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Review

Understanding and managing the adverse effects of antiretroviral therapy

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ABSTRACT

Highly active antiretroviral therapy (HAART) has changed the landscape of HIV disease in a way that seemed unthinkable a decade ago; from an almost uniformly fatal disease to a chronic manageable one. The first HAART regimens worked in suppressing virus, but were encumbered by a variety of short term and long term side effects. More recent regimens became simpler, easier to take, and with fewer adverse events. As we look to people living perhaps a normal life span with HIV, the increasing number of antiretroviral agents available means that individualizing treatment has become more feasible and the longer downstream adverse events related to HAART, such as its effect on cardiovascular disease and diabetes, renal and hepatic disease, have begun to dominate our choice of drugs. A knowledge of both the short and long term adverse events associated with HAART is essential for providers and for patients. For new drugs to be acceptable in the current field, they will have to pass a litmus test of tolerability. Since adverse events are often remarkably idiosyncratic, pharmacogenomics may offer a way of predicting side effects and their severity from a particular drug or drug class in individual patients. This article forms part of a special issue of Antiviral Research marking the 25th anniversary of antiretroviral drug discovery and development, *Vol. 85, issue 1, 2010.*

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1. Introduction

Adverse events (AEs) play a major role in determining adherence to highly active antiretroviral therapy (HAART) and adherence is perhaps the most significant determinant of a regimen's success (d'Arminio Monforte et al., 2000). AEs are also becoming increasingly important in our efforts to fine tune HAART in order to diminish downstream toxicities that can, along with HIV itself and the increasing age of patients living with HIV, contribute to an increase in prevalence of the chronic diseases of aging in the HIV-positive population.

While randomized, controlled clinical trials are the gold standard for evaluating the efficacy of drugs they may underestimate short term toxicity in the general clinic population because of the desire of the subjects to stay in the trial and the support from the trial staff in enabling them to do so. Long term toxicities may be missed because of the often younger age of the subjects in clinical trials and because the relatively short term duration of these trials may not detect toxicities with a low prevalence rate. Finally, patients in clinical trials are viremic at the outset and the effects of viremia may disguise the effects of the drug. Cohort studies may provide useful data in evaluating long term drug toxicity and are powered to find effects with a relatively low prevalence; they have the disadvantage of both lead time bias and potential channeling bias that can be difficult or impossible to control for and may create misleading effects.

AEs of antiretroviral drugs can be usefully divided into short and long term toxicities and also by a class of agent used. Both short term and long term AEs will be reviewed in this article. Table 1 summarizes the predominant AEs for each antiretroviral class and individual clinically used antiretroviral therapeutic. In addition, the role of pharmacogenomics in predicting AEs will be discussed.

Table 1
Adverse effects associated with different classes of antiretrovirals.

Class	Drug	Adverse effects
NRTIs	Zidovudine	Anemia, nausea, rash, myopathy, dyslipidemia
	Stavudine didanosine	Nausea, lipoatrophy, DSPN, dyslipidemia, pancreatitis, lactic acidosis, hepatic steatosis, heart disease (?) DSPN
	Abacavir	HSR, hepatotoxicity, heart disease (?)
	Tenofovir	Renal insufficiency, bone loss
NNRTIs	Efavirenz	CNS adverse effects, rash, hepatotoxicity, lipoatrophy (?), teratogenicity, hypertriglyceridemia
	Nevirapine	Rash, HSR, hepatotoxicity
	Etravirine	Rash, hepatotoxicity
PIs	All PIs	Nausea, diarrhea, rash, dyslipidemia, insulin resistance, hepatotoxicity
	Atazanavir	Jaundice, scleral icterus, nephrolithiasis
	Indinavir	Jaundice, scleral icterus, nephrolithiasis
	Lopinavir fosamprenavir	Heart disease
Entry inhibitors	Enfuvirtide	Injection site reactions, pneumonia, HSR
	Maraviroc	Cough, fever, respiratory tract infections, rash, hypotension (postural) hepatotoxicity, HSR
Integrase inhibitors	Raltegravir	Headache, insomnia, dizziness, fatigue

Table 2
Adverse events in CNA30024 study (DeJesus et al., 2004).

Adverse event	ABC arm (+EFV) ($N=324$)	ZDV arm (+EFV) ($N=325$)
Most frequent (>10%)		
Nausea	23%	37%*
Fatigue	16%	26%*
Vomiting	12%	21%*
Cough	13%	8%
Treatment limiting (<10%)		
Hypersensitivity reaction (HSR)	8%	<1%
Anemia	0%	4%

Table 3
Adverse events in GS 934 study (Gallant et al., 2006).

