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Review Article

POPULATION PHARMACOKINETICS OF ANTIRETROVIRAL AGENTS: AN OVERVIEW

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ABSTRACT
Despite significant advances in Highly Active Antiretroviral Therapy (HAART) during the past few years, challenges like virologic and/or immunologic failures, adverse effects of medications; drug-drug interactions, viral resistance and dosage individualization still pose significant obstacles to successful treatment. In population pharmacokinetic model, parameter values are reasonably estimated and concentrations of a drug predicted at any time during a dosage regimen in an individual with a set of characteristics such as demographics, abnormal lab parameters and disease state whose effects on drug disposition are accounted for by the model equations. This pharmacokinetic information is used to extrapolate the safety and efficacy findings to the wider patient population who may receive the New Chemical Entity in question. Today, Population Pharmacokinetic analyses are a regular part of the documentation of a New Chemical Entity (NCE). The results from Population analyses are most frequently used to characterize the pharmacokinetics in the target Population, to provide pharmacokinetic data in special populations and to support dosing recommendations for these populations.
KEYWORDS: Pharmacokinetics of ARV; HAART; Dosage Adjustment of HAART;

INTRODUCTION

To date, various antiretroviral (ARV) agents including fixed-dose combinations have gained approval by the Food and Drug Administration (FDA) and are currently available in the market for the treatment of human immunodeficiency virus (HIV) infection. Recent advances in simplification of ARV therapy regimens including reductions in adverse effects, pill burden and dosing frequency allows goals of therapy to be achieved more readily.[1, 2] The advent of modern ARV treatment, particularly the implementation of highly active antiretroviral therapy (HAART) has reduced HIV-related mortality and extended life expectancy for HIV patients. Modern treatment has rendered the perception of HIV infection to that of a serious chronic condition requiring close management. Clinical management of HIV-1 infection is a complicated undertaking that requires understanding the pharmacokinetic properties of more than 25 drugs from five classes of antiretroviral compounds. The approved ARV agents inhibits different stage or phase in the viral life cycle; and are further organized according to their mechanism of action as protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), integrase inhibitors, and entry/fusion inhibitors.[3]

An important objective in the clinical development of drugs is the identification of factors that may cause deviations from expected blood levels of a drug and pose a particularly acute problem in the treatment of the HIV infection.[4, 5] Individualized, model-based, target-oriented optimal concentration-controlled dosing of HIV medications can be beneficial to patients for whom there are limited dosing guidelines, such as children, adolescents, or patients with altered physiologic function. Barriers to this approach include lack of training, expertise, and access to appropriate software to assist the clinician.[6] Current HAART guidelines from the United State Department of Health and Human Services (US-DHHS) recommend using three drugs representing at least two classes for management of HIV infection, with initial treatment regimens include combinations of two NRTIs with an NNRTI, a PI (preferably boosted with ritonavir [RTV]), an Integrase inhibitor (namely raltegravir [RAL]) or a CCR5 antagonist (namely Maraviroc [MVC]). In clinical trials, NNRTI, PI, Integrase inhibitor, or CCR5 antagonist-based regimens have all resulted in suppression of HIV RNA levels and CD4 cell increases in a large majority of patients.[7]

The pharmacokinetic parameters of most drugs are not expected to change when different doses are administered or when the drug is given through different routes of administration or as single or multiple doses. The kinetics (e.g. clearance and volume of distribution) of these drugs are said to be linear or dose-independent, and this is a characteristic of first-order kinetics. The term linear simply means that if the dose is increased, the plasma concentration or area under the plasma concentration-time curve (AUC) will be increased proportionally. However, for some drugs, this may not be valid i.e. the kinetic parameters, such as clearance, volume of distribution, and half-life, may vary depending on the administered dose. This is because one or more of the kinetic processes of the drug amongst absorption, distribution, and/or elimination may be via a process other than simple first-order kinetics. For these drugs, the relationship between the AUC and dose is not linear. Additionally, different doses of these drugs may not result in parallel plasma concentration-time courses expected for drugs with linear pharmacokinetics.[8]

In general, the trough concentration is assessed for efficacy, as it is often the lowest value during a dosing interval and therefore presents the greatest risk for viral escape. The maximum drug concentrations, usually 2 to 4 hours post dose, are often evaluated for toxicity management. Furthermore, the complete profile of kinetics with respect to a certain group of population can be evaluated by means of population pharmacokinetics.[9]

A population pharmacokinetic model is a set of descriptive equations with parameter values like clearance and volume of distribution etc. When parameter values are reasonably estimated, concentrations of a drug may be predicted at any time during a dosage regimen in an individual with a set of characteristics whose effects on drug disposition are accounted for by the model equations Population pharmacokinetic modeling deals with many of the obstacles associated with therapeutic optimization, even in the outpatient setting. Further it is the study of variability in drug concentrations between individuals. It comprises the assessment of variability within the population and to account for the variability in terms of patient characteristics such as age, renal function or disease state.[10]

Important population pharmacokinetic study design factors include the number of subjects (total and sub-population), sampling scheme (Number of samples per subject, nominal sampling time, variability of actual sampling time, and whether extensive samples are taken in some subjects).

In addition, the study design should also account for study conduct factors such as compliance of the patients (the variability of dosing time, whether the variability is recorded and accounted for in the analysis, consistent dosing pattern, missing doses, and whether the missing doses are recorded and accounted for in the analysis). Other non-design, drug-specific factors may also affect the quality of the study result. They include inter-subject and intra-subject variability of the pharmacokinetics.[11]

Dosing time and sampling time should be recorded during the study conduct and accounted for in the data analysis. If the deviations from the nominal times might be non-ignorable, analysis plans to deal with this are particularly important. Compliance is an important factor that influences the study outcomes. It should be considered in the study design and simulation, and if compliance is to be used in the analysis of the study, the latter should include consideration of the possibility that compliance is a confounder.[12]

More samples per subject, and more importantly, more subjects usually provide better study performance if the study design remains otherwise the same. Studies with greater intra or intersubject variability require more samples per subject or more subjects per age group to achieve similar performance. Distribution of the sampling times among subjects should cover the full dosing interval as much as possible to describe the concentration-time profile.[11]

