ORIGINAL RESEARCH ARTICLE

Drug Saf 2011; 34 (11): 1101-1114
0114-5916/11/0011-1101/$49.95/0

Effect of Safety Issues with HIV Drugs on the Approval Process of Other Drugs in the Same Class

An Analysis of European Public Assessment Reports

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Abstract

Background: Knowledge on the safety of new medicines is limited at the time of market entry. Nearly half of all drugs used to treat HIV registered in the EU required ≥1 Direct Healthcare Professional Communication (DHPC) in the past 10 years for safety issues identified post-approval.

Objective: The aim was to evaluate the extent to which regulators and industry have addressed the risk of safety issues for HIV drugs based on prior experience with other drugs in the same class and whether doing so impacts development time of these drugs.

Methods: HIV drugs receiving ≥1 DHPC in the Netherlands between January 1999 and December 2008 were identified. Each drug with a DHPC ('index' drug) was paired with subsequently approved HIV drug(s) in the same class (Anatomical Therapeutic Chemical [ATC] 4th level) ['follow-on' drugs]. Characteristics of safety issues were extracted from the DHPCs of the 'index' drugs. European Public Assessment Reports (EPARs) were reviewed regarding whether the safety issues had been considered during development and approval. Consideration of previously identified safety issues in 'follow-on' drug applications was assessed regarding attention paid to adverse drug reaction (ADR) symptoms in pre-marketing studies, Summary of Product Characteristics (SmPC) and postmarketing commitments, and whether size of the safety population was in accordance with Regulatory guidelines. 'Index' drugs were also paired with drugs in the same class already on the market ('older' drugs). For 'older' drugs, we identified whether the safety issue led to appropriate changes in the current SmPC (January 2011) compared with the SmPC at the time of marketing authorization.

Clinical development time was assessed using time from first patent application to market authorization as proxy, and comparison was made between 'index' and 'follow-on' drugs.

Results: For 9 (43%) of the 21 centrally authorized HIV drugs, 11 serious safety issues that required a DHPC were identified. Two drugs were excluded from our analysis (DHPCs related to contamination/medication error). Six 'index' drugs were paired, each with one to six 'follow-on' drugs. Three concerned drug-drug interactions (DDIs); the other three were intracranial haemorrhage, neuromuscular weakness and severe skin/hepatic reactions. All but one 'follow-on' drug had information in the EPAR on that specific ADR (i.e. attention was paid to the ADR). The DDIs were addressed in pre-marketing studies and/or the SmPC. Two of the other ADRs were addressed by postmarketing surveillance commitments; intracranial haemorrhage was not addressed. Three safety issues for two 'index' drugs could not be paired with a 'follow-on' drug as no drug in the same class was approved after the corresponding DHPCs were issued.

Five of the nine safety issues were added to at least one of the current SmPCs for the 'older' drugs already on the market at the time of DHPC issue. Two safety issues were already in the SmPC of the 'older' drugs at time of market approval and two were not introduced into the SmPC of 'older' drugs.

Population size to assess short-term safety complied with the guidelines for four 'index', seven 'follow-on' and three 'older' drugs; population size to assess long-term safety complied for one, three and two drugs, respectively. For five drugs, EPARs did not provide adequate information on population size. No statistically significant difference in development time between 'index' and 'follow-on' drugs was found.

Conclusion: Generally, safety issues were taken into account in the approval process of other drugs in the class. The approaches were different and determined by the nature of the ADR. Taking safety issues into account in the approval process did not seem to impact on the time taken to perform the pre-approval clinical programme.

Background

As new drugs enter the market, their full safety profile is usually not fully established.[1-4] Clinical trials on which marketing applications are based are primarily designed to assess efficacy, have a relative short duration, include sometimes low-risk patients with narrowly defined co-morbidities, and generally do not include enough patients to identify safety issues that are relatively rare (incidence less than 1 : 1000).[5] Thus, it seems almost inevitable that new safety issues emerge post-approval. Serious safety issues requiring regulatory action are identified in approximately 10% of all marketed drugs, with higher rates for specific classes of drugs, such as drugs to treat HIV (referred to hereafter as HIV drugs).[6]

Most (serious) adverse drug reactions (ADRs) related to the drug's mechanism of action can be predicted and identified pre-approval. In contrast, the ADRs identified post-approval are often unpredictable (idiosyncratic) or due to off-target (unexpected) pharmacological effects. It is, therefore, important that for pharmacologically related new drugs (similar drug class or molecule) coming to the market, the risk of

ADRs that could be class-related are thoroughly evaluated in the drug development programme, in particular during the market authorization process.[7]