Adverse event	FTC/TDF EFV QD ($N=257$)	ZDV/3TC BID EFV QD ($N=254$)
Any adverse event	10 (4%)	23 (9%)
Anemia	0	14 (6%)
Nausea	1 (<1%)	4 (2%)
Fatigue	0	3 (1%)
Vomiting	0	3 (1%)

2. Short term adverse events

2.1. Gastrointestinal toxicities

Gastrointestinal (GI) related toxicities of nausea, vomiting and diarrhea were the major reasons for discontinuation in the acute phase of treatment in a retrospective review from the HOPS database (O'Brien et al., 2003). As time passes, there may be an under appreciation of the chronicity of some of these GI AEs because patients learn to live with them and believe it is part of having to take HAART.

Nucleoside (or nucleotide) and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs, respectively) have relatively few GI AEs. In the RECOVER study (Palacios et al., 2005), discontinuation for GI AEs was 3% among NRTI treated patients. In CNA30024 study (DeJesus et al., 2004) (Table 2), there were statistically significantly more GI AEs (37% versus 21% for nausea, 21% versus 12% for vomiting) in the zidovudine (ZDV) arm than in the abacavir (ABC) arm; this study assessed all events, not necessarily only those leading to discontinuation. In GS 934 study (Gallant et al., 2006), adverse events leading to study drug discontinuation through week 48 were 4% for GI AEs with ZDV Vs <1% for tenofovir (TDF) (Table 3). Another NRTI that has been associated with GI toxicity is didanosine (DDI), which has the disadvantage of having to be taken without food.

In general, the NNRTI class is not associated with GI toxicity. In 2NN (Van Leth et al., 2004), a study comparing nevirapine (NVP) and efavirenz (EFV), grade 3/4 nausea, vomiting and diarrhea were <2%.

Regarding protease inhibitors (PIs), GI toxicity is one of the main treatment limiting AEs for this class of drugs. In two large recent studies in naïve patients, Artemis (De Ortiz et al., 2008) (Table 4) and Castle (Molina et al., 2008) (Table 5), two newer PIs, atazanavir (ATV) and darunavir (DRV) had less GI AEs than lopinavir (LPV)

Table 4
Adverse events in Artemis study (De Ortiz et al., 2008).

Adverse event (grade 2–4 with ≥2% incidence)	TDF/FTC DRV/r QD ($N=343$)	TDF/FTC QD LPV/r QD or BID ($N=346$)
All gastrointestinal	23 (7%)	47 (14%)
Diarrhea	14 (4%)	34 (10%)
Nausea	6 (2%)	10 (3%)

Table 5
Adverse events in Castle study (Molina et al., 2008).

Adverse event (grade 2–4 with ≥2% incidence)	TDF/FTC ATV/r QD (*N* = 441)	TDF/FTC QD LPV/r BID (*N* = 437)
Jaundice/scleral icterus	16 (4%)	0
Diarrhea	10 (2%)	50 (11%)
Nausea	17 (4%)	33 (8%)

when all evaluated PIs were boosted with RTV. In the KLEAN (Eron et al., 2006) study, grade 2–4 GI AEs for fosamprenavir/r (FPV/RTV) were the same as with LPV/RTV, with the incidence reaching 12% for diarrhea and 6% for nausea.

Integrase inhibitors and entry inhibitors (fusion inhibitors and CCR5 receptor blockers) have not generally been associated with GI AEs.

The treatment of nausea/vomiting can be either supportive or pharmacologic. Supportive care involves the evaluation of causes (infections, gastritis, esophageal disease, CNS disease, etc.), patient education, advice and support, medications with meals (except ddI), and nutritional counseling. Pharmacologic treatment includes antiemetic agents, acid reducing agents or switching medications.

The treatment of diarrhea may involve again, the search for the cause, for example travel, a new sexual contact or recent use of antibiotics may be clues. Also, assessing gliadin antibodies for Sprue or investigating for lactose intolerance can help identify the cause. There may be a need for nutritional counseling, for example to increase fiber in the diet and reduce the use of refined foods. Pharmacologic intervention may include the use of antidiarrheal agents or involve switching medications. Crofelemer, a chloride ion channel blocker currently in clinical trials, may offer benefit in the future.

2.2. Rash

Rash is a common short term AE and while it can be caused by almost any drug, the NNRTIs are the main offenders in HAART. The rash associated with NNRTIs is usually erythematous, maculopopular and widespread. Rash has been observed in 10–17% of patients receiving NNRTIs (Carr and Cooper, 2000). The incidence of moderate to severe rash is approximately 8–12% with rash-related discontinuation rates of approximately 2%.