Chiefly, population pharmacokinetic models allow for discrimination between the sources of error between observed (measured) and predicted drug concentrations i.e., variability between patients, between occasions in a single patient, and residual variability due to model misspecifications or environmental factors that also influence drug disposition.[6]

Moreover, because models provide information on the pharmacokinetic parameter values in a population of patients, the parameter values of an individual patient who belongs to that population, even if not among the original contributors to the model, can usually be estimated fairly well even with only a single measured drug concentration, although precision and accuracy improve with multiple samples from the individual.[13]

Once a set of therapeutic drug pharmacokinetic parameter estimates exists for an individual patient, the clinician can predict likely blood concentrations in the patient at any given time after a dose. More important, opportunity arises to control the dose in a systematic manner for achieving clinically selected target concentrations with maximum precision and therefore to better control the patient's expected clinical response.[14]

Nonlinear mixed-effects modeling (NONMEM) program has been previously applied to evaluate the population pharmacokinetics of several individual ARV agents, using plasma drug levels obtained during monotherapy. However, such a pharmacokinetic analysis has not yet been performed after administration of these drugs in combination therapy.[15, 16, 17]

NEED FOR THE STUDY

The selection of HAART for treatment-naive HIV-infected individuals is complex. In addition to patient adherence, patient Population, gender, drug–drug and drug–food interactions, and comorbid medical conditions can influence exposures of antiretroviral agents.[18] despite significant advances in HAART during the past few years, challenges such as virologic and/or immunologic failures, adverse effects of antiretroviral medications, among others, still pose significant obstacles to successful treatment.[1]

The real-life impact of the rigorous dosing schedules and the accompanying side effects of antiretroviral treatment lead itself to poor adherence. Adherence to combined antiretroviral therapy (CART) is a predictor of suppression of HIV replication, drug resistance, disease progression and death.[19-21] A number of gender-based differences in pharmacokinetic exist in women compared with men; these include body size and composition, plasma volume, hepatic and gastrointestinal CYP450 enzyme activity, drug transporter differences, and physiologic alterations occurring during pregnancy. In clinical studies, women often experience increased rates and severity of adverse drug events and drug discontinuations to all classes of ARVs. Despite increasing Populations of HIV- infected females and people 50 years or older, the pharmacokinetics of many ARVs has not been adequately studied in these patient Populations.[22, 23]

Therapy of HIV infection with currently available antiretroviral agents is frequently frustrated by a high degree of variability between patients in in-vivo drug exposure following the administration of fixed doses of drug. The pharmacokinetic information is used to extrapolate the safety and efficacy findings to the wider patient Population who may receive the new chemical entity (NCE) in question. Today, Population pharmacokinetics analyses are a regular part of the documentation of an NCE and form one way in which an applicant can choose to provide pharmacokinetic information. Currently, results from Population analyses are most frequently used to characterize the pharmacokinetic in the target Population, to provide pharmacokinetic data in special Populations (elderly, children, renal impaired etc.) and to support dosing recommendations for these Populations.[10] While combination treatments represent the major therapeutic strategy for HIV infection, the identification of the individual characteristics which account for the significant intersubject variability in the pharmacokinetic parameters of each drug is of particular importance in defining quantitative relationships between

drug exposure and both virological and clinical endpoints.[17] Doses that result in excessive plasma concentrations are unlikely to be detected unless and until clinical toxicity develops, and without such monitoring of concentration data, dose-dependent versus dose-independent toxicity cannot be distinguished.[6] Drug development process geared toward a "one-size- fits-all" dose and not target-oriented therapy and for many of the regimens their no commitment or mechanism to update dosing guidelines as post-market evidence emerges. Carefully studied therapeutic drug management has been shown to improve efficacy, reduce complications, and/or reduce hospitalization costs significantly.[14]

PHARMACOKINETIC PRINCIPLES

Pharmacokinetics is the study of how a drug is absorbed, distributed, metabolized, and eliminated from the body; it is what the body does to a drug or toxin. In general, the trough concentration (the level immediately prior to the next dose) is assessed for efficacy, because it is often the lowest value during a dosing interval and therefore presents the greatest risk for viral escape. The maximum drug concentrations, usually 2 to 4 hours post dose, are often evaluated for toxicity management. For most agents (e.g., protease inhibitors [PIs] and nonnucleoside reverse transcriptase inhibitors [NNRTIs]), the PK is assessed in the plasma; however, for some agents, this compartment may not be the compartment of affect. The nucleoside reverse transcriptase inhibitors (NRTIs) need to be converted to their active moiety inside the cell to exert their effects, and plasma levels of these agents have not been shown to correlate with their antiviral activity.[24] Newer agents, such as the chemokine receptor blockers, exert a prolonged post antiviral effect after the agent has been cleared from the plasma (believed to be due to its allosteric binding to the receptor).[25,26,27] As a result, the plasma PK of these agents may not be helpful in determining efficacy.

The PK assessment of an agent is performed in a controlled setting where all study individuals are taking the same dose at the same time each day, with the same food/fluid requirements and without any known agents that could produce a drug–drug interaction. In addition, studies are often performed in healthy, non-HIV-infected volunteers, and until recently, many have been performed with few, if any, female participants. Even when evaluated under these conditions, agents can display wide interpatient variability. Under real-world conditions, where these factors can vary greatly from patient to patient, plasma trough concentrations of PIs and NNRTIs have been shown to display upward of 100-fold and 10-fold variability, respectively.[5, 6, 7]

For NRTIs, intracellular di- and triphosphate half-lives vary substantially and can be impacted by sample collection and assay methodology.[8-10, 28-30] In early HAART, manipulation of drug exposures through the use of therapeutic drug monitoring showed promise by improving viral responses and/or minimizing drug toxicities.[11-13] However, with the advent of low-dose ritonavir boosting, the levels of PIs are substantially increased to well above the concentrations needed to inhibit wild-type HIV, even when the wide interpatient variability is taken into account.[14, 31]