The evaluation of idiosyncratic ADRs may be particularly challenging in therapeutic areas with a large unmet medical need and the accompanying pressure to prevent unnecessary delay in access to new drugs. HIV/AIDS is still considered a disease with such high unmet medical need by the European Medicines Agency (EMA). Prolongation of the development phase for HIV drugs to evaluate a potential but rare risk might negatively affect public health by delaying access to potentially beneficial drugs.[8] Also, additional study requirements will add to the costs that are associated with development of new drugs, further hampering their development.[9] Therefore, for HIV drugs, 'accelerated approval' in Europe is possible through approval procedures under Exceptional Circumstances or Conditional Approval, allowing drugs to be approved with more limited clinical data packages.[10-12]

However, a considerable number of new serious ADRs have been identified with these HIV drugs post-approval. The EMA has acknowledged this risk and stipulated that safety issues based on class experience may be relevant for subsequent new HIV drugs and should be monitored long term using appropriate methods.[7,13]

In this study, we aim to evaluate the extent to which regulators and industry have addressed the risk of safety issues for HIV drugs based on experience with other drugs in the same class. In a separate exploratory analysis we assessed the impact of (increasing) regulatory requirements on development times for new HIV drugs.

Methods

Study Drugs

All HIV drugs approved by the EMA from the start of the EMA Central Procedure on 1 January 1995 until 31 December 2008 were reviewed. We identified those HIV drugs with new important safety issues that required a Direct Healthcare Professional Communication (DHPC) in the period 1 January 1999 to 31 December 2008, referred to as 'index' drugs. DHPCs are paper-based letters sent by the Marketing Authorization Holder (MAH), in cooperation with the regulatory authorities, to relevant healthcare professionals. In the US, the equivalent of DHPCs are Dear Healthcare Professional Letters.[14] We excluded those DHPCs with safety issues that were related to the production process, route of administration or to the device. First, HIV drugs from the same drug class (Anatomical Therapeutic Chemical [ATC] 4th level)[13] that received marketing approval after the initial safety issue with the 'index' drug were studied (referred to as 'follow-on' drugs) [figure 1]. Second, we studied those HIV drugs that were already approved at the time the 'index' drug received a DHPC (referred to as 'older' drugs).

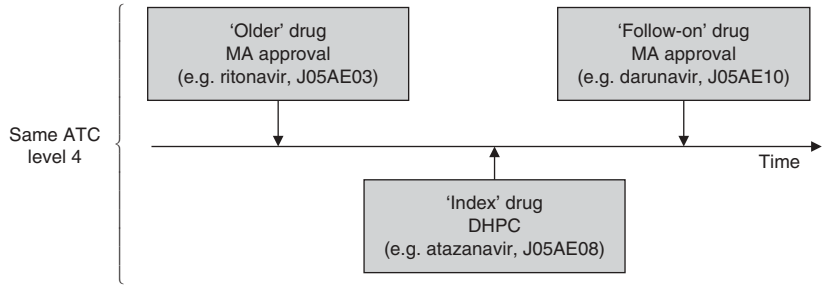

Fig. 1. Definition of 'index', 'follow-on' and 'older' drugs. 'Index' HIV drugs are defined by a Direct Healthcare Professional Communication (DHPC) issued for a new drug safety issue. 'Follow-on' drugs are HIV drugs in the same class (Anatomical Therapeutic Chemical [ATC] 4th level) as the 'index' drug that were granted marketing authorization *after* the date of the DHPC. 'Older' drugs were HIV drugs in the same ATC-4 class as the 'index' drug that were granted Marketing Authorization (MA) *before* the DHPC was issued.

Table I. Scoring system of European Public Assessment Reports

Grade	Markers/symptoms of the ADR seen or evaluated	Markers/symptoms linked to the possibility of the ADR	Investigation or discussion on the presence or absence of the ADR
– (insufficient)	No	No	No
+	Yes	No	No
++	Yes	Yes	No
+++ (excellent)	Yes	Yes	Yes

ADR = adverse drug reaction.

Characteristics of Safety Issues

DHPCs were retrieved from the Dutch Medicines Evaluation Board (MEB) website.[15] The data extracted from DHPCs were as follows:[6]

- type of ADR;
- incidence rate of the ADR;
- the research method by which the safety issue was identified (e.g. clinical trials, spontaneous ADR reports or epidemiological studies);
- precursory symptoms or markers identified.

Review Procedure

European Public Assessment Reports (EPARs), which contain publicly available summary reports of the clinical dossier that was the basis for the marketing authorization, were retrieved from the EMA website.[16] Two reviewers (AHA and PGMM) evaluated the clinical studies, as presented in the EPARs, and independently extracted the data. Discrepancies were resolved by consensus. This was done for both the HIV drugs for which the safety issue was initially communicated postmarketing ('index' drugs) and for the HIV drugs of the same class (ATC 4th level) ['follow-on' drugs][13] that received a marketing authorization after the safety issue was communicated by the DHPC.

