and -364 TT genotype carriers before initiating ATV therapy.[65] Variants in *CYP3A4*, *CYP3A5*, and *ABCB1* genes have also been explored in relation to ATV concentrations in other studies. [66, 67] These studies reported that wild type *ABCB1* *CGC* haplotype carriers (1236C/2677G/3435C) have decreased ATV clearance. *CYP3A5* expressors (*1 carriers) have faster ATV clearance than *CYP3A5* non-expressors (*3/*3, *6/*6, *7/*7). [67] Darunavir (DRV) prevents the HIV aspartyl protease from cleaving the HIV polyprotein. The EC₅₀ of darunavir is 1–2nM. [68, 69] The variants in *SLCO3A1* were found to influence darunavir PK parameters. In a pharmacogenomics based POPPK analysis of darunavir and ritonavir (600/100 mg twice daily for at least 4 weeks) in 75 Caucasian individuals, *SLCO3A1* rs8027174 GT/TT genotype carriers had a low clearance of darunavir and rs4294800 'A' allele carriers had higher central volume of distribution. [70] DRV is largely metabolized by CYP3A. CYP3A4 together with CYP3A5 metabolize almost 50% of current drugs. CYP3A5*3 (rs776746, 6986A>G) is the most loss-of-function variant. Homozygous CYP3A5*3/*3 is considered as CYP3A5 non-expressor. CYP3A5*1 carriers are classified as CYP3A5 expressors. Research has shown that a significant lower plasma DRV was observed in CYP3A5 non-expressors compared to CYP3A5 expressors who were under the treatment of DRV plus etravirine (ETR) which is a second-generation of NNRTI. [71] CYP3A4*22 (rs35599367, C>T) was discovered as a CYP3A4 mutant with low activity. It is predicted that CYP3A4*22 carrier would lead to higher plasma drug concentration.

2.5 Protease inhibitor boosting

Protease inhibitors are highly protein bound and substrates of P-glycoprotein (PGP) and CYP3A. There is high variability both intra-patient and inter-patient. In order to increase the drug exposure while maintaining the dosage and minimizing the toxicity, pharmacologic boosting of the compounds is used. Ritonavir, a potent CYP3A4 and PGP inhibitor is used at a sub-therapeutic dose (100 or 200mg) as a pharmacoenhancer to increase PK parameters of the boosted drug, including plasma trough concentration (C_{trough}), plasma maximum concentration (C_{max}), half-life ($t_{1/2}$) and the AUC which represents the drug exposure to the body after administration of a dose. By increasing the C_{trough} , C_{max} , $t_{1/2}$ and the parameter reflects the total drug exposure over time, a pharmacoenhancer maintains the efficacy while reduced toxicity. [72] Ritonavir is metabolized by CYP2J2, CYP3A4, CYP3A5 and CYP2D6. In a population pharmacokinetic (POP) study of LPV/RTV, a lower RTV L was observed in patients with *CYP3A4* rs35599367 C>T SNP and *OATP1B1*. [73] Lopinavir has an EC₅₀ of 17nM and the dosage in adult is 400mg with ritonavir 100mg twice a day. Cobicistat (COBI) is a derivative of RTV which has a morpholine ring. Unlike ritonavir, COBI is a weak CYP2D6 inhibitor and has no effects on CYP1A2, CYP2C9 or CYP2C19. It has been shown that the exposures of COBI were nonlinear and greater than dose-proportional over the range of 50–400mg. The C_{max} , AUC, C_{trough} following multiple doses were 1.2 µg/ml, 10.9 µg·h/ml and 0.07 µg/ml at steady state. [9] Darunavir or atazanavir with ritonavir is a part of a first-line antiretroviral regimen. ATV 400mg combined with RTV at

300/100mg or plus COBI 150mg has been approved for treatment of HIV infection naïve or experienced patients. [9]

2.6 Other inhibitors

Maraviroc (MVC) interrupts the entry of HIV by inhibiting CCR5 binding. Maraviroc is specific for CCR5 viral strains. The half-life is 22.9 hours.[74] The heterozygous CCR5 genotype is associated with milder disease progression. Maraviroc (MVC) is a substrate of *SLCO1B1*, CYPs 3A4 and 3A5, and P-gp. Siccardi et al. reported the association of the *SLCO1B1* 521 'C' allele with higher plasma concentrations of MVC (PMID: 21217360). [75] Lu et al., explored the impact of *CYP3A5* genotypes on MVC concentration in healthy volunteers and observed that *CYP3A5**1(wild type) allele carriers had lower concentrations of MVC compared to *CYP3A5* dysfunctional alleles (*2,*3,*6, and *7). [76] However, Vourvahis et al. commented on the work of Lu et al., and emphasized the usefulness of TDM. Further, authors suggested that the *CYP3A5* genotype has limited relevance when MVC is administered with ritonavir. [77]

