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Translating Efficacy into Effectiveness in Antiretroviral Therapy

Beyond the Pill Count

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Abstract

Durable and sustained suppression of HIV replication can be achieved as demonstrated in several recent clinical trials of antiretroviral (ARV) regimens. However, the efficacy demonstrated in the experimental setting does not always translate to effectiveness in the clinical setting. The frequency and number of medications (conventionally referred to as the pill count) contribute to regimen effectiveness. However, clinicians and HIV-infected patients recognise that there are several other characteristics of an ARV regimen that are equally important contributors to its effectiveness. Potency and durability, the potential for drug-drug interactions, and the occurrence of adverse events also contribute to the effectiveness and complexity of a drug regimen. A comprehensive consideration of factors associated with efficacy will optimise the translation to effectiveness for the individual infected with HIV.

The hallmark of contemporary therapy for HIV/AIDS is the potent and sustained suppression of HIV replication to levels that cannot be detected in plasma (without the application of ultrasensitive techniques). This can be achieved through combination antiretroviral (ARV) therapy (ART). The development of ARV drugs with different mechanisms of action and an understanding of how to combine these agents into well tolerated and effective regimens have led to an enhanced quality of life for patients.[1-3] Yet, the high rates of efficacy demonstrated in clinical trials can be more difficult to reach in clinical practice. The focus of this article is on factors and strategies that translate the efficacy achieved in clinical trials into effectiveness in the community treatment setting.

1. Efficacy and Effectiveness

The efficacy of an ART regimen is a reflection of its performance in ideal circumstances, such as in randomised clinical trials conducted by expert clinicians. The performance of the regimen in patients receiving care in real-world circumstances, usually determined through observational studies, defines its effectiveness. Evidence from clinical trials in HIV-infected, treatment-naive individuals demonstrates the efficacy of the majority of ARVs.[3,4] Clinical trials place certain expectations and demands upon the patient, such as a willingness to participate, frequent clinic visits, extensive laboratory evaluations, and potential exclusion from participation for certain concurrent medical conditions and drugs. Furthermore, clinical trials monitor and ensure adherence (that the drug regimen is taken) and compliance (that requirements of the drug regi-

men, such as dietary restrictions, are understood and followed) with the treatment regimen. They measure the efficacy of treatments where the response of treated individuals is compared with those of untreated individuals or to an established 'gold-standard' drug/regimen.[5] However, the effects of the drug may differ in populations that may not be represented in clinical trials (e.g. those with opportunistic infections), or among those individuals who do not adhere or comply fully with the drug regimen. Consequently, a clinical trial will demonstrate what works in controlled conditions (efficacy) but the results may not translate precisely into success in day-to-day clinical practice (effectiveness).[6]

Bartlett et al.[7] systematically reviewed clinical ART trials published or presented between 1994 and July 2004 to determine the ARV efficacy of triple combination therapy. Efficacy of triple combination therapy was measured by monitoring changes in plasma HIV RNA and CD4+ cell counts. This study demonstrated that virological response rates have been improving over time as a result of improved regimen potency.[7] Pairwise comparisons demonstrated that boosted protease inhibitors (PIs) were associated with superior suppression of HIV RNA following 48 weeks of therapy compared with unboosted PIs and nucleoside reverse transcriptase inhibitors (NRTIs); there was no difference in suppression of HIV RNA between boosted PI-based and non-NRTI (NNRTI)-based regimens.[7] In addition, boosted PIs were associated with significantly higher CD4+ cell counts compared with NNRTIs, NRTIs and unboosted PIs. The number of doses and dosage forms taken per day was not a consistent indicator of virological suppression.[7]

A recent prospective comparison of a boosted PI- or NNRTI-based regimen is ACTG (AIDS Clinical Trials Group) 5142, which was presented by Riddler et al.[8] at the 16th International AIDS Conference. A total of 753 ARV-naive participants were recruited to compare the efficacy of efavirenz (EFV) with lopinavir/ritonavir (LPV/RTV). After 96 weeks of treatment, the proportion of subjects with HIV RNA <50 copies/mL was 77% for LPV/RTV (plus two NRTIs), while that for EFV (plus two NRTIs) was 89%. However, participants who received LPV/RTV achieved a significantly greater median increase in CD4+ cell count of 285 cells/mm^3 compared with 240 cells/mm^3 in the EFV arm.