Factors That Can Affect ARV Drug Exposures

Factors Affecting Drug Exposures

Many factors can alter the plasma levels of ARVs. The PK of many agents, especially which of ARVs evaluated in the early to mid 1990s, was derived using either healthy, non-HIV-infected volunteers or a homogenous population of HIV-infected patients (e.g., men who have sex with men). As infection rates have shifted from predominantly young gay white males to a more diverse patient population, including females, people of color, and those 50 years of age and older, evaluation of the PK differences and toxicities in diverse populations have become a priority. For example, efavirenz is predominantly metabolized by the cytochrome P450 2B6 (CYP 2B6) isoenzyme.[15, 32] Pharmacogenomic evaluations have shown African Americans to display greater T/T genotypes at codon 516 (the gene responsible for encoding CYP 2B6) than European Americans (20% vs. 3%, respectively), resulting in prolonged elimination of efavirenz, significantly higher plasma efavirenz levels, and increased rates of both short- and long-term efavirenz toxicities.[16-18, 33-35] Other pharmacogenomic differences that have been shown include indinavir- and atazanavir-induced hyperbilirubinemia (UGT1A1);[19, 20, 36, 37] abacavir hypersensitivity reactions (HLA B5701); [21, 22, 38, 39] and nelfinavir plasma exposures (CYP2C19 681).[34] Whether these or other pharmacogenomic differences can be utilized to help select patient-specific HAART has yet to be determined.

Drug–Drug Interactions

The drug–drug interactions between various ARVs are complex and in many cases, not formally studied. These interactions occur via a number of mechanisms, most common are: altered oral bioavailability, hepatic and/ or renal alterations, or complex drug-transporter interactions (e.g., P-glycoprotein, multidrug-resistant proteins). In general, caution needs to be exercised when dealing with potential interactions with an agent that has a narrow therapeutic index (the range between concentrations required for efficacy and toxicity). Tenofovir in combination with atazanavir (with or without low-dose ritonavir) decreases atazanavir plasma concentrations by roughly 25%.[40] Co administration of tenofovir and didanosine results in significant increases in didanosine drug exposures; [41] that could increase the risk for didanosine associated adverse drug events.[42] Nevirapine plasma concentrations are decreased in the presence of rifampin but appear to be sufficient for clinical efficacy; [43] because both agents can cause transaminitis, clinicians should carefully assess hepatic function when these agents are used together.

Drug–Food Interactions

Many ARVs have food or fluid restrictions to ensure optimal drug dissolution and absorption or minimize potential drug toxicity. It should be recognized that these recommendations are derived from PK sampling, where standardized meals are employed, and often do not reflect the diets of many patients. This is especially true among HIV-infected patients living in non-industrialized countries, where diets are dramatically different than those observed in North America and Europe. Consequently, additional PK studies are under way for many ARVs, to determine precisely what "take with food" entails. The most appropriate recommendation for patients stabilized on HAART is to maintain consistency in their daily diets, to

minimize fluctuations in ARV exposures that could potentially lead to viral breakthrough or increase the risk for adverse drug events.[44]

Comorbid Medical Conditions

In general, the NRTIs are renally eliminated and PIs hepatically metabolized. As a result, alterations in renal and/or hepatic function can alter the PK of many ARVs. Most NRTIs (except drugs such as Abacavir) require dosage adjustments for altered renal function when the calculated Creatinine clearance falls below 50 mL/min, with additional adjustments needed with continued diminished function.[44]

In those situations where renal dysfunction requires dosage modifications, the use of fixed-dosed formulation products (e.g., Combivir [lamivudine + zidovudine], Epzicom [abacavir sulfate + lamivudine], Trizivir [abacavir sulfate + lamivudine + zidovudine], Truvada [emtricitabine + tenofovir disoproxil fumarate], and Atripla [efavirenz + emtricitabine + tenofovir disoproxil fumarate]) may be difficult and may require the use of the individual agents alone with the proper dosage adjustment for each agent. As the general population of HIV-infected patients gets older, including those newly infected patients aged 50 years or older, the impact of decreased renal function with increased age on the PK and tolerability of these agents needs to be carefully assessed. Coinfection with either hepatitis B or C is common; therefore, clinicians should carefully assess liver function before initiating ARV therapy and throughout treatment. For patients with moderate to severe hepatic insufficiency, the use of atazanavir and amprenavir oral solution is not recommended, and tipranavir/ritonavir is contraindicated.[44] The PK of ARVs is only altered when there is sufficient end-organ damage that affects function. As a result, clinicians should carefully assess renal and/or hepatic function in these patients both before initiating and during ARV therapy.

PHARMACOKINETIC OF ANTIRETROVIRAL DRUGS

Protease Inhibitors (PIs)

PIs binds and inhibit viral protease, which cleaves gag and gag-pol polyproteins to release structural proteins and proteins required for viral replication.[45-46] Till date nine PIs which are commonly used for antiretroviral treatment: atazanavir, darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, and tipranavir. Gastrointestinal intolerability has limited the clinical use of ritonavir at US Food and Drug Administration (FDA)-approved doses. However, low-dose ritonavir (100–200 mg) is now frequently used as a boosting agent to increase the overall exposure of concomitantly administered PIs by inhibiting cytochrome P450 (CYP) 3A4 and p-glycoprotein, a cellular efflux transporter, which affect the metabolism and absorption of other PIs.[47-49] Perhaps the most beneficial contribution of ritonavir boosting is a two- to sevenfold increase in the minimum concentration (Cmin) with a concomitant increase in overall exposure due to decreased clearance for boosted PIs, reducing the opportunity for drug-resistant mutations.[47,50] Nelfinavir and atazanavir are the only PIs that are available without ritonavir boosting, because boosting does not significantly influence drug exposure.[48] The use of low-dose ritonavir as a boosting agent for PIs has increased the durability of drug regimens containing PIs, lowered the pill burden for patients, increased the overall exposure of the boosted drug without increasing the dose, and raised the benchmark for virologic response to suppression of HIV-1 viral RNA to less than 50 copies/ mL.[48] One of the most important considerations with potent inhibition of CYP 3A4 is interactions with other drugs that use this same metabolic pathway.[48]