2.7 Combination therapy

According to FDA guideline, the most common backbone of initial antiretroviral treatment for the majority of the patients are: ABC/3TC, TAF/FTC, TDF /FTC. Based on the particular medical condition of each patient, different combinational antiretrovirals should be prescribed. For patients who are infected with both hepatitis B (HBV) and HIV or HLA-B*5710 testing is not available, TAF/FTC or TDF/FTC based regimen are recommended since both TAF and TDF maintain activity against both viruses. Compared to TDF, TAF is less toxic to kidney function and bone mineral density. ABC is indicated to lead to cardiovascular events. [3] INSTI plus NRTIs combinational therapy with the NRTIs as the backbone, complete the initial ARV due to the high efficacy and low adverse effect. Drug-drug interactions associated with CYP3A4 are not observed for RAL and DTG, two of the most commonly used INSTIs. DTG based regimens can be administered if the patient's resistance test is not available due to a low baseline level of resistance in the general population. Boosted PIs plus NRTIs regimen is used when drug adherence of the patients or the resistance testing result is unknown. DRV/r is one of most used combination due to its high genetic barrier to resistance, low risk of transmitted PI resistance and treatment-emergent resistance. ATV/r has been shown to be associated with a lower risk of atherosclerosis development.[3, 78, 79] Compared to INSTIs, boosted PIs are associated with a higher rate of treatment discontinuations.[80–82] For patients co-infected with TB, EFV of NNRTI category NRTI combination is recommended since EFV maintains minimal interaction with rifamycin. However, if HIV RNA>100,000 copies/ml, EFV plus ABC/3TC is not recommended.[83]

3.0 : Viral genetic characteristics

In addition to host genetics, variations between HIV strains can also cause drug resistance. For example, mutations in reverse transcriptase can cause resistance to NRTIs (Q151M, M184V, and K65R) and NNRTIs (Y181C, Y188C, K103N, G190A, and V106A). Mutations in the viral protease enzymes (L90M, V82A, V82T, and V82F) can cause resistance to PIs as

well. Furthermore, cross-resistance impairs the success of alternative regimens. For instance, if a patient receiving first generation NNRTIs develops resistance to it, they will be resistant to second generation of NNRTIs even if they never take it. [84] Conventionally, genotypic and phenotypic assays are employed to detect the presence of resistance mutations. Because phenotypic testing (PT) is expensive and time consuming, genotypic testing (GT) is most commonly utilized in identifying resistance strains.

4.0 : Influence of comorbidities on HIV precision medicine

Chronic HIV infection, unhealthy lifestyles, and ART contribute to increased risk of comorbidities in individuals with HIV. Compared with HIV-negative individuals, individuals with HIV have significantly higher prevalence of cardiovascular disease (9% vs 6%), liver disease (10% vs 6%), kidney disease (12% vs 4%), osteoporosis and fractures (10% vs 8%). [85] Hyperlipidemia and endocrine diseases are the most common comorbidities in the United States, and though they occur with similar prevalence among patients regardless of HIV infection, they are also frequent comorbidities in HIV patients. [85, 86] During ART for patients with a concomitant disease, precision HIV medicines may allow for greater efficacy and fewer side effects.

4.1. Cardiovascular disease (CVD):

The heightened risk of CVD in HIV patients has been attributed to smoking, dyslipidemia, poor kidney function, vitamin D deficiency and side effects of ARV medicines. [87–91] ART regimens can induce or exacerbate CVD both directly and indirectly. Therefore, it is important to consider cardiac risk when selecting precise ARV medicines for HIV patients with CVD.

