Contemporary Antiretroviral Drugs

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Contemporary antiretroviral agents afford enhanced potency and safety for patients living with HIV. Newer antiretroviral drugs are often better tolerated than those initially approved in the early stages of the HIV epidemic. While the safety profile has improved, adverse drug reactions still occur. We have segregated the antiretroviral agents used in contemporary practice into class groupings based on their mechanism of antiviral activity (non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors, and entry inhibitors) while providing a review and discussion of the hepatoxicity seen in the most relevant clinical literature published to date. Clinical literature for individual agents is discussed and agent comparisons afforded within each group in tabular format.

human immunodeficiency virus hepatotoxicity antiretroviral therapy

1. Introduction

Since the introduction into practice of the first antiretroviral drug zidovudine in 1987, the development of new antiretroviral drugs has evolved at a rapid pace. The Food and Drug Administration (FDA) has approved 34 antiretroviral drugs (characterized by eight different mechanisms of antiviral activity) and 24 fixed-dose combinations for the treatment of the HIV infection [1]. Antiretroviral therapy itself has evolved from regimens with high pill burden, an inconvenient multiple daily dosing schedule, and treatment-limiting toxicities, to the current era of fixed-dose combinations and single-tablet regimens, allowing the entire treatment to be provided with a once-daily single tablet. Furthermore, dual-drug and long-acting injectable therapies have entered clinical practice [2][3]. Antiretroviral drugs introduced in recent years are more potent and much better tolerated than their earlier counterparts. However, their use is not devoid of adverse drug reactions; these continue to be encountered, albeit at a lower rate than with older antiretroviral drugs.

As the organ primarily responsible for the metabolism of many medications, the liver is a common target for drug-induced injury. This holds true for antiretroviral drugs [4][5]. In Table 1, we can see the antiretroviral drugs actively used in the contemporary treatment of the HIV infection.

Table 1. Antiretroviral agents (by mechanism of action) used in contemporary management of HIV.

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Protease Inhibitors (PIs)	Integrase Strand Transfer Inhibitors (INSTIs)	CCR5 Antagonist	CD4-Directed Post-Attachment Inhibitor	Attachment Inhibitor
Abacavir (ABC)	Doravirine (DOR)	Atazanavir (ATV)	Raltegravir (RAL)	Maraviroc (MVC)	Ibalizumab (IBA)	Fostemsavir (FTR)
Emtricitabine (FTC)	Efavirenz (EFV)	Darunavir (DRV)	Elvitegravir (EVG)			
Lamivudine (3TC)	Etravirine (ETR)	Lopinavir (LPV)	Dolutegravir (DTG)			
Tenofovir disoproxil fumarate (TDF)	Rilpivirine (RPV)		Bictegravir (BIC)			
Tenofovir alafenamide (TAF)			Cabotegravir (CAB)			

2. Inhibitors

2.1. Non-Nucleoside Reverse Transcriptase Inhibitors

Non-nucleoside reverse transcriptase inhibitors have been historically associated with hepatic injury and toxicity [6]. Multiple mechanisms for the cause of hepatotoxicity with NNRTI use have been suggested including direct cholestatic injury, hypersensitivity reaction, or mediation of immune reconstitution syndrome, though hypersensitivity appears to be the most commonly reported cause in the literature among NNRTIs [7][8][9]. These hypersensitivity reactions are likely secondary to an intermediate metabolite created during metabolism via the cytochrome P450 pathway, leading to an immunogenic reaction [9]. A review of the clinical trials evaluating hepatic toxicity with NNRTI use can be found in Table 2.

Table 2. Clinical trial evaluation of hepatic toxicity and incidence for non-nucleoside reverse transcriptase inhibitors.

Reference	Drug(s)	No. of Study Patients	Hepatic Evaluation	Overall Incidence of Cases/100 Persons Exposed	Study Design	Patient Population
Sulkowski 2002 [10]	Efavirenz	312	Combined Grade 3 and 4 Grade 3: AST/ALT 5.1–10× ULN	8	Prospective	Treatment-naive; 40% HCV-positive; 52% concurrent