Effectiveness of available drug regimens is improving. Between 1996 and 2002, patient response to ART included significant improvements in suppressing HIV replication and significant improvements in CD4+ cell counts. In a 2002 study, 80% of patients receiving ART for ≥1 year achieved a viral load <400 copies/mL and a median increase in CD4+ cell count of 142 cells/mm^3.[9] The results of this observational study were adjusted for the ART regimen, treatment-naive patients, and other clinical and demographic variables. The authors suggested that the improved response may be attributable to a greater focus on medication adherence, improved ARV tolerability and ease of administration.[9]

Lampe et al.[10] found that over a 7-year period (1996–2002) of triple-combination ART use in clinical practice, the risk of initial virological failure (defined as a viral load of >500 copies/mL) of treatment has at least halved. In this multicohort study from five clinics in Europe and Canada, there were three strategies for participant inclusion: (i) including all subjects with missing viral load measurements counted as virological failure (n = 3825); (ii) including all subjects with viral load measurement (n = 3120); and (iii) including all subjects receiving ART at viral load measurement (n = 2890). From 1996 to 2002, the risk of virological failure fell from 38.9% to 24.8% for strategy 1, 28.4% to 12.0% for strategy 2 and 22.8% to 8.2% for strategy 3. The reductions in risk were greatest from 1996 to 1999, with subsequent weaker trends. From this study, it is clear that in the period from 1996 to 2002, the efficacy of triple-combination ART improved dramatically.

Observational studies and cohort studies can determine effectiveness in patients who may not fully comply with the regimen or who have concurrent medical conditions.[5,11] However, observational and cohort studies are subject to a bias because the treatment is given to those whose need is greatest. This practice is known as 'confounding by indica-

tion'.[5,11] Extrapolation of data from cohort studies is difficult because information regarding 'confounding by indication' can be limited, further hampering the ability of the study to determine the effectiveness of a regimen.[5] Consequently, group effectiveness will not be as great as efficacy for individuals for a number of reasons. For example, some individuals will not take the drug regimen because of adverse effects, costs or concerns regarding its efficacy. Others may adhere with the regimen but not comply fully with administration requirements.[5]

The differences between the settings in which efficacy and effectiveness are established reveal several factors involved in the translation of regimen efficacy: (i) drug potency; (ii) adverse events; (iii) drug interactions; (iv) dose; and (v) administration requirements.[12]

All of these attributes must be considered to maximise regimen adherence, compliance and effectiveness. This review examines these attributes and explores their contribution to regimen effectiveness.

2. Regimen Potency and Durability

Drug potency is paramount to achieving sustained virological suppression of HIV replication and this was recognised by patients in a telephone survey conducted by Sherer et al.[13] in 2005 as the most significant attribute when choosing an ARV regimen.

The inhibitory quotient (IQ) is a model used to estimate drug potency against HIV replication. The IQ is calculated as the ratio of drug concentration, usually the trough (C_{trough}), to the concentration needed to inhibit 50% of the viral replication of a given virus *in vitro* (50% inhibitory concentration [IC_{50}]). Several methods to calculate IQ have been proposed including genotypic IQ (GIQ), virtual IQ (VIQ) and normalised IQ (NIQ), but there is no accepted standard. A number of investigations of the association of virological response and IQ, GIQ, VIQ and NIQ have been performed. However, the usefulness of the IQ concept in clinical practice remains limited at least in part due to the lack of availability of the parameters necessary for calculation (virus susceptibility and measured C_{trough}) and data demonstrating an improved clinical outcome associated with the use of the IQ.[14]