With or without co-treatment with PK enhancers, PIs can increase the risk of cardiovascular events. However, in a D:A:D study, this association was not observed with ATV.[92] The mechanism of this phenomenon is not clear, however, it could be related to the effects of plasma lipids. [93] Furthermore, while ritonavir-boosted PIs increase the risk of cardiovascular disease, the risk could be decreased by use of DTG-based regimens. [94] TDF was suggested to decrease intrinsic lipid when administered as co-formulation of TDF/FTC. [95] EFV can directly impair endothelial cell function and increase the likelihood of development of atherosclerotic lesions. [96, 97] EFV-containing medicines could increase the risk of CVD as well. [98, 99] EFV- or RPV-based regimens should be avoided in patients at high risk of *torsade de pointes* or those taking other medications with a known risk of *torsade de pointes*. [100, 101] Therefore, according to FDA guidelines, the regimen including ATV/r, DTG based combination is recommended for high CVD risk individuals.

Drug-drug interaction exists between the antiretrovirals and cardiac medications. Due to the inhibition effects on CYP enzyme, calcium channel blockers, beta-blockers, and antiarrhythmic medication should be used with caution and monitored closely when co-administered with PIs and boosters. However, beta-blockers which are not metabolized through a CYP pathway, such as atenolol, labetalol, nadolol, are suggested when co-administered with PIs and boosters. Digoxin concentration can also be increased, even to the toxic level when co-administered with PIs and boosters due to the inhibition effects of PIs

and boosters on the drug efflux transporters. Drug monitoring of digoxin is recommended. NNRTIs reduce calcium channel blocker drug concentration but does not interact with beta-blockers since NNRTIs induce CYP3A4 which metabolizes calcium channel blocker but not beta-blockers. Diuretics, ace inhibitors, and angiotensin II receptor blockers have low drug-drug interaction with ART.[3, 102] Based on the patient specific cardiovascular medication, antiretrovirals should be prescribed accordingly.

4.2. Liver failure:

Liver failure can be caused by viral hepatitis, alcoholic or non-alcoholic fatty liver disease, drug induced liver injury (DILIs), and other diseases. [103, 104] Drugs metabolized in the liver may require dosage adjustment in the patients who are Child-Pugh Class B or C (the classification of severity of cirrhosis). ABC, NVP, and TPV are contraindicated in Child-Pugh Class B or C patients, mainly because of hypersensitivity reactions and direct drug toxicity. [105, 106] Although PK enhancers are metabolized in the liver extensively, their metabolites are sufficiently safe that dosage does not need to be adjusted in mild-to-moderate liver failure patients.

On the other hand, HBV-HIV co-infected patients should be treated immediately, as co-infection increases the liver pathogenesis and decreases the clearance rate of hepatitis B antigen (HBeAg). [107] Individual-NTRI regimens, 3TC, FTC, TDF, and TAF have activity against both HIV and HBV. Compared with TDF, TAF also has less of an impact on the progression of chronic kidney disease and bone side effects.[108] Both anti-HIV and anti-HBV drugs should be included as full suppression of antiretroviral medication. Entecavir which is active against both HIV and HBV must be used with ART since entecavir selects mutant strains and leads to resistance to 3TC and FTC when used alone. 3TC or FTC treatment alone for HBV/HIV infection also leads to drug resistance. Entecavir combined with 3TC and FTC, rather than administered separately, is recommended therefore. Hepatitis C (HCV)-HIV co-infection can also accelerate the progression of liver fibrosis .[109] Clinical trial data has indicated that the combination of LDV/SOF (90 mg/400 mg) once daily for 12 weeks were safe and effective.[110] Due to the induction or inhibition of the PIs and boosters, drug-drug interactions occur: dosage adjustment is recommended for co-administration of daclatasvir with ritonavir-boosted atazanavir. Thus, ensuring that co-infected individuals receive specific dosing regimens different than individuals infected only with HIV offers an opportunity for improved outcomes in this patient population.

4.3. Abnormal kidney function.

Abnormal kidney function occurs in up to 30% of individuals with HIV, who are at an increased risk for both acute and chronic kidney disease. [111] With improvements in ART, HIV patients are living longer lives. However, longer life-spans also lead to long-term ARV exposure, which further increases the risk of kidney injury. [112] In addition to ART side effects, the virus also increases the risk of renal impairment in the form of HIV-associated nephropathy, non-collapsing focal segmental glomerulosclerosis, immune-complex kidney disease, and comorbid kidney disease.[113] These diseases mainly present in glomerular-dominant, tubule interstitial-dominant and vascular-dominant. Mocroft et al. estimated glomerular filtration rates (eGFRs) in HIV-positive patients, the results of which indicated

that tenofovir, and ATV reduced eGFR and increased the risk of CKD.[114] In a clinical-pathological study, tenofovir was associated with proximal tubular dysfunction [115]. In the case of life-long antiretroviral treatment, chronic metabolic complications is a concern, which might increase the risk of vascular chronic renal disease [116]. TAF is less likely superior compare to TDF for individuals with renal impairment or who are at a risk for renal impairment, since TAF leads to less toxicity to renal markers.