NVP and EFV associated rashes are generally of mild-to-moderate severity, but severe rashes have been observed in approximately 6.5% of patients receiving NVP (Fagot et al., 2001) and 4% of those receiving EFV, generally within the first 4 weeks of therapy. Etravirine (ETV), the newest available NNRTI, had an all grade rate of rash of 17% in the DUET study with a higher incidence in women versus men: 28% versus 16% (Madruga et al., 2007). This increased effect in women has been described for other NNRTIs as well (Ofotokun and Pomeroy, 2003). The discontinuation rate due to ETV-associated rush was 2.2%. In September of 2009, a letter from the manufacturer of etravirine warned physicians about the rare occurrence of toxic epidermal necrolysis and Stevens Johnson syndrome with this drug.

Management of rash includes treating through (often possible), use of antihistamines or corticosteroids, and discontinuing or switching therapy.

2.3. Hypersensitivity reaction

Hypersensitivity reactions (HSR) to some antiretroviral drugs can occur, notably with ABC and NVP. HSR is characterized by fever, rash, myalgia, abdominal pain, elevated liver transaminases lethargy, respiratory distress, musculoskeletal headache, paresthesia and edema; renal or hepatic failure. An important feature of drug HSR is that re-challenging the patient with the offending drug can lead to a serious and possibly fatal anaphylactic reaction. The introduction of HLA-B5701 screening has meant that this reaction with ABC is now rare (Mallal et al., 2008). The test has a very high negative predictive value. For NVP, a CD4 count of >250 c/mm^3 in women and >400 c/mm^3 in men is predictive of an HSR, although switching to NVP at higher counts in the presence of an undetectable viral load may be safe (Kesselring et al., 2009).

2.4. Toxicity of central nervous system

Central nervous system (CNS) toxicity is commonly associated with the NNRTI EFV. This has been demonstrated in multiple studies, perhaps best in a substudy of ACTG 5095, namely ACTG 5097 (Clifford et al., 2003). In ACTG 5095, patients were randomized to three treatment groups, AZT/lamivudine (3TC)/EFV Vs AZT/3TC/ABC Vs AZT/3TC/ABC/EFV. The main findings in ACTG 5097 demonstrated a significant number of short term CNS AEs associated with EFV, but these were mostly resolved by week 4 after the initiation of EFV treatment. There were no major differences in mood disorder (e.g. anxiety, depression) between the treatment groups.

Significant symptoms reported at Day 7 in the *pooled* EFV arms included: vivid dreams, off-balance or unsteady walking, lightheadedness or drowsiness, feeling like falling over, spinning or room spinning. There have been other studies demonstrating that more subtle CNS AEs may persist for longer, but would resolve over time in most patients (Hawkins et al., 2005). Approaches for the management of these CNS AEs include treating through (most often possible), prescribing antihistamines, anti-anxiety agents, antidepressants or a drug switch for those patients whose symptoms persist.

In the Startmrk (Lennox et al., 2009) trial, comparing EFV with the integrase inhibitor raltegravir (RAL) in naïve patients, both combined with tenofovir (TDF)/FTC, CNS AEs at week 8 were 10.3% and 17.7% for the RAL and EFV arm, respectively ($P = 0.015$); this difference persisted through week 48. Main CNS AEs for RAL included headache, insomnia and dizziness.

2.5. Anemia

Anemia is an adverse event primarily associated with ZDV and its effect of myelosuppression. In GS 934 study, 6% of patients in the ZDV/3TC arm had discontinued the study at 48 weeks because of anemia (Pozniak et al., 2006). Similar results have been seen in other trials (Moyle et al., 2004). Clinical Management may involve correcting underlying metabolic disorders, the use of epoetin alfa or blood transfusions, and ultimately discontinuing ZDV.

2.6. Jaundice and scleral icterus

These side effects are the result of an increase in indirect (unconjugated) bilirubin that is produced naturally from red blood cell breakdown. Unconjugated bilirubin undergoes glucuronidation by uridine diphosphate glucuronyl transferase (UGT) enzyme in the liver to form conjugated bilirubin. The PIs ATV and IDV inhibit UGT1A1 enzyme, causing increases of indirect bilirubin (Rayner et al., 2001). The decreased UGT activity is similar to Gilbert's syndrome. In the Castle study of ATV/r versus LPV/r in naïve patients,

4% of patients in the ATV arm had grade 2–4 jaundice and/or icterus (Molina et al., 2008). In BMS 045, a study of ATV/r versus LPV/r in treatment-experienced patients, 7% in the ATV arm experienced grade 2–4 jaundice and 3% developed scleral icterus (Johnson et al., 2006). This side effect is cosmetic only but may cause distress to the patient, especially if he or she works in contact with public and may be perceived to be ill with hepatitis. It may also lead emergency room physicians to suspect liver disease, especially in patients who also have mild elevations of transaminases. In addition, the severity of the effect may fluctuate in time. Treatment is to discontinue ATV or IDV therapy or switch to another drug if necessary.