Drugs with a low IQ (such as that arising from sub-optimal adherence) increase the risk of plasma drug concentrations falling below that which is needed to suppress viral replication, and this increases the potential for virological failure and the accumulation of resistance-conferring mutations.[15] Selection of drugs with a high IQ minimises the impact of inter-patient variability in drug absorption and disposition, and the effects of drug interactions. Furthermore, suppression of any pre-existing or emerging mutant HIV strains that have increased IC_{50} values will minimise the potential of breakthrough of resistant virus.[15] Drugs with high IQ values may be considered 'forgiving' because they can reduce the impact of poor adherence.[15] An example of two regimens with high IQ values is the KLEAN study[16] of fosamprenavir plus ritonavir (FPV + RTV) versus LPV/RTV each administered with abacavir plus lamivudine (ABC + 3TC) to ARV-naive patients. Eron et al.[16] found FPV + RTV twice daily to be as efficacious and tolerable as LPV/RTV, each administered with ABC + 3TC. In addition, emergence of treatment resistance was rare for both groups, with no incidence of reduced susceptibility to either therapy.

Drug potency can be maximised by increasing concentrations (or systemic exposure). This can be accomplished by increasing the dose of a drug, or as is commonly done with most PIs, coadministering with a boosting dose of RTV.[15,17] The latter strategy has been demonstrated to be well tolerated and effective, and to provide potent and durable suppression of HIV replication. For example, in a randomised, placebo-controlled trial comparing LPV/RTV to nelfinavir (NFV), each in combination with stavudine (d4T) and 3TC, in 653 patients, LPV/RTV was superior to NFV in maintaining a viral load <400 copies/mL through 48 weeks (84% vs 66% with persistent virological response through 48 weeks).[18] This trial is a clear demonstration of the concept that ARVs with a high IQ that maintain

plasma concentrations above the IC_{50}, regardless of patient variations, are associated with more durable viral suppression and a lower risk of selecting for drug-resistant virus.[19] Durability of a drug regimen is important because maintaining long-term suppression of viral replication without the acquisition of viral mutations is the goal of ARV therapy.[4,20] For example, LPV/RTV has demonstrated excellent durability over 7 years (360 weeks) of follow-up. No primary PI-resistance mutations have been observed in these treatment-naive subjects who had episodes of viremia (>500 copies/mL HIV-1 RNA).[21] A potential downside of using higher doses and drug combinations[15] may be an increase in adverse events, which is discussed in section 3.[17]

Genotypic or phenotypic resistance testing prior to initiation of ART or switching ARV drugs may improve regimen effectiveness.[22] Drug susceptibility testing is currently recommended in this setting as some treatment-naive patients may have been infected with drug-resistant virus.[22] In patients who are switching drug regimen as a result of viral rebound, resistance testing is equally as important to identify possible cross-resistance to other ARVs.[22] Once viral susceptibility is known, the clinician can select an ART regimen that maximises the likelihood of an effective and durable response.

3. Adverse Events

Immediate and delayed longer-term adverse events, which may affect safety, tolerance and an individual's sense of well-being, are of major concern to patients.[23] Indeed, adverse events have been reported to be the most common reason for discontinuation of ART.[12,20,24] Up to 50% of treatment-naive and treatment-experienced patients are reported to discontinue part or all of their treatment within 12 months, most frequently as a result of toxicities or patient choice.[20] Gastrointestinal adverse effects, typically nausea and vomiting, are the most cited reason for treatment discontinuation.[12,24]

Certain adverse events are related to dose and dose administration schedules, and drug formulations. A patient survey was conducted by Schrader et al.[25] to investigate the effects of switching from LPV/RTV soft-gelatin capsules once or twice daily to the new formulation of LPV/RTV once daily. They found that 80% of respondents reported no or rare antidiarrhoeal use after switching to the LPV/RTV tablets once-daily regimen. A study reported by Johnson et al.[26] found that once-daily administration of LPV/RTV soft-gelatin capsules was associated with a significantly increased occurrence of diarrhoea when compared with twice-daily soft-gelatin capsule administration (occurring in 16% and 5% of patients, respectively; $p = 0.036$).