4.4. Hyperlipidemia.

Hyperlipidemia is defined as abnormally elevated levels of any or all lipids or lipoproteins in the blood, and in individuals with HIV occurs due to high triglycerides and low high-density lipoprotein (HDL) levels .[117] Enhanced levels of TNF and IL-6 and down regulated clearance of lipids may contribute to high triglycerides levels in people with HIV. Increased hepatic synthesis of very low-density lipoprotein could be responsible for the low level of HDL. [118] Moreover, a viral infection could induce dyslipidemia by interferon- α in acute-phase reactants .[119] On the other hand, the incidence of dyslipidemia can be increased by some drugs in ART treatment, particularly PI-containing regimens. PIs inhibit lipogenesis and adipocyte differentiation. [120] Furthermore, the PK enhancer RTV increases hepatic synthesis and plasma circulation of triglyceride.[121] Tenofovir is recommended to avoid dyslipidemia. [122, 123]The drug-drug interaction between statins and ART regimens should be observed as well, however. [124] PIs significantly increase serum statin level by inhibiting statin metabolism. The increased statin level leads to the risks of myopathy and rhabdomyolysis. For patients who are on simvastatin and lovastatin should be avoided to be administered with PIs and boosters. NNRTIs delavirdine increases statin level by inhibiting CYPs metabolism. Efavirenz reduces serum statin level by increasing statin metabolism.[83] Patients who are on statin need to be monitored when prescribed with antiretrovirals like delavirdine or efavirenz.

5.0 : Strategies on HIV precision medicine

5.1 Selecting a suitable starting regimen

Plasma viral load and CD4 counts are two laboratory markers of HIV-infected patients. In accordance with the most recent guidelines, ART treatment should be started immediately after HIV diagnosis. Even during recent HIV infection, starting ART treatment up to 6 months after infection can reduce the risk of HIV transmission by 40–68%. [125, 126] Therefore, if individuals are able to commit to taking ART, it should be started, regardless of the CD4 count. The risk of tuberculosis and cancer decreases with immediate initial ART treatment. Nevertheless, some ART regimens should be assessed with particular attention to potential PK interactions between ARTs and TB drugs. For example, rifampin decreases the concentration of NNRTIs and PIs since it is an inducer of cytochrome P-450 and PGP. Therefore, initiation of ART should be started within the first 2 weeks of TB treatment in patients with CD4 cell counts <50 cells/mm³. [127] ART initiation should be started within 8 weeks of TB treatment for those with CD4 counts $\geq$ 50 cells/mm³. [128]

5.2 Therapeutic drug monitoring

To date, therapeutic drug monitoring (TDM) is not the standard of care for individuals with HIV, although there is evidence that in some cases it can be associated with improved outcomes in individuals started on antiretroviral (ARV) therapy. [129] The reasons for this include the cost associated with TDM, the time and expertise necessary properly interpret TDM levels, a lack of laboratories which have this expertise and the assays for many of these drugs, that in many situations there is a lack of knowledge of effective and toxic concentrations of the drugs which are used, as well as an uncertain relationship between plasma and intracellular concentrations of drugs.[130] Despite this, there are times where TDM use may be warranted. These times may include when there is a potential identified drug-drug interaction, in people who do have not experienced a virologic response despite reported adherence, or if there is a change in physiologic status, including gut, hepatic, or renal function.[92] With few exceptions, however, these times where TDM may be utilized are retrospective attempting to determine why drug concentrations are sub-therapeutic, rather than occurring before a potential interaction occurs. This delay may result in worsened outcomes for these individuals, including the risk of resistance and opportunistic infections. Precision medicine for individuals with HIV offers the promise to identify individuals who may benefit from TDM prospectively, rather than retrospectively being initiated in individuals who do not experience a therapeutic response.