2.7. Additional short term adverse effects

There are multiple other short term toxicities that have been described in the literature and seen in the clinic. Examples are acute pancreatitis in patients treated with ddI or d4T (Reisler et al., 2005), nephrolithiasis associated with IDV (Wellons et al., 2000) and less commonly, with ATV (Chan-Tack et al., 2007). Lactic acidosis has been described especially in association with the first generation NRTIs (D-drugs, mainly d4T and ddI) (Gérard et al., 2000) and its fast onset can develop into a life-threatening AE. Acute renal failure with many antiretroviral drugs, including tenofovir (Karras et al., 2003) is luckily rare and usually manageable with immediate drug withdrawal and clinical support. Drug induced hepatitis, characterized by elevation of AST/ALT to levels at least twice of the upper limit of normal (ULN) can occur with drugs from all categories (Sulkowski et al., 2000). Injection site reactions (pruritic, painful, raised red bumps) have been noted with enfurvitide (Ball and Kinchelow, 2003). Fatigue, dizziness and dyspepsia are common AEs associated with many antiretroviral drugs. Nail discoloration has been seen in association with ZDV (Don et al., 1990).

3. Long term adverse events

Patients now increasingly rarely die of AIDS, or from any opportunistic disease related to AIDS, in the developed world. The realization that HIV itself and HAART are both risk factors for dying from the diseases of aging has prompted not only much greater attention to the treatment of co-morbidities that increase the risk of death, but also to fine tuning HAART to reduce that risk and to the consideration of starting treatment earlier.

This has led to much greater attention being placed on cardiovascular disease (CVD), cancer, liver and renal disease. There has also been more attention paid to lipodystrophy as not only new stigmata of HIV but a risk factor for CVD. Neurocognitive function is under more intense scrutiny and distal sensory peripheral neuropathy (DSPN) remains an intractable target.

3.1. Cardiovascular events

CVD remains the leading cause of death worldwide (Strong et al., 2005). DAD is a large, multinational, 33,000 patient cohort that was designed in part to look at the relationship between HAART and cardiovascular AEs. Investigators of this cohort had initially shown an increased risk for myocardial infarction (MI) of 16% for each year of combination HAART (Friis-Møller et al., 2007) an effect that was largely driven by PI use. Subsequently, the investigators presented data at CROI (Lundgren et al., 2009) on the relative risk of HAART in the context of 581 MIs diagnosed in the cohort. A follow-up patient analysis was performed from the DAD enrollment until the first MI event, either the 1 February 2008 or 6 months after the patient's last clinic visit, whichever came first. There had to be at least 30,000 patient years of exposure for a drug to be included in the analysis. In 2009, data for 33,308 patients from 11 cohorts was included in the analysis. All models included adjustment for demographics, cardiovascular risk factors and the use of other antiretrovirals. Further analyses included adjustment for the latest measure of lipids, metabolic parameters, CD4 count and HIV RNA load. The results indicated that in the PI class, an increased risk for MI was associated with IDV (relative rate of 1.12 per year) and LPV (relative rate of 1.13 per year) but not with Saquinavir (SQV) or Nelfinavir (NFV). This increased risk remained present after adjusting for the use of RTV as a booster and for metabolic factors such as serum lipid and glucose levels. Notably, there was no risk of increased cardiovascular AEs associated with the use of NNRTIs.

Among NRTIs, there was an increased risk for recent (within the previous 6 months) use of ABC and ddI with relative rate of 1.68 and 1.41, respectively. There was no effect seen for the other NRTIs, including TDF which was not included in the interim DAD cohort analysis presented in 2008 (Lundgren, 2008).

The French regulatory authorities requested the Agence Nationale de Recherche sur le Sida (ANRS) group to review their data using the French Hospital Database in regard to the association of HAART and MIs (Lang et al., 2009). This was a nested, case–control study that looked at a cumulative exposure to specific NRTIs, recent (current or within last 6 months) and past exposure (>6 months ago) to specific NRTIs and cumulative exposure to specific PIs. Over 115,000 HIV-infected patients enrolled between 1989 and 2006. There were 289 patients with a first definite or probable MI prospectively reported between January 2000 and December 2006. For each MI case, up to 5 controls with no history of MI matched for age, sex and clinical center. Data collected for cases and controls included cardiovascular risk factors and treatments, together with HIV history and treatment. From these data, logistical regression models were constructed. The results showed an increase risk for MI with the cumulative use of LPV/RTV with an odds ratio of 1.38 per year, and FPV/RTV with an OR of 1.55 per year. Again, there was no increased risk for the use SQV or NFV, or NNRTIs, confirming the observations from the DAD cohort analyses.