Reference	Drug(s)	No. of Study Patients	Hepatic Evaluation	Overall Incidence of Cases/100 Persons Exposed	Study Design	Patient Population
			Grade 4: AST/ALT > 10× ULN			protease inhibitor use
van Leth 2004 2NN [11]	Efavirenz	400	Combined Grade 3 and 4 Grade 3: AST/ALT 5.1–10× ULN Grade 4: AST/ALT > 10× ULN	4.5	Prospective	Treatment-naive; 10% HCV-positive; 4% HBV-positive
Girard 2012 DUET-1 and DUET 2 (96 Week Pooled Data) [12]	Etravirine	599	Grade 3: AST/ALT 5.1–10× ULN Grade 4: AST/ALT > 10× ULN	Grade 3: 4.4 Grade 4: 3.9	Prospective	Treatment-experienced; 12% HBV-and/or HCV-positive
Molina 2011 ECHO [13]	Rilpivirine	346	Combined Grade 3 and 4 Grade 3: AST/ALT 5.1–10× ULN Grade 4: AST/ALT > 10× ULN	AST: 2 ALT:1	Prospective	Treatment-naive; 3% HBV-positive; 2% HCV-positive
Cohen 2011 THRIVE [14]	Rilpivirine	340	AST/ALT 5.1–10× ULN	2	Prospective	Treatment-naive; 4% HBV-positive; 5% HCV-positive
Nelson 2012 [15]	Rilpivirine	686	Combined Grades 1–4 Grade 1: AST/ALT 1.25–2.4× ULN Grade 2: 2.5–4.9× ULN Grade 3: 5–9.9× ULN Grade 4: ≥ 10× ULN	2.2	Prospective	Treatment-naive; 8.4% HBV-and/or HCV-positive

Reference	Drug(s)	No. of Study Patients	Hepatic Evaluation	Overall Incidence of Cases/100 Persons Exposed	Study Design	Patient Population
Molina 2020 DRIVE-FORWARD [16]	Doravirine	383	AST/ALT ≥ 5× ULN	ALT: 1 AST: 2	Prospective	Treatment-naive
Orkin 2020 DRIVE-AHEAD [17]	Doravirine	363	AST/ALT 5–9.9× ULN	ALT: 0.8 AST: 0.6	Prospective	Treatment-naive; 3% HBV- and/or HCV-positive
Johnson 2019 DRIVE-SHIFT [18]	Doravirine	447	ALT/ALT ≥ 3× ULN plus bilirubin ≥ 2× ULN and alkaline phosphatase < 2× ULN	0	Prospective	Treatment-experienced; 3% HBV- and/or HCV-positive

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; ULN, upper limit of normal.

2.2. Integrase Strand Transfer Inhibitors

Integrase strand transfer inhibitors (INSTIs) have emerged as key components of initial antiretroviral regimens given their virologic efficacy and tolerability. Hepatotoxicity associated with INSTIs is rarely reported in the literature with no describing mechanism listed for when it does occur (Table 3) [19]. In a review of the incidence of hepatotoxicity with INSTI use in 4366 people participating in The EuroSIDA study, a prospective observational pan-European cohort study of people living with HIV-1 across Europe, there was only one discontinuation due to hepatotoxicity [20].

Table 3. Clinical trial evaluation of hepatic toxicity and incidence for integrase strand transfer inhibitors.

Reference	Drug(s)	No. of Study Patients	Hepatic Evaluation	Overall Incidence of Cases/100 Persons Exposed	Study Design	Patient Population
Steigbigel 2010 BENCHMRK-1 and -2 (Week 96	Raltegravir	462	AST/ALT > 10× ULN	AST: 0.7 ALT: 1.3	Prospective	Treatment-experienced; multidrug resistant

Reference	Drug(s)	No. of Study Patients	Hepatic Evaluation	Overall Incidence of Cases/100 Persons Exposed	Study Design	Patient Population
Pooled Data) [21]						
Lennox 2010 STARTMRK (Week 96 Data) [22]	Raltegravir	281	AST/ALT/ALK Phos > 5× ULN TBILI > 2.5× ULN	AST: 3.2 ALT: 1.8 ALK Phos: 0 TBILI: 0.7	Prospective	Treatment-naive; 6% HBV and/or HCV
DeJesus 2012 GS-236-0103 [23]	Elvitegravir/cobicistat	352	Combination of all grades for AST/ALT elevations	AST: 17.6 ALT: 15.3	Prospective	Treatment-naive; 1% HBV; 5% HCV
Sax 2012 GS-US-236-0102 [24]	Elvitegravir/cobicistat	347	Combination of all grades for AST/ALT elevations	AST: 15 ALT: 18	Prospective	Treatment-naive; 1% HBV; 5% HCV
Squillace 2017 SCOLTA [25]	Elvitegravir/cobicistat	280	Grade 1–2: AST/ALT 1.25–2.4× ULN (if baseline WNL) or baseline (if baseline value abnormal) Grade 3–4: AST/ALT ≥2.5× ULN (if baseline WNL) or baseline (if baseline value abnormal)	Grade 1–2; treatment-naive: 3.8 Grade 1–2; treatment-experienced: 8.5 Grade 3–4; treatment-naive: 1.3 Grade 3–4; treatment-experienced: 1	Prospective	72.1% treatment-experienced; 27.9% treatment-naive; 21.8% HCV
Min 2011 [26]	Dolutegravir	28	Combination of all grades for AST/ALT elevations	0	Prospective	Treatment-experienced and treatment-naive; integrase strand transfer