Precision medicine thus offers the opportunity to prospectively, rather than retrospectively, provide therapeutic drug monitoring (TDM) to patients who may benefit from it. For example, numerous ARVs are substrates of influx and efflux transporters including P-glycoprotein (PGP), Breast Cancer Resistance Protein (BCRP), and Multidrug Resistance Protein 1 (MRP1). Importantly single nucleotide polymorphisms exist for many of these enzymes and transporters.[131–134] A *SLCO1B1* SNP can be responsible for significantly higher lopinavir, but not ritonavir concentrations in individuals. [135] Advanced knowledge in cases like this may allow for prospective sorting of patients who would benefit from TDM from those who are unlikely to benefit from TDM, and the initiation of TDM at the initiation of therapy for those who would benefit. In an interesting case with lopinavir/ritonavir monotherapy in individuals after virologic suppression, individuals with the *MDR1 TT* variant were significantly less likely to have treatment failures compared to individuals who did not have this polymorphism. [136] Notably, while adherence was the most strongly associated factor with treatment efficacy, being able to identify individuals who do not have this polymorphism may identify subjects who would benefit from TDM and higher lopinavir/ritonavir doses. Having advanced knowledge for cases when therapeutic drug monitoring may be beneficial for patients may lead to better HIV disease outcomes and improved quality of life.

5.3 Useful tools for facilitating HIV precision medicine

Therapy prediction engines predict the likelihood of therapy success. The first generation of therapy prediction engines, virtual phenotypes, predict the resistance of virus against antiretrovirals. The second generation incorporates the information of virtual phenotype and clinical data from patients to predict the efficacy of therapy. The second generation is still under research and not used in the clinic routinely. Several therapy prediction engines are

available on the internet: The EUREsist, and the RDI TREPS system.[142, 143] However, the lack of validity and complicated interpretability of these prediction engines limits their utility in clinics. Therefore, further research needs to be done to validate therapy prediction engines. Beerenwinkel et al. developed computational methods for the analysis of integrated genotypic, phenotypic, and clinical data to provide personalized genotype-driven therapy options. [144]

Assessment of drug resistance using genotypic resistance sequence of virus is performed using mutation tables and the resistance algorithms. Mutation tables are designed manually by experts based on the literature, laboratory, clinical data, and their clinical experience, and these tables are regularly updated and published. [145] In resistance algorithms, the computer tests the pertinent portion of a viral genome against all rules in the set.[146, 147] Currently the statistical analysis approach (e.g. Geno2pheno server) using clinical data, including HIV resistance, type of treatment, and treatment duration, is also considered to interpret the genotypic resistance. This approach predicts HIV resistance more informative than mutation tables and resistance Algorithms. [148]Virtual phenotypes and therapy prediction engines are two generations of prediction systems for HIV resistance and the efficacy of ART. [147, 149]

Virtual phenotyping (VP) predicts ARV susceptibility by comparing HIV mutations from genotyping (obtained in the laboratory) with a database containing both genotypic and phenotypic information. Publically available software, including the Stanford HIV-SEQ database and VircoNET can be used for this purpose.[150, 151] In a comparison test, Genotypic testing and Virtual phenotyping methods allowed superior interpretation for drug resistance compared to laboratory-based Phenotypes. [152] Further use of VP is recommended by expert guidelines in developed countries.

HIV-1 primarily uses CCR5 as a co-receptor to enter cells.[153] However, during the course of infection, a mutated virus may emerge that are able to use either the CCR5 and CXCR4 co-receptor or CXCR4 exclusively. MVC is antagonizes the CCR5 receptor and blocks the spread of the R5-strain of HIV-1. Since MVC is an antagonist for CCR5, but not CXCR4, a phenotypic tropism test is performed before initiating therapy with MVC. This test is also performed for patients who exhibit virologic failure with CCR5 antagonists. Since phenotypic testing is expensive and time consuming, viral genotyping should be utilized to determine viral tropism. Currently, the most widely used bioinformatics tools for genotypic co-receptor tropism testing (GTT) are WebPSSM and Geno2Pheno (G2P). [154, 155] However, these two tools are designed for the HIV-1B virus. More recently a GTT tool called PhenoSeq was developed, which is claimed to be reliably predictive for the tropism of HIV-1 subtypes A, B, C, D, 01_AE and 02_AG. [156]

6.0 : Immune Recovery and Precision HIV medicine

Immune recovery after the initiation of antiretroviral therapy is of key importance. Even among individuals who do experience a virologic response after the initiation of antiretroviral therapy, not all of these patients will experience a rebound in their CD4 count. This is important as a rebound in CD4 counts is associated with improved outcomes and

quality of life, including decreased incidence of opportunistic infections.[157] Determining the factors, both genetic and otherwise which predict a response to antiretroviral therapy is of key importance.