In case of NRTIs, an association between ABC and the risk of MI was confirmed, in this study only for the first year of ABC use with an OR of 1.97. There was a trend but not a significant association between recent use (6 months) after the first year. No other NRTI, including ddI, showed any association with increased risk of MI. In an unpublished analysis from the ANRS, the effect for ABC was only seen in virologically suppressed patients, suggesting that viremia may overshadow the drug effect. In a further analysis presented at the IAS meeting in Capetown in 2009, this effect went away after controlling for other cardiac risk factors (OR = 0.97) (Costagliola, 2009) Risk factors included hypertension, smoking, family history of premature coronary artery disease, use of cocaine and/or IV drug use, plasma HIV-1 RNA level, CD4/CD8+ cell ratio, and exposure to FTC, ATV, RTV, and tipranavir (TPV).

Two other studies, SMART (Lundgren et al., 2008) and STEAL (Cooper et al., 2009) also showed an association between ABC and an MI or CVD, respectively. There was no such association found in studies conducted by the commercial sponsors (Cutrell et al., 2008) or in the ACTG analysis from AIDS clinical trials group longitudinal linked randomized trials-ALLRT (Benson et al., 2009). Most recently, data was presented on this subject at the IAS meeting in 2009 from the VA cohort (Bedimo et al., 2009). Cumulative ABC exposure was associated with a nonstatistically significant increase in risk of acute myocardial infarction (AMI) and cerebrovascular accidents (CVA). This association was further attenuated by adjusting for the presence of chronic kidney disease prior to therapy initiation or for traditional cardiovascular risk factors. Of note, the mean duration of drug exposure was rather limited at 1.93 years in this cohort.

A viable explanation of the pathogenesis of these findings would go a long way to establish them. Previous analysis from the SMART (Lundgren et al., 2009) study found a relationship between ABC

use and an increase in highly sensitive C-reactive protein and interleukin-6 (IL-6) levels. This has not been reproduced in other studies such as HEAT (McComsey et al., 2009) or in the MACS cohort (Palella et al., 2009). Small studies have found an association between ABC and decreased flow mediated dilation following brachial artery clamping, a marker for endothelial dysfunction (Hsue et al., 2009) and decreased platelet function (Satchell et al., 2009), but these findings need to be confirmed in other studies. In the BICOMBO study, where fully suppressed patients were switched to either TDF or ABC based regimens, there were no differences in changes in biomarkers of inflammation, endothelial dysfunction, insulin resistance, and hypercoagulability (Martinez et al., 2009).

Overall, the association between ABC and MI needs to be further studied. The putative association between ABC and LPV/RTV with an increased risk of MI needs to be considered carefully when prescribing HAART, especially to patients with higher levels of conventional risk factors for CVD. Further evaluation of these connections is underway in other cohorts and studies. Aggressive treatment of conventional co-morbidities for CVD is essential.

Dyslipidemia is a side effect of many HAART regimens, especially those including PIs, and has been associated with an increased risk for cardiovascular disease. RTV as a pharmacokinetic booster has an independent effect on lipids (Shafran et al., 2005). In the Artemis and Castle studies previously referenced, DRV and ATV had significantly lower increases in triglycerides than LPV when each of these PIs was boosted with RTV. In the AI424-089 study, ATV was evaluated with and without RTV). ATV/RTV was associated with greater increases in total cholesterol and LDL cholesterol than ATV alone. The difference in effect on HDL cholesterol was negligible (Moyle, 2007).

In a metaanalysis, TDF was identified as NRTI with the least lipid effect (Hill et al., 2009). Rilpivirine (TMC278) is a new NNRTI in phase 3 clinical trials that has a less effects on lipid profile than EFV (Santoscoy et al., 2008a,b). With respect to additional comparisons of EFV to other antiretroviral drugs, the STARTMRK trial (Lennox et al., 2009) of RAL versus EFV, both in combination with TDF and FTC, RAL had little effect on either cholesterol or triglycerides compared to EFV, which increased both LDL and HDL cholesterol and more significantly, was associated with elevation in triglycerides. In GS 903 (Gallant et al., 2004), d4T raised triglycerides significantly more than TDF.

Insulin resistance and type II diabetes is known as a major risk factor for CVD. Early in the HAART era, IDV was known to be associated with insulin resistance via the inhibition of the GLUT4 transporter that is induced in various cell types including adipocytes in response to insulin. In the Mediclas study (van Vonderen et al., 2009) treatment with ZDV/3TC and LPV/RTV induced a significant increase in insulin resistance while NVP and LPV/RTV did not, underscoring the role of ZDV. In a recent in vitro study in fully differentiated primary human adipocytes, LPV and RTV were shown to be the most potent inhibitors of insulin-stimulated glucose uptake while ATV and DRV were shown to have the least effect (Bahador et al., 2006). In vitro, ATV appears to have the least effect while LPV has an early effect that dissipates with time in a summary published by Lee et al. (2005).

Treatment of HAART-associated lipid and glucose metabolism disorders includes weight loss and exercise, dietary restrictions, adding statins to reduce cholesterol, fibrates and fish oil to reduce triglycerides, adding metformin and/or other agents to reduce plasma glucose, or ultimately switching antiretroviral agents.