Other adverse events that have been cited as the reason for discontinuation include: abnormal fat distribution; concerns regarding cardiovascular disease; dyslipidaemia; hypersensitivity reaction; toxicities arising from the liver, pancreas, nervous system, kidneys or the endocrine system; diabetes mellitus; haematological toxicity; and hyperlactataemia or lactic acidosis.[20,23,27]

Stone et al.[28] reported that adverse events were the third most important attribute contributing to adherence. The occurrence of adverse events has also been suggested to be predictive of discontinuation of treatment.[12,24,29] Furthermore, Duran et al.[29] reported that patients who experienced a high number of symptoms shortly after commencing ART were at higher risk of future non-adherence. Some studies suggest that the prevalence of adverse events declines during the early stages of treatment. Obviously, patients should be encouraged to consult their physicians to discuss the severity of events.[12,24,30]

Educating patients about potential ARV-related adverse events encourages communication between patient and physician, providing the opportunity for better management if they should occur.[31] Better communication between patients and physicians may also help to minimise the number of patients who discontinue therapy as a result of adverse events.[31]

4. Drug Interactions

There are numerous potential drug-drug interactions in HIV medicine. Interactions can occur between the different ARV drugs in an ART regimen,

and may also occur between an ARV drug and the following: (i) drugs prescribed to treat opportunistic infections or concomitant conditions; (ii) over-the-counter drugs; (iii) recreational drugs (including alcohol); and (iv) herbal medicines.[32]

Drug interactions occur when the pharmacokinetics or the pharmacodynamics of one drug are altered by the administration of another drug or food. Pharmacokinetic interactions result from alterations in the absorption, distribution, metabolism or elimination of a drug, resulting in a change in drug concentrations in the body (or systemic exposure). The use of RTV in combination with other PIs to enhance their bioavailability or inhibit metabolism is an example of a beneficial pharmacokinetic interaction. The induction of PI drug metabolism by rifampicin (rifampin) is an illustration of an adverse pharmacokinetic interaction.

Pharmacodynamic interactions are the result of synergistic, additive or antagonistic drug effects or toxicities. Certain drug combinations, such as those including the NRTIs zidovudine (AZT) and 3TC, create an additive or synergistic pharmacodynamic effect. A combination such as AZT and d4T, however, results in an antagonistic effect. The remainder of this section focuses on pharmacokinetic interactions.

Pharmacokinetic drug-drug and drug-food interactions may be clinically insignificant or beneficial. On the other hand, they may have adverse consequences such as severe toxicity or treatment failure. Knowledge of ARV drug-drug interactions changes rapidly and readers are advised to consult the most up-to-date information sources. The Department of Health and Human Services (DHHS) guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents[33] contain drug-drug interaction tables that are an excellent reference tool for clinicians.

PIs typically inhibit cytochrome P450 enzyme (CYP)3A4-mediated metabolism with the relative potency of inhibition (greatest to least) being: RTV, indinavir (IDV), LPV, NFV, amprenavir (APV), saquinavir (SQV).[17] PIs may have enzyme or drug transporter-inducing effects, with the relative potency for induction (greatest to least) being: tipranavir plus RTV (TPV + RTV), FPV + RTV and LPV/RTV, FPV and NFV. IDV and SQV do not appear to have inducing properties. The NNRTIs EFV and NVP are well known inducers of drug metabolism. Coadministration of NVP, for example with methadone, will result in lower plasma concentrations of the latter, leading to withdrawal symptoms and resulting in some patients discontinuing therapy.[34,35] Levels of lipid-lowering agents, such as lovastatin or simvastatin, can be significantly increased by RTV-boosted PIs, resulting in the potential for serious adverse events such as myopathy or hepatitis.[36] Rifampicin and the herbal supplement hypericum (St John's wort) induce CYP3A activity, which reduces plasma concentrations of all PIs, and concomitant administration is contraindicated.[37]