Gene expression in peripheral blood mononuclear cells (PBMCs) can predict if individuals will have a recovery in CD4 T cells, which is strongly associated with better long term disease outcomes.[158] Similarly, MDR polymorphisms can be associated with more pronounced responses to antiretroviral therapy as compared to individuals without these polymorphisms: 26% higher bioavailability was observed in patients who are homozygous for ABCB1(rs3842); MDR1 3452 TT was also shown to be associated with a less likelihood of virologic failure and of the EFV-resistant virus. [159–162]

CCR5 genotype may also have a role in the rate and extent of immune reconstitution. CCR5 is one of the two co-receptors, which along with CD4 is necessary for HIV virions to internalize. CCR5 genotypes which favor less of a decline in CD4 T cell counts are also associated with a faster recovery once antiretroviral therapy has been initiated.[163] Notably, however, not all investigators have observed this effect.[164]

Polymorphisms in the expression of drug transporters and metabolic enzymes, important factors which influences plasma and intracellular concentrations of antiretrovirals have also been investigated as a factor in the rate and extent of immune recovery, with notably mixed results. Some have shown that SNP variants in drug transporters can be associated with a faster immune recovery.[159, 165, 166] Others have shown no associations between transporter expression and immune recovery.[167–169] CYP polymorphisms have more consistently been shown to have an effect on immune recovery.[166, 170–172] Additional research is necessary to further clarify the importance of drug transporter expression on immune recovery in individuals with HIV, as is developing strategies to identify subjects who may benefit from strategies targeted towards CYP and/or metabolic enzyme expression.

7.0 Conclusion

Complex factors are involved in applying precision medicine including drug properties, Pharmacogenetics of patients, treatment history and HIV RNA level. The current clinically available lab tests and useful tools are a good start to enter into the era of precision ART. However, limitations have to be overcome to deepen the knowledge of PK, PD profile of the drugs, to improve the current assays and tools in order to fulfill the increasing needs.

8.0 Expert Opinion

According to the FDA guidelines, lab tests including drug-resistance testing, viral tropism assay when considering a CCR5 antagonist, HLA-B*5701, and drug monitoring CD4 T cell count, HIV RNA viral load are important tests for the administration of ART. Those tests are supportive of precision ART, but limitations are also applied.

Due to high rates of mutations and the transmission of drug resistance, drug-resistance testing, which identifies virus specific genetic characters, also serves as an essential tool to apply for precision antiretrovirals. Genotypic testing, phenotypic testing, and virtual

phenotype are available methods for drug-resistance lab tests. Genotypic resistance testing is performed at baseline in individuals newly diagnosed or failed with ART in the clinical setting routinely. Sanger-based sequencing, which is based on the selective incorporation of chain-terminating dideoxynucleotides, is widely used for the detection of mutations in the clinic. Commercial kits, such as ViroSeq® (Abbott), TRUGENE® (Siemens Healthcare), HIV Genotype (Quest Diagnostics) and etc, are available on the market. Compared to the phenotypic testing, this method is relatively cheaper and faster with two weeks of turnaround time. However, the limitations of this method exist: only a narrow range of mutated virus can be detected (15% to 20% of the viral population). [173] This limitation can be overcome by another newer assay, next-generation sequencing. Viral mutations of both high and low mutations of frequency can be detected with the lowest ranges from 0.1% to 1%. [174–176] Though the next-generation sequencing is gradually rolled out in the clinical utility, barriers including the high start-up costs, requirements for the technical expertise to implement and maintain the instrument prevent the technology from being widely used in the clinical settings. However, with improved detection for the low frequent mutations and high throughput sequencing, this technology provides a potential for replacing the Sanger-based sequencing. Another limitation for current drug-resistance testing is the detection limit of viral load. For patients whose viral load is lower than 1,000 copies per ml, the commonly used testing assays may not provide accurate results. Thus there is a high demand in the research and clinical area to overcome this limitation. Converting and amplifying viral RNA might serve the purpose. Research for well-optimized PCR protocols which has a broad HIV-1 subtype coverage, a wide range of viral load span, high sensitivity and reproducibility is a promising research area.[177]