3.2. Hepatic adverse events

A number of antiretroviral agents can cause hepatotoxicity (Table 1). NVP is associated with acute liver disease via an HSR. Analysis of ATHENA cohort by pre-therapy and current CD4+ cell counts demonstrated an overall rate of 6.2% for the NVP-associated HSR with a risk similar both in treatment-naive and treatment-experienced patients (Wit et al., 2008). Independent risk factors included detectable HIV-1 RNA, high pre-treatment and current CD4+ cell counts and female gender. The HSR reaction can result in acute liver necrosis and death and can be difficult to predict as there may be few clinical or laboratory warning signs. NVP is not recommended in female and male patients with a CD4+ cell counts of >250 and >400, respectively.

Many HAART regimens include drugs that may cause a chronic hepatitis characterized by a rise in liver transaminase levels (AST, ALT). This is usually reversible by discontinuing the drug. ddI is not recommended for use while treating hepatitis C virus infection with pegylated interferon and ribavirin because of drug–drug interactions between ddI and ribavirin that increases the phosphorylation of ddI, potentially leading to mitochondrial toxicity (Hartman et al., 1991). AZT is not recommended because of overlapping anemia with ribavirin. Abacavir has been associated with a decrease in HCV virologic response compared to other NRTIs (Mira et al., 2008) but the mechanism of competition with ribavirin for guanosine receptors has not been validated.

3.3. Renal adverse events

Renal dysfunction has been associated primarily with TDF since the parent NRTI tenofovir is actively accumulated in the proximal renal tubule via the action of renal-specific organic anion transporters 1 (Cihlar et al., 2001). Small (approximately 6–10 ml/min), but statistically significant changes in creatinine clearance have been associated with the use of TDF (Gallant et al., 2006). These changes are not usually clinically significant in the presence of normal renal function at baseline, but may become so if renal disease is present. In the Hopkins cohort study (Gallant et al., 2005), the drop in GFR was −19 ml/min for TDF and −11 ml/min for other NRTIs. Further analysis showed that these differences were found only in treatment experienced patients. There was no association with race in this cohort or with risk factors such as diabetes and hypertension if renal disease was absent. Recently, a genetic marker for TDF associated tubular damage has been described (Rodríguez-Nóvoa et al., 2009). This is a genotype CC at position −24 of the MRP2 gene, which was surprising as tenofovir is not a substrate for MRP2 efflux transporter (Ray et al., 2006). When associated with older age (>50) and low weight (<60 kg), the predictive value was high. Markers of renal tubular dysfunction include glucosuria in non-diabetics, aminoaciduria, urine phosphate wasting, β2-microglobulinuria, and abnormal uric acid excretion. Fanconi syndrome is an example of acute proximal tubular dysfunction. It has been reported in patients receiving TDF and adefovir (Eaton, 2005), most often in patients with prior reduced creatinine clearance and poorly controlled HIV disease, which is now relatively rare. Accumulation of the drug in renal proximal tubules due to a potential imbalance in the uptake and efflux via organic anion transporters and multidrug-resistant proteins, respectively, has been implicated in drug-induced Fanconi syndrome (Izzedine et al., 2005).

If TDF is used in the presence of impaired renal function, then it is important to follow the prescribing guidelines with monitoring for renal function.

As referenced above, nephrolithiasis is associated with PIs IDV and to a lesser extent also ATV.

3.4. Lipodystrophy

Lipodystrophy is an umbrella term for several conditions, including lipoatrophy and/or lipohypertrophy, often associated with dyslipidemia and insulin resistance (Grinspoon and Car, 2005).

These symptoms may occur together or separately. Lipoatrophy is defined as fat loss in face (cheeks), extremities, buttocks, and subcutaneous abdominal fat. Patients often complain of prominent veins because of reduced surrounding fat lipohypertrophy is defined as visceral abdominal fat accumulation, dorsal cervical fat pad, parotid area fat accumulation, development of lipomata or enlargement of breasts in women (Grinspoon and Car, 2005). This syndrome has been associated with an increase risk for coronary heart disease (Hadigan et al., 2003).