Reference	Drug(s)	No. of Study Patients	Hepatic Evaluation	Overall Incidence of Cases/100 Persons Exposed	Study Design	Patient Population
						inhibitor-naive
van Lunzen 2012 SPRING-1 [27]	Dolutegravir	205	AST/ALT ≥ 5× ULN	0.5	Prospective	Treatment-naive; 9% HCV
Raffi 2013 SPRING-2 [28]	Dolutegravir	411	AST/ALT ≥ 5× ULN	0.5	Prospective	Treatment-naive; 2% HBV; 10% HCV
Sax 2017 [29]	Bictegravir	64	Grade 2–4: AST/ALT ≥ 2.5× ULN	AST: 9 ALT: 6	Prospective	Treatment-naive
Gallant 2017 GS-US-380-1489 [30]	Bictegravir	314	Grade 3–4: AST/ALT ≥ 5× ULN	AST: 5 ALT: 2	Prospective	Treatment-naive
Sax 2017 GS-US-380-1490 [31]	Bictegravir	314	Grade 3–4: AST/ALT ≥ 5× ULN	AST: 2 ALT: 3	Prospective	Treatment-naive; 3% HBV; 2% HCV
Markowitz 2017 ECLAIR [32]	Cabotegravir	94	Grade 2–4: AST/ALT	1	Prospective	HIV-uninfected
Rizzardini 2020 FLAIR and ATLAS (Week 48 Pooled Data) [33]	Cabotegravir	591	AST/ALT ≥ 5× ULN	2	Prospective	Treatment-experienced; 7% HCV

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; ULN, upper limit of normal.

2.3. Protease Inhibitors

Protease inhibitors (PIs) are an integral part of HIV treatment, particularly for those who are treatment-experienced. PIs in contemporary use (atazanavir, darunavir, lopinavir) are paired with low-dose ritonavir or cobicistat as pharmacologic boosters [34]. As a drug class, PIs are associated with adverse effects including dyslipidemia, hepatotoxicity, and lipodystrophy [35]. PIs carry warnings for increased ALT/AST in those with viral hepatitis or pre-existing liver disease, acute hepatitis leading to hepatic failure and death. However, attribution of hepatic toxicity to PIs alone can be challenging given common confounding factors such as drug-drug interactions, polypharmacy, comorbidities, and co-infection with hepatitis B and/or C; a defined injury mechanism for the PI class is also lacking [36]. Table 4 describes a literature review of the incidence and evaluation of hepatotoxicity associated with PI use.

Table 4. Clinical trial evaluation of hepatic toxicity and incidence for protease inhibitors.

Reference	Drug(s)	No. of Study Patients	Hepatic Evaluation	Overall Incidence of Cases/100 Persons Exposed	Study Design	Patient Population
Torti 2009 MASTER and Italian ATV [37]	Atazanavir	2404	Grade 3–4: ALT > 5× ULN Grade 3–4 TBILI > 2.5× ULN	ALT: 6.4 TBILI: 44.6	Retrospective	Longitudinal multicenter cohort; 47.3% HCV, 7.3% HBV
McDonald 2012 CASTLE [38]	Atazanavir/ ritonavir	441	Grade 3–4: AST/ALT > 5× ULN Grade 3–4 TBILI > 2.5× ULN	AST: 3 ALT: 3 TBILI: 44	Prospective	Treatment-naive
Gallant 2017 [39]	Atazanavir/ ritonavir	348	Grade 3–4: AST/ALT > 5× ULN Grade 3–4 TBILI > 2.5× ULN GGT > 5× ULN	AST: 3 ALT: 3 TBILI: 66 GGT: 2	Prospective	Treatment-naive
	Atazanavir/ cobicistat	344		AST: 4 ALT: 4 TBILI: 73 GGT: 4		
Walmsley 2002 Study 863 [40] (M-98-863)	Lopinavir/ritonavir	326	Grade 3–4: AST/ALT > 5× ULN	AST or ALT: 4.5	Prospective	Treatment-naive