CCR5 antagonist test and HLA-B*5701 allele test are two other lab tests recommended by FDA for ART administration. Identifying the pharmacogenetics of patients' is another way to apply for the precision medicine. Patients with the HLA-B*5701 allele are at a higher risk of hypersensitivity to react with abacavir. HLA-B*5701 screening is recommended prior to prescribing abacavir. Genotypic testing of viral tropism is widely used in the clinical settings to test patient's dominant virus population. The genetic test of *CYP2B6 516 G>T* is useful to identify side effects of patients using efavirenz. *UGT1A1*28* testing prior administration of atazanavir can reduce the risk of hyperbilirubinemia. These current tests in the clinic are essential to practice precision antiretrovirals. However, improvements are in need: patients' genetic tests are not always available, and the tests can be costly and time-consuming. Furthermore, drug response may be effected by multiple genes and not just the one code for the specific protein. These tests reduce the risk of side effects and improve drug efficacy, but going forward will require knowledge of genetic risk factors and the development of new DNA technologies. With advanced knowledge of the human genome and new technologies, including DNA microarrays, DNA chips, and human genome analysis, in the future patients' specific gene characteristics will be basic information for physicians to choose drug combinations, optimizing drug concentration and minimizing the side effects.

Except for the lab tests, other means such as therapy prediction engines would also promote personalized ART. Therapy prediction engines predict clinical outcomes by giving a list of different therapy options ranked based on the likelihood of success. Therapy prediction engines, including EuResist prediction[179] and RDI TREPS system[180] are available

online. Patient treatment history, baseline CD4 cell counts and patient history information, but significantly not HLA information are utilized by current prediction systems. From the very first prediction system which consisted of resistance scores returned from the virtual phenotypes to later ones which include estimated viral resistance, drug-drug interactions, and estimations on the expected evolutionary development of virus, therapy prediction engines are more advanced and required more research. It will be essential for therapy prediction engines to include more complete information on drug properties, fitness differences between susceptible and resistant strains, mutations.[181] Some other patient-specific information, including the CD4 count and monitored drug concentrations, can also be used to make more accurate predictions. By overcoming the limitations of validation and becoming more interpretable, this powerful tool will be more acceptable in the clinical world.

HIV reservoir which serves as the major barrier to cure HIV, is another interesting research area for application of precision ART. The sub-therapeutic drug concentration in these sanctuary sites provides the resource of viral rebound when the ART is disrupted. Factors which contribute to the intracellular drug concentration, such as drug transporter, metabolism enzymes, may become the targets of improving precision ART.

Though memory CD4⁺ T cells are the primary HIV reservoirs, an increasing number of research has shown other cell types: macrophages, microglia, and astrocytes in the central nervous system. Integrated HIV-1 from autopsy brain tissues of HIV infected individuals has been detected in the macrophages and astrocytes.[182] Tissue macrophages were also shown to lead to viral rebound after disrupting of ART in vivo.[183] Macrophages have been shown to express clinical relevant drug transporters. [184, 185] Drug transporters play a crucial role in drug disposition and drug concentrations. For example, PGP Protease inhibitors are substrates of PGP. Research has shown that PGP inhibition largely increased plasma drug concentration and penetration of drugs in the central nervous system (CNS). [186] Research also indicated that drug transporters were associated with PI concentration in the sanctuary sites. Thus, polymorphisms of these drug transporters would be critical to ensure proper drug concentration and precision ART. Also identifying the existence of virus and mutant virus in the reservoirs would be beneficial to promote precision antiretrovirals.

Despite considerable research, precision medicine for the treatment of HIV is still new, and not part of routine care for most patients. More information including genetic mutations that causes drug resistance, mechanism of viral reservoir, availability of individual specific gene characters, and also drug adherence is needed to practice precision medicine. Additional close cooperation between the bench work and clinical work is required to move precision ART further.

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Table 1.