Acid-reducing agents, such as antacids, proton-pump inhibitors (PPIs) and histamine H_2 receptor antagonists, are frequently used in HIV-positive patients.[38] A study by Klein et al.[39] investigated the effects of a PPI, omeprazole and an H_2-receptor antagonist, ranitidine, on the pharmacokinetics of the LPV/RTV tablet formulation administered once and twice daily compared with atazanavir (ATV) plus RTV once daily.[39] Acid-reducing agents did not significantly alter the LPV/RTV exposure following coadministration with once- or twice-daily administration of the tablet formulation.[39] Conversely, the area under the concentration time curve (AUC) of ATV was significantly reduced (from 48% to 62%) by all acid-reducing agents that were assessed in this study.[39]

A number of other studies have been conducted to further investigate the effects of PPIs on the pharmacokinetics of PIs. These have found inconsistent results. In healthy volunteers, exposure to the boosted PI IDV was reduced by almost one-half when administered with omeprazole 20mg or 40mg. Another study found no effect of esomeprazole on APV concentrations when FPV, ranitidine and esomeprazole were administered concomitantly. A further investigation found that coadministration of omeprazole with LPV/RTV had no effect on LPV levels.[40] The pharmacokinetics of single doses of

TPV + RTV (500mg + 200mg), given with food alone and after 5 days of omeprazole 40mg once daily have recently been evaluated in 15 healthy volunteers. The geometric mean ratios (and 90% CIs) for the TPV AUC and maximum concentration were 1 (0.89, 1.12) and 1.05 (0.94, 1.17), respectively. These data indicate that omeprazole had no adverse affect on TPV bioavailability, and concomitant therapy, given with food, should be acceptable.[41]

Agarwala et al.[42] have demonstrated how adverse pharmacokinetic interactions may be avoided by temporal separation of different drugs in real-life HIV therapy situations. The effects of concomitant administration of ATV (with or without RTV) with the H_2-receptor antagonist famotidine 40mg twice daily were evaluated in healthy men and women aged between 18 and 50 years. When compared with a regimen of ATV alone (400mg once daily), simultaneous famotidine administration reduced ATV AUC and minimum concentration by ≈40–50%. However, by temporal separation of the two drugs, it was possible to attain concentrations of ATV similar to those achieved in the regimen of ATV alone (400mg once daily). This was achieved by administering ATV 10 hours after the morning dose of famotidine and 2 hours prior to the evening dose.

Up to 80% of patients are reported to be unaware of drug interactions between PIs and acid-reducing agents.[38] This highlights the need for patient education regarding the potential of drug interactions between ARV drugs and other medications, including those available over the counter.[38]

5. Special Populations and Drug Interactions

Different considerations may be necessary when selecting a drug regimen, including the potential for drug interactions,[43] for the following types of special populations: (i) patients with acute HIV infection; (ii) HIV-infected adolescents; (iii) injecting drug users; (iv) women of child-bearing age; (v) pregnant women; and (vi) patients with co-infection (e.g. hepatitis B virus, hepatitis C virus or tuberculosis).[33] The pharmacodynamics and pharmacokinetics of some ARVs may be altered as a result of impaired renal excretion in patients with severe renal insufficiency.[43] Examples of ARVs that are eliminated renally include the NRTIs emtricitabine (FTC), 3TC and tenofovir disoproxil fumarate (TDF); therefore, dose adjustments for reduced creatinine clearance are necessary. However, all current PIs undergo relatively little renal clearance, and renal insufficiency is thought to have little effect on the pharmacokinetics and elimination.[37] Oral contraceptives may fail during concomitant RTV administration as ethinylestradiol concentrations are decreased, making alternative contraceptive measures necessary in women of child-bearing age.[44] In addition, some NNRTIs, such as EFV, also interact with oral contraceptives. EFV has recently been reclassified from US FDA pregnancy risk category C to D because fetal birth defects have been associated with administration in animals.[45]