Reference	Drug(s)	No. of Study Patients	Hepatic Evaluation	Overall Incidence of Cases/100 Persons Exposed	Study Design	Patient Population
González-García 2010 Study 730 [40] (M05-730)	Lopinavir/ritonavir once daily	333	Grade 3–4: AST/ALT > 5× ULN	AST: 1 ALT: 1	Prospective	Treatment-naive
	Lopinavir/ritonavir twice daily	331		AST: 2 ALT: 1		
Pollard 2004 Study 888 [40] (M98-888)	Lopinavir/ritonavir	148	Grade 3–4: AST/ALT > 5× ULN	AST: 5 ALT: 6	Prospective	Single PI-experienced, NNRTI-naive
Zajdenverg 2010 Study 802 [40] (M06-802)	Lopinavir/ritonavir once daily	300	Grade 3–4: AST/ALT > 5× ULN	AST: 3 ALT: 2	Prospective	Treatment-experienced
	Lopinavir/ritonavir twice daily	299		AST: 2 ALT: 2		
Orkin 2013 ARTEMIS [41] Week 192	Lopinavir/ritonavir	346	Grade 2–4 AST/ALT Grade 2–4 TBILI	AST: 14.9 ALT: 15.8 TBILI: 5.5	Prospective	Treatment-naive, HCV or HBV 12.5% (DRV/r) 13.9% (LPV/r)
	Darunavir/ritonavir	343		AST: 12.9 ALT: 12.6 TBILI: 1.2		
Madruga 2007 TITAN [42]	Lopinavir/ritonavir	297	Grade 2–4 AST/ALT	AST: 9 ALT: 9	Prospective	Treatment-experienced, HCV or HBV 13% (LPV/r), 18%(DRV/r)
	Darunavir/ritonavir	298		AST: 7 ALT: 9		
Arasteh 2009 POWER-1, 2, 3 (Week 96 Pooled Data) [43]	Darunavir/ritonavir	467	Grade 2–4 AST/ALT Grade 2–4 TBILI	AST: 10 ALT: 9 TBILI: 2	Prospective	Extensive treatment-experienced

of GP120 and CCR5 for viral fusion and entry into CD4 cells. Maraviroc received FDA approval in August 2007 for use for treatment-experienced patients and carries a black box warning for hepatotoxicity. However, the combined clinical trial data and extended evaluation of maraviroc use over five years in close to 1000 patients do not justify the concern prompted by the black box warning [44].

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; DRV/r, darunavir/ritonavir; HBV, hepatitis B virus; HCV, hepatitis C virus; LPV/r, lopinavir/ritonavir; TBILI, total bilirubin; NNRTI, non-nucleoside reverse transcriptase inhibitor; ULN, upper limit of normal.

2.4.2. Ibalizumab

Ibalizumab-uiyk is a recombinant humanized monoclonal antibody. It exerts an antiviral effect by binding to domain 2 of the CD4 receptor. When the HIV GP120 protein binds to the CD4 receptor, steric hindrance from ibalizumab prevents the conformational changes necessary for fusion and viral entry into the cell.

Clearance of ibalizumab occurs via protein and cellular degradation [45]. Ibalizumab does not require hepatic phase 1 or 2 metabolism, nor is ibalizumab expected to concentrate in the liver, so toxic hepatic effects are not anticipated. This is reflected in the available clinical trial data to date in heavily treatment-experienced patients with advanced drug-resistant HIV infection.

2.4.3. Fostemsavir

Fostemsavir is a prodrug that is hydrolyzed to the active agent, temsavir. Temsavir binds directly to GP120 and prevents attachment to CD4 receptors.

Four dosing approaches for fostemsavir (400 mg twice daily, 800 mg twice daily, 600 mg once daily, and 1200 mg once daily) were all well tolerated in 200 patients through 48 weeks in AI438011, a phase 2 clinical trial that compared the safety and efficacy of fostemsavir vs. ritonavir-boosted atazanavir (each in combination with raltegravir and tenofovir DF) in treatment-experienced HIV-1-infected subjects. No discontinuations due to drug-related hepatic adverse effects occurred [46]. At 48 weeks, patients all transitioned to the fostemsavir 1200 mg once daily dosing scheme. Long-term follow-up of this cohort through 192 weeks (median duration of 4.5 years) yielded no discontinuations due to a hepatobiliary adverse effect, suggesting long term fostemsavir use is not associated with hepatoxicity [47].

3. Summary and Conclusions

The antiretroviral drugs used in the contemporary treatment of HIV infection are potent and well-tolerated. However, liver-related adverse drug reactions continue to be reported, albeit at lower rates than noted with earlier drugs. There is no established standard of care for hepatic injury secondary to ART. Elimination and/or minimization of other hepatotoxins (i.e., acetaminophen, alcohol) is a sensible first step. Screening for and treating viral hepatitis as indicated is also an important measure. A careful consideration of the risks and benefits of stopping or changing the suspected offending drug(s) in an ART regimen should be undertaken with the advisement of an HIV specialist.

Monitoring patients on ART for the emergence of liver injury, in particular in those with conditions that pose a higher risk, such as viral hepatitis and alcohol use, should remain a key component of the management of HIV infection.

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