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs are an integral component of HAART, usually administered with two NRTIs or one NRTI and a PI as part of initial antiretroviral therapy.[51-52] NNRTIs inhibit the reverse transcriptase enzyme by binding to a pocket near the active site and inducing allosteric changes in the enzyme.[53-54] Etravirine was approved in January 2008 based on the results of the phase 3 DUET 1 and 2 trials, which were conducted in highly treatment-experienced patients, including those with previous resistance to commercially available NNRTIs. Etravirine twice daily is approved for the treatment of HIV in treatment-experienced patients with previous failure or intolerance to another NNRTI-based regimen. Pooled 24-week analysis of the DUET studies indicated that 74% of etravirine-treated patients achieved HIV-1 RNA <400 copies/mL compared with 51.5% of patients receiving OBT alone. At Week 24, the mean decrease in plasma HIV-1 RNA was –2.37 $\log_{10}$ copies/mL in the etravirine treatment arm and –1.68 $\log_{10}$ copies/mL in the OBT arm. The mean increase in $CD4^+$ T lymphocyte count was 81 cells/mm³ in the etravirine treatment arm versus 64 cells/mm³ in the OBT treatment arm.

Rilpivirine is currently in phase 3 clinical trials for treatment-naïve patients. Similar to etravirine, rilpivirine has been demonstrated to have a higher genetic barrier to resistance than first-generation NNRTIs and may be an alternative to efavirenz as an initial NNRTI because of rilpivirine's lower incidence of rash, central nervous system (CNS) disorders, and lipid abnormalities.[55] A remarkable pharmacologic difference between NNRTIs and PIs is the extended half-life of NNRTIs. Efavirenz and nevirapine, the two most commonly used NNRTIs, have long terminal half-lives (t1/2): 25–30 hours for nevirapine and 40–55 hours for efavirenz.[53]

Rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases α, β, and γ. Rilpivirine is approximately 99.7% bound to plasma proteins in vitro, primarily to albumin. The distribution of rilpivirine into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans. In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system. The terminal elimination half-life of rilpivirine is approximately 50 hours. After single dose oral administration of 14C-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in feces and urine, respectively. In feces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine.[56]

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTIs were first class of antiretroviral drug approved by the FDA for HIV-1 therapy. They form the backbone of HAART triple-drug combinations, with initial regimens containing two NRTIs.[50, 51] NRTIs are analogs of naturally occurring nucleosides that lack a 3′-hydroxyl group. Drugs in this class require intracellular conversion to their triphosphate (TP) forms to inhibit chain elongation of the nascent strand of DNA being transcribed by HIV-1 reverse transcriptase.[57-58] Currently eight NRTIs are FDA approved: zidovudine, stavudine, zalcitabine, abacavir, lamivudine, didanosine, emtricitabine, and tenofovir DF (the noteworthy nucleotide reverse transcriptase inhibitor in this family). No new NRTIs have been introduced in recent years, although several are in early stages of clinical development.[58] The main thrust in this field has been toward increasing adherence by decreasing pill burden; this has been accomplished through the development of once-daily dosing regimens and coformulation of NRTIs with permissive pharmacokinetics.[59, 60] As a class, NRTIs have relatively uncomplicated plasma pharmacokinetics. They are rapidly but somewhat poorly absorbed and are less than 5% protein bound (except for abacavir, lamivudine, and zidovudine). NRTIs are renally eliminated and interact minimally with CYP enzymes.[60] Therefore; they are generally a low risk for drug–drug interactions, although some well-characterized interactions occur. Plasma half-lives of older NRTIs (abacavir, didanosine, stavudine, zalcitabine, and zidovudine) range from 0.5 to 3 hours, although emtricitabine, lamivudine, and tenofovir have half-lives ranging from 5 to 17 hours. Emtricitabine and tenofovir were approved for once-daily dosing due to their favorable pharmacokinetics; central to which was their extended plasma half-life, which resulted in increased overall exposure that was amenable to once daily dosing Because intracellular half-lives tend to be much longer than plasma half-lives, lamivudine, abacavir, didanosine, and an extended-release formulation of stavudine (FDA approved, but not currently available) were also approved for once-daily dosing. [59, 60]

Integrase Inhibitors

Integrase inhibitors work by blocking HIV integrase from incorporating viral DNA into the human host cell's genome. The integrase inhibitor raltegravir received accelerated FDA approval in October 2007. Raltegravir is currently approved for the treatment of HIV in treatment-experienced patients; however, some studies in treatment-naïve patients have also been conducted, and others are in progress, although elvitegravir may be approved in 2008.[55] Raltegravir is orally administered, 400 mg twice daily without regard to food, and has demonstrated excellent efficacy, safety, and tolerability in treatment-experienced patients.[61] Its main route of metabolism is via uridine diphosphate- glucuronosyl-transferase 1A1 (UGT-1A1); therefore, use caution when coadministering raltegravir with other drugs that use UGT-1A1 (e.g. rifampin).[50, 62] Raltegravir demonstrates high levels of interindividual pharmacokinetic variability, possibly attributable to altered gastric pH, UGT- 1A1 polymorphisms, UGT-1A1 expression levels, or drug interactions.[64, 65] Pharmacokinetic studies of raltegravir reported the concentration at 12 hours post-dose (C12h) as 63 ng/mL, which exceeds the concentration required to inhibit 95% of viral replication (IC95) (14.6 ng/mL) by more than fourfold, and the terminal t1/2 as 7 to 12 hours.[65, 66] Raltegravir is about 83% protein bound to plasma proteins, is not a substrate for CYP enzymes or p-glycoprotein, and has no known clinically significant interactions with drugs that use the CYP system.[62] Co administration with atazanavir increased the C12h of raltegravir by 77%, whereas co administration with tipranavir decreased the C12h of raltegravir by 55%; these alterations are due to respective inhibition or induction of UGT1A1. No dose adjustment is recommended because these values are within the normal pharmacokinetic variability of this drug.[62-63] One outstanding feature of raltegravir is that it elicits rapid viral decay kinetics, reducing viral levels to 70% of those seen with efavirenz during the initial phase of viral decay. Furthermore, it is effective against strains of virus that harbor resistance mutations to other drug classes, and cross-resistance has not been observed.[66] Integrase inhibitors offer a new therapeutic option for highly treatment- experienced patients.