Lipodystrophy has been associated primarily with the use of certain NRTIs and PIs. One of the potential mechanisms whereby NRTIs can cause lipoatrophy is via mitochondrial DNA (mtDNA) depletion (Nolan et al., 2003). However, a downregulation of mitochondrial gene expression as well as expression of nuclear genes involved in lipid metabolism in the absence of mtDNA depletion has been described (Mallon et al., 2005). In vitro, NRTIs affect mtDNA differently, with ddC, stavudine (d4T), and ddI being the main offenders (Birkus et al., 2002). In a study of mtDNA in subcutaneous fat biopsies from HIV-infected individuals (Nolan et al., 2003), the thymidine analogues d4T and ZDV markedly reduced mtDNA levels, with d4T being the most active, while TDF and ABC had no effects. In ACTG 5142 (Riddler et al., 2008), a comparison of EFV and LPV/RTV with backbones of d4T, ZDV and TDF, the rate of lipoatrophy was greater in the EFV arms, even when combined with TDF (12% versus 6%). This was an unexpected finding and it may be mediated only by the NRTI backbone. The incidence rate of lipoatrophy in studies such as ACTG 5202 (EFV versus ATV with either ABC or TDF) is anticipated with interest.

Treatment may involve substituting TDF or ABC for thymidine analogues, polylactic acid injections for facial lipoatrophy, weight loss and exercise for fat accumulation, liposuction for dorsocervical fat accumulation and breast reduction surgery. Tesamorelin (growth hormone-releasing factor analog), completed phase 3 clinical trials for visceral fat reduction. Results showed that patients treated for 26 weeks achieved an average 11% decrease in visceral adipose tissue (measured by Dexa scan) from baseline without significant changes in subcutaneous adipose tissue. In addition, a trend for improvement in triglyceride levels was recorded for the treated group versus placebo and was significantly different versus baseline (Falutz et al., 2009).

3.5. Distal sensory peripheral neuropathy

Distal sensory peripheral neuropathy is subjectively described as numbness and/or pain in the extremities, most often in the feet. Signs include absent ankle reflexes and loss of sensation to vibration and pin prick.

Recently, several cohort studies confirmed the presence of DSPN with at least 1 sign or symptom in 30–57% of patients with 5–40% being symptomatic (Ellis et al., 2009). In both cohorts, older age and nadir CD4+ counts were strong predictors of DSPN, as were any use of the d-drugs, mainly d4T and ddI, which are still widely used in the developing world.

The d-drugs are known to be toxic to mitochondria, primarily via interfering with mtDNA replication. Mitochondrial toxicity leads to the impairment of ATP synthesis. At the pharmacology workshop in April 2009, comparing 6 patients taking DDI to 10 patients taking TDF and no ddI, it was shown that patients taking ddI had lower intracellular ATP levels (Hawkins et al., 2009). At the 2009 CROI meeting, Cherry et al. showed that Co-Enzyme Q, an important component of ATP production, was protective of neuron growth in the presence of d-drugs in an animal model (Cherry et al., 2009).

There is no effective treatment for DSPN. Avoidance of d-drugs, judicious use of analgesics and keeping the extremities warm are the mainstays of management. Acupuncture and the drugs pregabalin or gabapentin are often used despite absence of clinical data from controlled trials to support their use in HIV- or HAART-associated DSPN.

3.6. Additional chronic adverse events

Tenofovir has been shown to reduce bone mineral density (BMD) in the first 24 weeks of therapy compared to stavudine (Gallant et al., 2004) but only minimally (spine −1.7%; hip −3.3%). Upon continuing the therapy the bone loss plateaus or slightly increases. This effect did not increase the risk for fracture, but could be significant in patients at high risk for, or with existing osteoporosis. An aging HIV-positive population and the known risk for bone loss related to HIV itself (Overton et al., 2009) could make small drug effects more significant in the future.

In study 613 (Brown et al., 2009), treatment for 96 weeks with ZDV/3TC and EFV or LPV/r reduced total BMD by 2.3% and 2.5% respectively, with no difference between regimens and no changes when the LPV/r arm changed to LPV/r monotherapy at 24–48 weeks. Although ZDV is known to induce osteoclast activity (Pan et al., 2004), these results suggest that non drug factors, such as hypovitaminosis D for example, may be more important in bone loss in HIV patients. Black race and CD4+ nadir were predictive of BMD decline in this study.

With respect to additional potential chronic effects, no association with HAART has been shown for malignancy, respiratory disease or neurocognitive impairment, although there is interest in the relative ability of HAART to penetrate the CNS.

4. Adverse events of antiretrovirals in clinical development

A limited number of new drugs are either in, or are about to start, phase 3 clinical trials.

TMC-278 or rilpivarine (RPV) is a new NNRTI that has been examined in a head to head trial with efavirenz (Santoscoy et al., 2008a,b). Serious AEs were similar in the RPV and EFV groups (12.2% versus 14.6%), as were rates of grade 3 or 4 toxicities (27.2% versus 21.3%) and grade 3 or 4 lab abnormalities (26.5% versus 23.6%). Rash was seen less often in the RPV group, (9% versus 21%, $P < 0.01$), as were dizziness and sleepiness (31% versus 48%, $P < 0.01$), and abnormal dreams or nightmares (3% versus 11%, $P < 0.05$). In the RPV group, triglycerides decreased by a mean of 9.9 mg/dL while increasing in the EFV group by a mean of 29.2 mg/dL. Qtc prolongation was seen in both groups; for RPV it was least in the 25 mg dose.