6. Dose Administration

The common conception is that a low number of tablets or capsules (often referred to as a low pill count) results in better patient adherence. Indeed, a number of ARV drugs are now available as a coformulation to reduce pill count, including reverse transcriptase inhibitors such as 3TC/AZT (Combivir®)[1]; 3TC/AZT/ABC (Trizivir®); TDF/FTC (Truvada®); ABC/3TC (Epzicom®); and EFV/FTC/TDF (Atripla®). The only PI available as a coformulation is LPV/RTV (Kaletra®).

Atripla® was approved by the FDA in July 2006. It is a single, fixed-dose, combination tablet containing EFV 600 mg, FTC 200mg and TDF 300 mg. The individual components of Atripla® have long half-lives, thus allowing a once-daily dose administration. The emergence of this combination drug has allowed for comparable potency and tolerability with a favourable convenience profile when compared with other HIV therapy regimens.[46]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Low pill count and dose administration frequency are associated with improved patient adherence and compliance, and are, therefore, often considered to comprise a simple and perhaps effective drug regimen. However, literature on this subject is contradictory. In order to maximise patient adherence, it is important to understand patient preferences. Previous studies have assessed patient preferences to determine attributes that may be likely to impact on patient adherence and compliance.[12,13,28,47,48] A telephone survey involving 387 participants reported that when patients were asked to score the relevant importance of ART regimen attributes, pill count and administration frequency, few patients perceived these attributes to be the most important compared with lowering viral load and increasing CD4+ cell count (figure 1).[13]

A study conducted by Moyle and the Assessing Patients' Preferred Treatments (APPT)-1 study team[49] published in 2003 revealed similar patient preferences. A total of 504 participants were recruited from five different European countries and asked to grade five different regimen characteristics by relative importance (5 = most important, 1 = important). Ranking appeared as follows: (i) adverse effects (4.1/5); (ii) potency (4.0/5); (iii) dose administration frequency (2.6/5); (iv) total daily pill load (2.4/5); (v) number of pills per dose (2.1/5). This rank order was similar across all five countries surveyed.

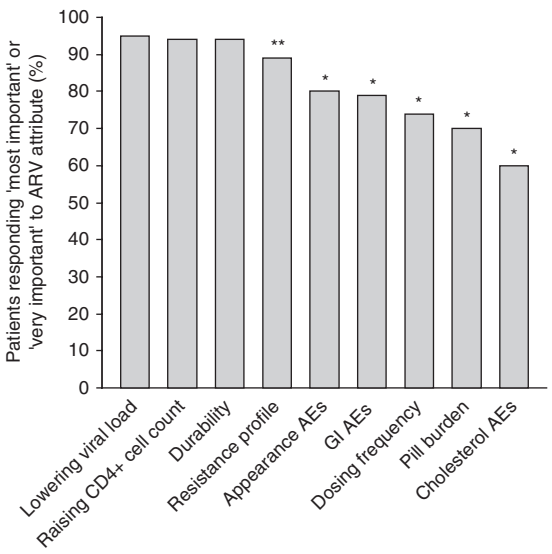

Fig. 1. Relative importance of antiretroviral (ARV) drug attributes reported by HIV-infected individuals (n = 387) [reproduced from Sherer et al.,[13] with permission].* $p < 0.01$, ** $p < 0.02$ comparing the following attributes: lowering viral load, raising CD4+ cell count and durability to the other attributes. **AEs** = adverse effects; **GI** = gastrointestinal.