Entry/Fusion Inhibitors

The two currently approved entry/fusion inhibitors are enfuvirtide and maraviroc, and each prevents entry via different mechanisms. The FDA approved enfuvirtide in 2003. Maraviroc is a CCR5 inhibitor that was approved by FDA in August 2007. Before initiation of therapy with maraviroc, an HIV tropism assay is necessary to determine which chemokine coreceptor the patient's strain of HIV uses for attaching to and entering host cells. Maraviroc is indicated only for treatment-experienced patients with HIV strains that use the CCR5 coreceptor exclusively; however, recent studies have also evaluated its use as a first-line therapy. It has been proposed that CCR5 inhibitors may be most useful in acute and early infection given the predominance of CCR5 coreceptors in early disease, but large-scale studies are needed to test this theory further. FDA approval of maraviroc was based on results from two phase 3 placebo-controlled studies, the Efficacy and Safety of Maraviroc plus Optimized Background Therapy In Viremic, Antiretroviral Treatment-Experienced Patients (MOTIVATE) 1 and 2 trials, which demonstrated that treatment with maraviroc leads to superior viral control compared with optimized background therapy (OBT) alone. The pooled 48-week analysis of these trials demonstrated that 239 of 426 patients (56%) treated with maraviroc had HIV-1 RNA <400 copies/mL compared with 47 of 209 patients (22%) who received OBT alone. At 48 weeks, 194 of 426 patients (46%) treated with maraviroc had HIV-1 RNA <50 copies/mL versus 35 of 209 patients (17%) in the OBT arm. The mean change in plasma HIV-1 RNA at Week 48 was -1.84 $\log_{10}$ copies/mL in the maraviroc arm versus -0.78 $\log_{10}$ copies/mL in the OBT arm. The mean increase in $CD4^+$ T lymphocyte counts was 124 cells/mm³ in the maraviroc arm versus 60 cells/mm³ in the OBT arm. The most common adverse events observed with maraviroc at a higher frequency than that observed with OBT (>8% incidence) included upper respiratory tract infections, cough, pyrexia, rash, and dizziness. During phase 3 studies, an increased risk of cardiovascular events (e.g., myocardial ischemia and/or infarction) was noted in the maraviroc treatment arm compared with the OBT arm (1.3% vs. 0). A boxed warning regarding hepatotoxicity that may be preceded by systemic allergic reaction is included in the prescribing information for

maraviroc. Vicriviroc is another CCR5 inhibitor under development by Schering-Plough. Phase 3 trials in treatment-experienced patients are currently under way. Less advanced in clinical development are various CXCR4 inhibitors, several of which have failed in development because of hepatotoxicity. The latest CXCR4 inhibitor, AMD070 (Enzyme), is currently in phase 1/2 studies. The most common adverse reactions observed in a dose-escalating study included sinus tachycardia, transient headaches, and gastrointestinal (GI) symptoms.[55, 67-71] General pharmacokinetic and population pharmacokinetic of antiretroviral drugs are summarized in Table 1 and Table 2.

Coreceptor Tropism Assays

HIV enters cells by a complex process that involves sequential attachment to the CD4 receptor followed by binding to both the CCR5 or CXCR4 molecules and fusion of the viral and cellular membranes. CCR5 inhibitors (i.e., maraviroc [MVC]), prevent HIV entry into target cells by binding to the CCR5 receptor. Phenotypic and, to a lesser degree, genotypic assays have been developed that can determine the coreceptor tropism (i.e., CCR5, CXCR4, or both) of the patient's dominant virus population. One assay (Trofile, Monogram Biosciences, Inc., South San Francisco, CA) was used to screen patients who were participating in studies that formed the basis of approval for MVC, the only CCR5 inhibitor currently available. Other assays are under development and are currently used primarily for research purposes or in clinical situations in which the Trofile assay is not readily available.

The vast majority of patients harbor a CCR5-utilizing virus (R5 virus) during acute/recent infection, which suggests that the R5 variant is preferentially transmitted compared with the CXCR4 (X4) variant. Viruses in many untreated patients eventually exhibit a shift in coreceptor tropism from CCR5 to either CXCR4 or both CCR5 and CXCR4 (i.e., dual- or mixed-tropic; D/M-tropic). This shift is temporally associated with a more rapid decline in CD4 T-cell counts, although whether this shift is a cause or a consequence of progressive immunodeficiency remains undetermined. Antiretroviral (ARV)-treated patients who have extensive drug resistance are more likely to harbor detectable X4- or D/M-tropic variants than untreated patients who have comparable CD4 T-cell counts. The prevalence of X4- or D/M-tropic variants increases to more than 50% in treated patients who have CD4 counts <100 cells/mm^3.

Phenotypic Assays

There are now at least two high-throughput phenotypic assays that can quantify the coreceptor characteristics of plasma-derived virus. Both involve the generation of laboratory viruses that express patient-derived envelope proteins (i.e., gp120 and gp41). These pseudoviruses are either replication competent (Phenoscript assay, VIRalliance, Paris, France) or replication defective (Trofile assay, Monogram Biosciences, Inc.). These pseudoviruses then are used to infect target cell lines that express either CCR5 or CXCR4. In the Trofile assay, the coreceptor tropism of the patient-derived virus is confirmed by testing the susceptibility of the virus to specific CCR5 or CXCR4 inhibitors in vitro. The Trofile assay takes about 2 weeks to perform and requires a plasma HIV RNA level ≥1,000 copies/mL.

The performance characteristics of these assays have evolved. Most, if not all, patients enrolled in premarketing clinical trials of MVC and other CCR5 inhibitors were screened with an earlier, less sensitive version of the Trofile assay. This earlier assay failed to routinely detect low levels of CXCR4-utilizing variants. As a consequence, some patients enrolled in these clinical trials harbored low, undetectable levels of CXCR4-utilizing viruses at baseline and exhibited rapid virologic failure after initiation of a CCR5 inhibitor. This assay has since been revised and is now able to detect lower levels of CXCR4-utlizing viruses. In vitro, the assay can detect CXCR4-utilizing clones with 100% sensitivity when those clones make up 0.3% of the population. Although this more sensitive assay has had limited use in prospective clinical trials, it is now the only one that is commercially available. For unclear reasons, a minority of samples cannot be successfully phenotyped with either generation of the Trofile assay. In patients with plasma HIV-1 RNA below the limit of detection, coreceptor usage can be determined from proviral DNA obtained from peripheral blood mononuclear cells; however, the clinical utility of this assay remains to be determined.