Elvitegravir is a new integrase inhibitor that is currently in phase 3 clinical trials. In phase 2 studies, it showed a low incidence of all AEs (Zolopa et al., 2007). Other drugs in this class have similarly shown a low rate of AEs.

Apricitabine (ATC; AVX754) is a novel cytidine NRTI currently in phase 3 clinical development. In vitro profiling of the drug indicated that unlike some of the other NRTIs, ATC exhibits low potential for mitochondrial toxicity (Cox and Southby, 2009). Safety analysis of phase 1 data showed that ATC is well tolerated with the most common adverse events reported being headache and rhinitis (Cahn et al., 2006). In phase 2 study, 39 patients completed the 96-week treatment with no serious adverse events related to ATC and no patients withdrawing from the study because of adverse events related to ATC treatment.

5. Genetic markers for the toxicity of antiretrovirals

Pharmacogenomics examines the influence of genetic variability on drug efficacy or toxicity by correlating gene expression or single-nucleotide polymorphisms with patient outcomes. It is fair to say that this discipline has begun to influence practice in small

but significant ways and is likely to increase its influence in time.

The PREDICT study (Mallal et al., 2008) showed that the presence of the allele HLA-B5701 is highly predictive of an HSR to ABC. Positive and negative predictive value was 60% and 100%, respectively. The used of a genetic tests for HLA-B5701 led to a reduction in ABC related HSR to <1% in the ARIES trial (Squires et al., 2008) compared to a rate of between 4 and 8% seen in other trials not using HLA screening. This is the first example of a clinical use of genetic screening in HIV disease management to get widespread approval.

Other potentially useful markers are the mutation at position 516G > T in CYP2B6 which signals a longer half-life and increased levels of efavirenz (Haas et al., 2004). Such a marker could be used to identify patients who are most likely to suffer from efavirenz-associated CNS AEs. Other haplotypes within CYP2B6 have been associated with a longer half life for nevirapine (Chantarangsu, 2009).

The genetic variant associated with Gilbert's disease, UGT 1A1*28, has been identified as part of a haplotype of four UGT1A variants spanning three genes at the *UGT1A* gene locus (Lankisch et al., 2006). This haplotype predisposes to hyperbilirubinemia in ATV treatment and may have an additional role as a pharmacogenomic risk factor for drug therapy.

Studies have been conducted to identify a genetic marker for renal tubular dysfunction associated with TDF. Initial assessment performed in a small cohort of patients with TDF-associated renal dysfunction identified a single substitution at position of 1249 of MRP2 gene as being potentially associated with the side effect (Izzedine et al., 2006). In an intriguing study at the 2009 HIV Pharmacology conference and due to be published next year, a retrospective analysis of 471 naïve patients in the Swiss HIV cohort who started therapy between 2004 and 2007 assessed the relationship between multiple genetic markers of AEs and the rate of drug discontinuation (Columbo, 2009) The results indicated that patients carrying the risk alleles were significantly more likely to discontinue certain antiretrovirals. However, a prospective trial of these types of markers would be needed to further establish their link with particular AEs. While there are many such associations reported between mutations and AEs, most have yet to make it into prime time.

In addition to association with AEs, certain polymorphisms, i.e. naturally occurring nucleotide substitutions in the genomic DNA have been shown to accurately predict virologic failure. An example is the nucleotide variation at position 3435 of the human P-glycoprotein (MDR-1) gene; the number of patients in each genotype group (3435 C/C, C/T, and T/T) still experiencing virological suppression at 24 months was 55/112, 72/125 and 74/133, respectively ($P = 0.07$) (Brumme et al., 2003). Greater than 80% of these patients were on a regimen of 2 NRTIs plus a PI. This was a small effect, though significant, for a slower time to immunological and virological failure for the C/C genotype.

6. Summary

Tolerability, both short term and long term, is now the principal reason for choosing one regimen versus another, given that the efficacy of various HAART combinations is fairly equivalent, especially in treatment-naïve patients. The success of recent HAART is in part due to the relative lack of AEs associated with current first line regimens. It has been often said that the best regimen is the one the patient will take. A lack of significant short term toxicity will drive better adherence and all treating physicians have a duty to their patients to avoid or at least minimize any long term damage the antiretroviral treatment may cause. Drug development in the HIV field has slowed, but not stopped. It is clear that success in the field is very largely dependent on the relative tolerability of new drugs compared with existing agents. Treatment for some of the most common side effects of HAART such as lipodystrophy and DSPN remains woefully inadequate and research must continue to find solutions. Finally, the burgeoning new science of pharmacogenomics offers further promise of fine tuning HAART and tailoring therapy for each individual patient.

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