Pharmacodynamic parameters of commonly used Antiretroviral drugs

Drug Category	Mechanism of action	Drug	Mutant Gene	Result	Reference
Nucleoside Reverse Transcriptase Inhibitors	Prevents HIV replication by inhibiting viral reverse transcriptase	Lamivudine (3TC)	MRP4 T4131 G	Increased concentration	[10]
		Abacavir (ABC)	HLA-B*5710 positive	Hypersensitivity reaction	[13], [15], [16]
		Tenofovir	<i>ABCC4</i> (rs1751034) 3463 'A'	Decreased intracellular concentration and increased renal clearance	[22]
Non-Nucleoside Reverse Transcriptase Inhibitors	Prevents HIV replication by inhibiting HIV reverse transcriptase in a noncompetitive manner	Efavirenz (EFV)	<i>CYP2B6</i> (rs3745274) rs2279345)	Increased concentration	[31]-[35]
Integrase Inhibitors	Prevents HIV genome from integrating into the host chromosomal DNA	Raltegravir (RAL)	<i>UGT1A1</i>	Not clinically significant	[50],[51]
		Dolutegravir (DTG)	<i>UGT1A1</i>	Not a significant decrease	[54]
			<i>ABCG2 421</i>	May increase concentration	[54]
		Elvitegravir (EVG)	<i>UGT1A1*28</i>	Not a significant decrease in clearance	[55]
Protease Inhibitors	Prevents HIV precursor proteins from cleaving into mature enzymes	Atazanavir (ATV)	<i>UGT1A1*28/*28,*28/*37,*37/*37</i>	Hyperbilirubinemia	[65]
			<i>ABCB1 CGC</i> (1236C/2677G/3435C)	Decreased concentration	[66]
		Darunavir (DRV)	<i>SLCO3A1</i> rs8027174 GT/TT	Decreased clearance	[70]
			<i>SLCO3A1</i> rs4294800 'A'	Increased central volume of distribution	[70]
			<i>CYP3A5*3/*3</i>	Decreased concentration	[71]
			<i>CYP3A5*1</i>	Increased concentration	[71]
			<i>CYP3A4*22</i> (rs35599367,C>T)	Predicted increased concentration	
Other Inhibitors	Prevents the entry of HIV by inhibiting CCR5 binding	Maraviroc (MVC)	<i>SLCO1B1</i> 521 'C'	Increased concentration	[75]

Table 2.

Pharmacogenetic characters of commonly used Antiretroviral drugs

Drug Category	Drug	Note	Reference
Nucleoside Reverse Transcriptase Inhibitors	Lamivudine (3TC)	High oral bioavailability Maximum concentration reached within 1.5 hours 70% excreted through urine	[7],[8]
	Abacavir (ABC)	83% bioavailability Reached maximum concentration between 0.6 to 2.5 hours 14.1 hours of intracellular half-life 83% excreted through urine and 16% through feces	[11],[12],[13]
	Tenofovir Disoproxil Fumarate (TDF)	Greater than 60 hours of intracellular half-life Higher plasma concentration than TAF More serious adverse effects including renal dysfunction and bone toxicity	[18]
	Tenofovir Alafenamide (TAF)	Higher intracellular drug concentration than TDF Lower circulating plasma concentration than TDF Minor adverse effects on the renal function and bone compare to TDF	[18]
	Emtricitabine (FTC)	Reached maximum concentration in 1 to 2 hours 10 hours of half-life 39 hours of intracellular half-life Excreted in urine primarily	[23]–[25]
Non-Nucleoside Reverse Transcriptase Inhibitors	Efavirenz (EFV)	40%–45% oral bioavailability Between 36 to 100 hours of half-life High protein binding Excreted unchanged through urine	[26]
	Rilpivirine (RPV)	High protein binding 38 hours of half-life Increased bioavailability with an acidic environment Drug exposure decreased when administered with food	[36], [37]
	Doravirine (DOR)	11.75 to 13.1 hours of half-life in in fed state 14.2 to 14.35 hours of half-life in fasted state	[40]
Integrase Inhibitors	Raltegravir (RAL)	7 to 12 hours of half-life	[48]
	Dolutegravir (DTG)	71 hours of half-life	[53]
	Elvitegravir (EVG)	Greater than 99% of protein binding Increased bioavailability , AUC and C_{max} with food intake Increased AUC and half-life with COBI co-administration	[56], [57]
Protease Inhibitors	Atazanavir (ATV)	High protein binding High risk of hyperbilirubinemia	[61],[62]
	Darunavir (DRV)	1–2nM of EC_{50}	[68], [69]
Enhancers	Ritonavir (RTV)	CYP3A4 and PGP inhibitor Increased PK parameters of the boosted drug at a sub-therapeutic dose (100mg or 200 mg)	[72]
	Cobicistat (COBI)	Derivative of RTV Non-linear PK parameters when administered outside the range of 50 to 400mg	[9]
Other Inhibitors	Maraviroc (MVC)	Specific for CCR5 viral strains 22.9 hours of half-life	[74]