Genotypic Assays

Genotypic determination of HIV-1 coreceptor usage is based on sequencing the V3-coding region of HIV-1 env, the principal determinant of coreceptor usage. A variety of algorithms and bioinformatics programs can be used to predict coreceptor usage from the V3 sequence. When compared to the phenotypic assay, genotypic methods show high specificity (~90%) but only modest sensitivity (~50%–70%) for the presence of a CXCR4-utilizing virus. Given these performance characteristics, these assays may not be sufficiently robust to completely rule out the presence of an X4 or D/M variant.

Recent studies in which V3 genotyping was performed on samples from patients screening for clinical trials of MVC suggest that genotyping performed as well as phenotyping in predicting the response to MVC. On the basis of these data, accessibility, and cost, European guidelines currently favor genotypic testing for determining coreceptor usage. An important caveat to these results is that the majority of patients who received MVC were first shown to have R5 virus by a phenotypic assay (Trofile). Consequently, the opportunity to assess treatment response to MVC in patients whose virus was considered R5 by genotype but D/M or X4 by phenotype was limited to a relatively small number of patients. It is also important to note that the genotyping approaches used in these studies are not routinely available from clinical laboratories in the United States at this time.

Given the uncertainty regarding the genotypic assays and fewer logistical barriers to obtaining a phenotype in the United States than elsewhere, the Panel recommends that a phenotype be used as the preferred coreceptor tropism screening test in the United States.

Use of Coreceptor Tropism Assays in Clinical Practice

Coreceptor tropism assays should be used whenever the use of a CCR5 inhibitor is being considered. Coreceptor tropism testing might also be considered for patients who exhibit virologic failure on MVC (or any CCR5 inhibitor).

Other potential clinical uses for the tropism assay are for prognostic purposes or for assessment of tropism prior to

starting antiretroviral therapy (ART), in case a CCR5 inhibitor is required later (e.g., in a regimen change for toxicity). Currently, sufficient data do not exist to support these uses. [72]

HIV TREATMENT GUIDELINES

Guidelines for the use of ARVs in adults and adolescents infected with HIV-1 were developed by a Department of Health and Human Services (DHHS) expert panel and provide guidance to clinicians on when to initiate ARV treatment, preferred and alternative treatment choices and goals, the use of ARVs in special population groups (e.g., injection drug users, patients co-infected with hepatitis B virus [HBV] and/or hepatitis C virus [HCV]), and management of the treatment-experienced patient. These guidelines also provide information on standard dosing for ARVs, dose adjustments for patients with renal and hepatic impairment, adverse events, and drug-drug interactions. Separate guidelines are available for the management of HIV infection in adults, adolescents, and children; the prevention of mother-to-child HIV transmission; and post exposure prophylaxis in occupational and nonoccupational settings. This article focuses on pertinent information from the treatment guidelines regarding adult and adolescent patients with chronic HIV-1 infection.[72]

The DHHS panel strongly recommends obtaining an HIV genotypic resistance assay, which may detect baseline (i.e., transmitted) viral resistance mutations and help guide the selection of ARV regimen, before ARV treatment is initiated. This recommendation was implemented after drug-resistant HIV strains (particularly strains resistant to NNRTIs) were detected in up to 15% of patients previously untreated with ARVs.[73]

Generally, in the absence of significant viral resistance at baseline, either an NNRTI- or a PI-based regimen is initiated, depending on factors such as concomitant medical conditions, pill burden, confidentiality (certain ARVs, such as ritonavir, should be refrigerated), and side effect profiles.[72] Efavirenz is a preferred NNRTI; when this agent is combined with NRTIs, the regimen has a low pill burden. Efavirenz has been associated with CNS side effects including dizziness, drowsiness, vivid dreams, sleep disturbance, and hallucinations. In clinical trials, 53% of patients receiving efavirenz reported CNS symptoms compared with 25% of patients in the control arm. Although CNS side effects resolve over time in most patients, these potential effects should be considered before efavirenz therapy is initiated.[74] Efavirenz is not a favorable option for pregnant women (especially during the first trimester of pregnancy) or for women of child-bearing age who are not on contraception, as this agent has a teratogenicity potential (pregnancy category D). Nevirapine is an alternative NNRTI treatment option; however, this agent is less commonly prescribed than efavirenz in the United States because of its association with liver toxicity (particularly in patients with high pre-nevirapine $CD4^+$ T lymphocyte counts) and skin rash (including severe reactions such as Stevens-Johnson syndrome). In the PI class, the preferred agents for initial therapy include ritonavir-boosted atazanavir, ritonavir-boosted darunavir or fosamprenavir, or fixed-dose lopinavir/ritonavir.[72] The panel's recommendations regarding when to initiate ARV therapy are summarized in Table 3.

The success of ARV therapy greatly depends on the patient's adherence to the treatment regimen. The detrimental effect of poor adherence is the emergence of viral strains that are resistant to ARVs. One of the common causes of suboptimal adherence to ARV therapy is poor tolerability of medications. Selected ARV-related adverse events are summarized in Table 4. Potential drug-drug and/or drug-food interactions should be taken into consideration when selecting an antiretroviral (ARV) regimen. A thorough review of current medications can help in designing a regimen that minimizes undesirable interactions.

CONCLUSION

Population Pharmacokinetics application along with exploration of clinical pharmacology data will result in improves drug regimen and treatment. More over the aspect of Population pharmacokinetics should also be considered during the drug discovery and development phase for more reliable and specific treatment. Further, only minor increase in amount of work and costs would be needed to generate many positive consequences for drug treatment.