Data Extracted

The EPARs were reviewed to establish if an earlier-identified safety issue had been critically addressed in the pre-clinical (animal) studies, pharmacokinetic studies and clinical trials. This was done for both 'index' and 'follow-on' drugs. Each issue was scored on pre-specified criteria regarding the identification of the ADR of interest, in line with the EMA guideline for clinical development of HIV drugs.[7] The score ranged from – (insufficient) to +++ (excellent) with respect to the effort put in establishing and describing these ADRs pre-approval (table I).

We compared the size of the study population of the 'index' drugs with their respective 'follow-on' drugs, as well as for 'older' drugs. Both short- and long-term safety populations were identified for which minimal requirements were set by the EMA as being 1500 subjects exposed and 100 patients treated for at least 1 year, respectively.[7,17,18]

We recorded whether the safety issue identified was also reflected in the initial Summary of Product Characteristics (SmPC) of each product at the time of marketing authorization, as retrieved from the European Commission website.[19] The SmPC is a document that includes information for the health professional on how to use the drug effectively and safely. For the 'older' drugs we identified whether the safety issue led to a change in the current SmPC (January 2011) compared with the SmPC at the time of marketing authorization that was approved before the safety issue in the 'index' drug had occurred.

Finally, it was recorded whether the drugs obtained a marketing authorization through the Exceptional Circumstances or Conditional Approval procedure.[20,21]

Clinical Development Time

A patent search in the Newport Horizon Global™ database[22] was performed. The clinical development time was defined as the time from the date of first patent application until the date of marketing authorization. Patent time was used as proxy for clinical development time as developers of drugs generally apply for a patent when the development process of the drug has not reached the point of clinical trials.[23]

Regression analysis was used to probe for a possible trend in clinical development time, and the Mann-Whitney U test was used to probe for a difference in clinical development time between the 'older', 'index' and their 'follow-on' drugs.

Results

Characteristics of Safety Issues

For 9 (43%) of the 21 centrally authorized HIV drugs, 11 serious safety issues that required a DHPC were identified (figure 2). We excluded two safety issues since they did not concern an ADR related to the pharmacology of the drug. Three of nine safety issues were drug-drug interactions (DDIs), which resulted in subtherapeutic plasma levels of the antiviral drug or loss of virological response due to mutation of the virus. Another three safety issues were idiosyncratic ADRs, including intracranial haemorrhage, neuromuscular weakness and severe skin/liver reaction. Assessment of incidence rate was only possible for two of the safety issues. Three safety issues could not be paired with a 'follow-on' drug as no drug in the same class was approved after the corresponding DHPCs were issued; these concerned drug hypersensitivity, myocardial infarction (MI) and renal disorder (table II).

Evaluation of Identified Safety Issues for Class-Related Drugs

The impact of six safety issues could be evaluated in the EPARs of one to six 'follow-on' drugs per safety issue (table III).

In the case of a drug-drug interaction with St John's wort by indinavir, described in table II, all 'follow-on' drugs underwent non-clinical (*in vitro*) and/or clinical pharmacokinetic investigations to assess the metabolism of the active compounds (table III). All these drugs were determined to be cytochrome P450 (CYP) 3A4 substrates as well as inhibitors or inducers of the isoenzyme and received a contraindication for concomitant use with St John's wort at the time of market authorization.[25-30] All three of the 'older' drugs did not mention an interaction with St John's wort in their original SmPC[31-33] but received a