Claxton et al.[47] reviewed the use of electronic monitoring to measure compliance in studies published between 1986 and 2000. In a total of 76 studies, compliance was significantly higher for once daily versus three times daily ($p = 0.008$) and for once daily versus four times daily ($p < 0.001$). Yet, there was no significant difference in compliance between once-daily and twice-daily dose administration regimens or between twice-daily and three-times-daily dose administration regimens.[47] Portsmouth et al.[48] showed improved adherence in patients switching from twice-daily to once-daily dose administration over a period of 24 weeks. Rode et al.[50] demonstrated that compliance was higher in patients receiving LPV/RTV once daily compared with twice daily. The estimated mean compliance ranged from 97.2% to 92.8% for LPV/RTV once daily compared with 92.2% to 80.8% twice-daily dose administration at baseline to week 4 and weeks 84–96 of therapy, respectively.[50] Despite differences in treatment compliance, both patient groups had comparable virological efficacy, rates of resistance and immunological improvement during 96 weeks of treatment.[50] A study by Stone et al.[28] also reported that, although twice-daily dose administration was perceived as the ideal dosage by patients, consideration of all attributes that influence dose administration complexity, such as food interactions and dose administration requirements, were equally important to ensure adherence.

ARV drugs with once-daily dose administration schedules, such as TDF, ATV, ABC and once-daily LPV/RTV, are often associated with a simple and effective drug regimen. However, for some drugs, when a daily dose is missed and the next dose is not taken until 24 hours later, drug plasma concentrations may fall to a greater degree than if only one of two daily doses had been missed. This may be

particularly problematic for drugs that will fail as a result of one single mutation. The low genetic barrier for the development of drug-resistant variants has been reported as a major disadvantage of the NNRTIs class of compounds.[51] Acquisition of mutations may also reduce the effectiveness of future ARVs as a result of cross resistance. However, prescription of forgiving drugs with a high IQ may counterbalance to some degree the effects of less-than-perfect adherence.[15]

A recent study exemplifies these concepts through a comparison of ATV and ATV + RTV, each in combination with dual NRTIs, in 200 ARV-naive patients. After 48 weeks of therapy, the proportion of patients who had achieved an HIV RNA level of <50 copies/mL was 70% in the ATV recipients compared with 75% in those who received ATV + RTV (intent-to-treat difference estimate 5%; 95% CI −7.0, 17.0). No PI-resistance mutations were detected in the ATV + RTV recipients who had virological failure; three subjects had virological failure with mutations in the ATV group. This study illustrates a regimen with a higher IQ (i.e. ATV + RTV) provided a greater efficacy in reducing HIV RNA and probably greater forgiveness for missed doses, despite the fact that the ATV + RTV regimen has a higher capsule burden than does the ATV regimen.[52]

7. Dose Administration Requirements

Many current ARVs have specific dose administration requirements, such as dietary restrictions (to be taken with/without food/water), which increase the complexity of the drug regimen. For example: (i) patients receiving IDV must ensure that they drink sufficient water to prevent nephrolithiasis;[53] (ii) didanosine must be taken on an empty stomach;[54] and (iii) the bioavailability of SQV[55] and RTV[36] is improved with high-calorie, high-fat foods and they must be taken within 2 hours of a full meal. If patients fail to comply with dietary restrictions associated with their ART regimens, systemic drug concentrations may significantly decrease, compromising treatment effectiveness.[15]