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Table 1: General Pharmacokinetics of FDA Approved ARVs: [1, 2, 4, 7, 9, 12, 24-25, 28, 32-34, 37-38, 56, 74-77]

S.no	Drug	Dose(mg)	F%	$t_{1/2}$ in hr	AUC h.µg/mL	C_{max} µg/mL	Vd(L/kg)	Clr (L/h)	Metabolism
1.	Darunavir	600	82	15	62.35	11-14	1.26	5.9l	CYP 3A4
2.	Etravirine	200	51%	36	04.53	00.41	422	--	CYP 3A4, 2C9, 2C19
3.	Raltegravir	400	--	9	06.35	02.00	0.38	0.6-1.1 mL/min/kg	UGT 1A1
4.	Maraviroc	150, 300, 600	33	22.9	00.93	00.62	194	--	---
5.	Zidovudine	200	65	1	02.00	01.20	1.6-2.8	1.78-2.6	AZT glucuronide (GAZT)
6.	Stavudine	40	82-99	1-2	01.90	00.85	24	16	Glucuronidation
7.	Zalcitabine	0.75	86	1.5	00.03	00.01	0.534	0.55	----
8.	Lamivudin	150	82	6	12.00	01.50	145	32	CYP P450
9.	Didanosine	200	19-40	1.4	01.20	00.90	3.56	1.64	----------
10.	Abacavir	300	76-100	1.2	05.80	02.20	0.86	24.3	ADH and GT
11.	Nevirapine	200	95	25-30	86.00	05.00	68	3.3	CYP450 3A4, 2C9, and 2C19 Potent 3A4 inducer; 2C9 and 2C19 inhibitor
12.	Delavirdine	400	85	5,8	99	19	0.41	6-7	CYP3A4
13.	Efavirenz	600		40-55	58	4.1	252	9.4	CYP450 3A mixed inducer/ inhibitor
14.	Saquinavir (Invirase®)	600	4	2	0.8	0.20	700	1.14	CYP 450 3A4 inhibitor and substrate
15.	Indinavir	800	30	1.5	17	7.0	97.3	22.2	Cytochrome P450 3A4 inhibitor (less than ritonavir)
16.	Ritonavir	600	---	3-5	61	11.2	96.6	2ml/min	Cytochrome P450 (3A4 > 2D6) substrate; Potent 3A4, 2D6 inhibitor
17.	Nelfinavir	750	20-80	3.5-5	18	4.0	2 -7	0.93	CYP2C19, 3A4 and 2D6
18.	Tenofovir	300	39%	17	2.5	0.329	1.3	90.95	---------
19.	Lopinavir	4 mg/kg	--	1	47.5	12.341	141	4.57	CYP3A4
20.	Rilpivirine	25mg	--	50	2397 ± 1032 ng(h)/mL	80 ± 37 ng/mL			Cytochrome P450 (CYP) 3A System

ABBREVIATIONS: F%, Oral Bioavailability; Cmax, Max Concentration of Drug; AUC, Area under Curve; Vd, Volume of Distribution; Clr, Clearance.

Table 2: Population pharmacokinetics of marketed antiretroviral agents.[77]

Drug class	Drug name	Pharmacokinetic characteristics
Protease inhibitors	Amprenavir (Agenerase®)	Rapidly absorbed; metabolised by CYP3A4; no food requirement; pb = 90%; bid
	Indinavir (Crixivan®)	Rapidly absorbed; metabolised by CYP3A4; administered with food; pb = 60%; tid
	Lopinavir/ritonavir (Kaletra®)	tmax ≈4h; lopinavir metabolised by CYP3A; ritonavir is a CYP3A4 inhibitor; administered with food; pb = 98–99% (lopinavir); bid
	Nelfinavir (Viracept®)	Rapidly absorbed; metabolised by CYP3A and 2C19; highly distributed; administered with food; pb >98%; bid or tid
	Ritonavir (Norvir®)	Peak 2–4h (delayed with food); metabolised by CYP3A4 and 2D6; administered with food; pb = 98–99%; bid
	Saquinavir (Fortovase®)	Rapidly absorbed; metabolised by CYP3A4; administered with food; pb = 97%; high first-pass effect; bid
	Saquinavir mesylate (Invirase®)	Poorly absorbed (F ≈4%); metabolised by CYP3A4; administered with food; pb = 98%; tid
Nucleoside reverse transcriptase inhibitors	Abacavir (Ziagen®)	Rapidly and extensively absorbed (F = 83%); metabolised by alcohol dehydrogenase; no CYP involvement; distributed into extravascular space; no food requirement; pb = 50%; bid
	Abacavir/lamivudine/zidovudine (Trizivir®)	Rapid and extensive absorption of all three agents; no CYP involvement; no food requirement; low pb for all agents; bid
	Didanosine (ddI, Videx®)	Rapidly absorbed (F = 42%); metabolism consistent with endogenous purines; no CYP involvement; administered in fasted state; pb <5%; bid
	Lamivudine (3TC, Epivir®)	Rapid and extensive absorption (F = 86%); limited metabolism; no CYP involvement; distributed into extravascular space; no food requirement; pb <36%; od or bid
	Lamivudine/zidovudine (Combivir®)	Both agents rapidly and extensively absorbed (F = 86% and 64% for lamivudine and zidovudine, respectively); limited metabolism; no CYP involvement; no food requirement; pb low (<36% and <38% for lamivudine and zidovudine, respectively); bid
	Stavudine (d4T, Zerit®)	Rapid and extensive absorption (F = 86%); no CYP involvement; highly distributed; no food requirement; pb is negligible; bid
	Tenofovir disoproxil fumarate (Viread®)	Rapidly absorbed (F = 25%); no CYP involvement; distributed into extravascular space; administered with food; pb <8%; 70–80% recovered in urine; od
	Zalcitabine (ddC, Hivid®)	Rapid and extensive absorption (F >80%); no CYP involvement; distributes to extravascular space; reduced absorption with food, but no food instruction provided; tid
	Zidovudine (AZT, ZDV, Retrovir®)	Rapidly absorbed (F = 64%); CYP involvement not specified; highly distributed; no food requirement; pb <38%; bid
Non-nucleoside reverse transcriptase inhibitors	Delavirdine (Rescriptor®)	Rapid and extensive absorption; metabolised by CYP3A and 2D6; inhibits CYP3A and reduces activity of CYP2C9, 2D6 and 2C19; no food requirement; pb >98%; tid
	Efavirenz (Sustiva®)	Peak concentrations 3–5h post-dose; metabolised by CYP3A4 and 2B6 with subsequent glucuronidation; highly distributed; administered with food at bedtime; pb >99.5%; od
	Nevirapine (Viramune®)	Peak within 4h; extensively (>90%) absorbed (F = 93%); metabolised by CYP3A4 and 2B6; pb = 60%; no food requirement; od for 2 wks, bid thereafter
Fusion inhibitors	Enfuvirtide (T20, Fuzeon®)	Peak 4–8h after SC injection (F = 84%); no CYP involvement; metabolised by hydrolysis; distributed primarily into vascular space; pb = 92%; bid

bid = twice daily; **CYP** = cytochrome P450; **F** = absolute bioavailability; **od** = once daily; **pb** = protein binding; **SC** = subcutaneous administration; **tid** = three times daily; **t**max = time to reach maximum concentration.

Table 3: U.S. Department of Health and Human Services Guidelines for Initiating Therapy in Treatment-Naive HIV-Infected Patients, 2004. [72, 78]

A. Patient Characteristics			
Clinical Category	**CD4 Count**	**Plasma HIV RNA**	**Recommendation**
AIDS-defining illness	Any value	Any value	Treat.
Asymptomatic	<200 cells/mm^3	Any value	Treat.
Asymptomatic	>200 cells/mm^3, but <350 cells/mm^3	Any value	Offer treatment, following full discussion of pros and cons with each patient.
Asymptomatic	>350 cells/mm^3	>100,000 copies/ml	Most physicians recommend deferring therapy, but some will treat.
Asymptomatic	>350 cells/mm^3	<100,000 copies/ml	Defer therapy.
B. Preferred and Alternative Regimens			
Preferred Regimens			**Number of Pills per Day**
NNRTI-based	EFV + (3TC or FTC) + (AZT or TDF) (not for use in first trimester of pregnancy or in women with high pregnancy potential)		2–3
PI-based	LPV/r + (3TC or FTC) + AZT		8–9
INSTI-Based	RAL + TDF/FTC		---
Preferred Regimen for Pregnant Women	LPV/r (twice daily) + ZDV/3TC		---
Alternative Regimens			**Number of Pills per Day**
NNRTI-based	EFV + (3TC or FTC) + (ABC or ddI or d4T) NVP + (3TC or FTC) + (AZT or d4T or ddI or ABC or TDF		2–4 3–6
PI-based	ATV + (3TC or FTC) + (AZT or d4T or ABC or ddI) FosAPV + (3TC or FTC) + (AZT or d4T or ABC or TDF or ddI)		3–6 5–8
3 NRTI-based‡	ABC + AZT + 3TC, only when a preferred or an alternative NNRTI- or a PI-based regimen cannot or should not be used		2
Regimens That Should Not Be Used			**Rationale**
AZT + d4T			Pharmacologic antagonism between AZT and d4T
ABC + TDF + 3TC once daily as a triple-NRTI regimen			High rate of early virological nonresponse seen in treatment-naive patients
TDF + ddI + 3TC combination once daily as a triple-NRTI regimen			High rate of early virological nonresponse seen in treatment-naive patients
ATV + IDV			Potential additive hyperbilirubinemia
ddI + DDC			Additive peripheral neuropathy

Table 4: Adverse effects of FDA ARVs [1, 2, 4, 7, 9, 12, 24-25, 28, 32-34, 37-38, 56, 77, 79-82]

S.no	Drug	Adverse effects
1.	Darunavir	Skin rash (7%), Stevens-Johnson syndrome, Erythrema multiforme, Hepatotoxicity, Diarrhea, Nausea, Headache, Hyperlipidemia, Transaminase elevation, Hyperglycemia,Possible increased bleeding episodes in pts with hemophilia.
2.	Etravirine	Potentially life-threatening rash, Nausea.
3.	Raltegravir	Nausea, Headache,Diarrhea, Pyrexia, Elevated creatine kinase, Myopathy, Rhabdomyosis
4.	Enfuvirtide	Local injection site reactions – almost 100% of patients (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis), Increased bacterial pneumonia, Hypersensitivity reaction (<1%), Rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases.
5.	Zidovudine	Bone marrow suppression, macrocytic anemia or neutropenia, Gastrointestinal intolerance, headache, insomnia, asthenia, Lactic acidosis with hepatic steatosis.
6.	Stavudine	Peripheral neuropathy, Lipodystrophy, Pancreatitis, Lactic acidosis with hepatic steatosis-higher incidence than w/ other NRTIs, Hyperlipidemia, neuromuscular weakness (rare).
7.	Lamivudine	Minimal toxicity , Lactic acidosis with hepatic steatosis.
8.	Didanosine	Pancreatitis, Peripheral neuropathy, Nausea,Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with use of NRTIs.
9.	Abacavir	Hypersensitivity, fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, shortness of breath, Lactic acidosis.
10.	Nevirapine	Rash including Stevens-Johnson syndrome, Symptomatic hepatitis, including fatal hepatic necrosis.
11.	Delavirdine	Rash, Increased transaminase levels,Headaches
12.	Efavirenz	Rash, Central nervous system symptoms, Increased transaminase levels, False-positive cannabinoid test
13.	Saquinavir	GI intolerance, nausea and diarrhea, Headache, Hyperlipidemia, Hyperglycemia, Fat maldistribution, Possible increased bleeding episodes in patients with hemophilia.
14.	Indinavir	Nephrolithiasis, GI intolerance, nausea, Indirect hyperbilirubinemia, Hyperlipidemia, Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, andhemolytic anemia, Hyperglycemia, Fat maldistribution
15.	Ritonavir	GI intolerance, nausea, vomiting, diarrhea, Paresthesias – circumoral and extremities, Hyperlipidemia, Hepatitis, Asthenia, Taste perversion, Hyperglycemia.
16.	Rilpivirine	Depression, insomnia, headache, and rash.