Patient preferences placed diet restrictions as the fourth most important attribute that would influence adherence.[28] An examination of a subset of 14 studies that considered dose timing revealed that mean dose-timing compliance was 59% ± 24%.[47] Dietary requirements can influence adherence and compliance, which can also affect treatment effectiveness. Formulation technology is a strategy used to address drug-food interactions, as well as other pharmaceutical and pharmacokinetic challenges. In 2005, a new melt-extrusion formulation of LPV/RTV[56] was approved by the FDA.[36] This tablet does not require refrigeration and has enhanced drug-loading properties.[36] The result is a new formulation containing LPV 200mg and RTV 50mg compared with LPV 133mg and RTV 33mg contained in the soft gelatin capsule. When administered at a dose of LPV/RTV 400mg/100mg or 800mg/200mg, the tablet formulation provides bioavailability similar to that of the soft gelatin capsule under recommended meal conditions. In addition, tablet administration reduces inter-patient pharmacokinetic variability of LPV. Finally, LPV and RTV systemic exposure from tablet administration was similar under fasting and non-fasting conditions in healthy volunteers, avoiding the necessity of dietary restrictions.[57]

8. Patient Adherence

When choosing an ART regimen, it is important to consider patient preferences and the ability of the patient to adhere to the prescribed regimen.[27] Non-adherence and non-compliance with a drug regimen can take many forms: disregarding the dose administration schedule, ignoring dietary restrictions, missing doses, taking incorrect doses, reducing medication to avoid adverse effects[28,47,58] and, in some cases, trading or sharing medications. Non-adherent patients have been reported to be confused by either how many pills to take, the appearance of the different pills or the instructions on how to take the medication.[59] Educating patients so that they understand the requirements of the drug regimen and the importance of adhering to and complying with the dose administration schedule is therefore

critical. Helping patients understand that poor adherence leads to suboptimal drug concentrations, the potential emergence of viral mutations (including those that may confer cross resistance to other ARVs), and loss of future treatment options is a powerful motivational tool. Education can empower the patient to make decisions about treatment, which can improve motivation and intent to adhere to the prescribed regimen.[31]

Lifestyle, behaviour and the ability to maintain a routine, influence patient adherence.[58] Activities, such as eating breakfast and completing a morning grooming routine, watching a favourite TV programme, attending a meeting and sleeping at home, have been shown to have a positive impact on adherence ($r = 0.63$; $p < 0.001$).[58] Conversely, missed doses have been associated with interruptions in the daily routine such as having unexpected visitors, sleeping away from home and running urgent errands.[58] Adverse events, such as memory problems, skin problems, vomiting and nausea, have also been independently associated with <90% adherence.[60] Treatment effectiveness can be influenced by patient adherence and compliance, which can be maximised through patient education and choosing a regimen that fits the lifestyle of the patient.

9. Conclusion

The ideal ART regimen would suppress HIV viral replication, improve immunological function, be well tolerated, simple to take and improve the quality of life of the patient.[27] Current ART regimens typically involve the administration of three or more medications; many regimens require more than once-daily dose administration. In addition, patients often take medications for treatment of other chronic conditions, or may require therapy or prophylaxis against opportunistic infections.

Numerous attributes contribute to the effectiveness of a drug regimen: potency and durability, adverse events, drug interactions, and dosage and dose administration requirements. Table I presents a list of factors to consider in regimen selection from the DHHS guidelines. Clinicians and patients recognise that a low pill count is not uniquely associated with an effective drug regimen and that this attribute should not be considered in isolation.

Table I. Factors to consider when selecting an initial regimen: Department of Health and Human Services guidelines[33]

Co-morbidity or conditions such as tuberculosis, liver disease, psychiatric disease, cardiovascular disease, chemical dependency or pregnancy
Adherence potential
Dose administration convenience regarding pill count, dose administration frequency, and food and fluid considerations
Potential adverse drug effects
Potential drug interactions with other medications
Pregnancy potential
Results of genotypic drug resistance testing
Gender and pre-treatment CD4+ T-cell count if considering nevirapine

With so many attributes to consider, selection of an ART regimen can be complex and demanding. ARV selection can influence patient adherence, patient compliance and, consequently, the overall effectiveness of a drug regimen. Ensuring that patients are involved in the selection of the regimen that best fits their lifestyle[58] and that they fully understand the requirements of their ART regimen, including possible drug interactions and adverse events, can increase compliance and potentially improve treatment effectiveness.

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