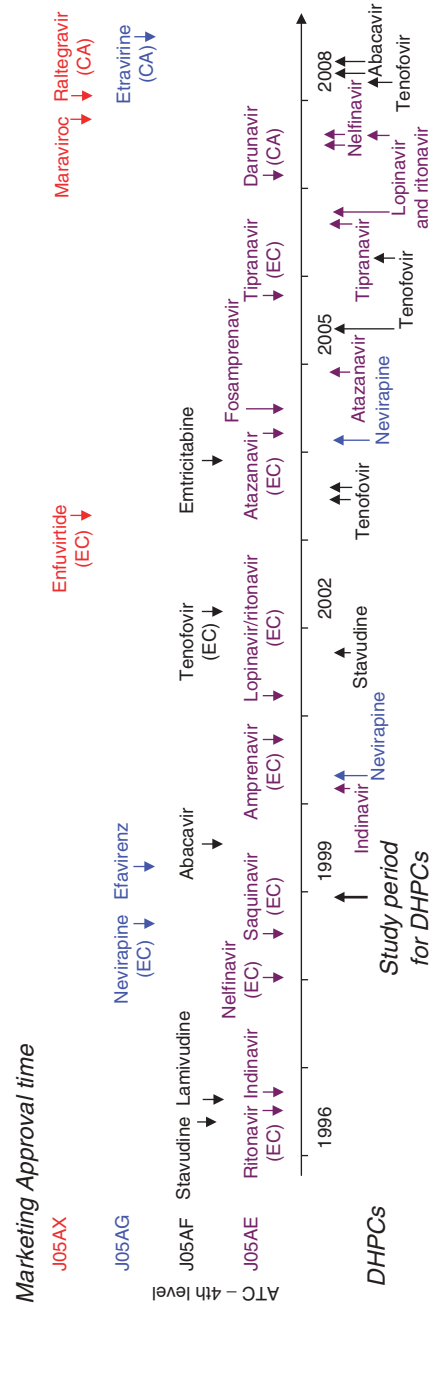

Fig. 2. Timeline of approvals and safety risk communication (Direct Healthcare Professional Communication [DHPC]) of HIV drugs. **ATC** = Anatomical Therapeutic Chemical; **CA** = Conditional Approval market authorization; **EC** = Exceptional Circumstances market authorization; Arrows above the x-axis represent the date of marketing approval and arrows below the x-axis represent the date of the DHPC.

Table II. Characteristics of the study drugs and adverse drug reactions (ADRs)

Drug (approval date)	DHPC date	ADR	Symptoms and/or mechanism of ADR	Discovery of ADR as presented in DHPC	Comment
Indinavir (Oct 1996)	Mar 2000	DDI with St John's wort	Plasma levels of indinavir lowered significantly Interaction is via the CYP metabolic pathway	ADR was discovered in a post-approval clinical trial (DDI study)	
Atazanavir (Mar 2004)	Dec 2004	DDI with omeprazole	Plasma levels of atazanavir lowered significantly Uptake of atazanavir is inhibited by the change in acidity Other PPIs and preparations that increase gastric pH are likely to have a similar effect	ADR was discovered in a post-approval clinical trial (DDI study)	
Nelfinavir (Jan 1998)	(i) Jun 2007[a] (ii) Jul 2007[a]	(i + ii) Therapeutic product contamination	Excluded from analysis		Not related to pharmacology
Lopinavir/ritonavir (Mar 2001)	(i) Sep 2006[a] (ii) Aug 2007[a]	(i + ii) Information capable of leading to medication error	Excluded from analysis		Not related to pharmacology
Tipranavir (Oct 2005)	Aug 2006	Intracranial haemorrhage	Increased risk of bleeding and prolonged bleeding	ADR was discovered in a post-approval clinical trial (DDI study). 14 cases (8 fatal) were reported, giving the incidence rate of 0.23%.	
Stavudine (May 1996)	Sep 2001	Neuromuscular weakness mimicking Guillain Barré syndrome	Non-specific symptoms and signs compatible with the acidosis syndrome appeared to precede the development of neuromuscular problems. Early symptoms of the lactic acidosis syndrome include nausea, vomiting, diarrhoea and abdominal pain, rapid and deep breathing, cramps, myalgia and paresthesia	The DHPC did not mention how the ADR was discovered. However, it was noted that 14 cases (5 fatal) have been reported	
Abacavir (Jul 1999)	Mar 2008	Drug hypersensitivity	HLA-B*5701 genotypes are sensitive to this ADR only. Patients should be genoptyped before initiating abacavir treatment	The PREDICT-1 double-blind clinical trial demonstrated that this already known ADR occurred in 48–61% of HLA-B*5701 genotypes and in <4% of non-carriers	No subsequent drug approved
	Apr 2008	Myocardial infarction	No established MoA, but MI had been identified as a possible risk in the pre-approval programme. Cardiovascular risk factors such as hypertension, dyslipidaemia and/or diabetes should be monitored	ADR was confirmed in a postmarketing cohort study.[24] The absolute MI rate was 6.1/1000 patient years	No subsequent drug approved

Continued next page

Table II. Contd

Drug (approval date)	DHPC date	ADR	Symptoms and/or mechanism of ADR	Discovery of ADR as presented in DHPC	Comment
Tenofovir (Feb 2002)	(i) Jul 2003 (ii) Oct 2003 (iii) Mar 2005	(i+ii+iii) Decreased efficacy: pharmacodynamics interaction with lamivudine + abacavir combination and lamivudine + didanosine combination	Mutation in the virus resulted in resistance and lack of virological response Seems to be related to the same types of mutations in the virus, and genotyping of the viral load was advised	ADR was discovered in a post-approval clinical trial (combination trials). 80 cases (c.a. 50%) of patients also using lamivudine + abacavir combination and 22 cases (c.a. 90%) of patients also using lamivudine + didanosine combination suffered virological non-response	
	(iv) Mar 2006 (v) Apr 2008	(iv+vi) Renal disorder; (acute) renal failure, nephrogenic diabetes insipidus	Creatinine clearance and serum sodium phosphate should be monitored	ADR was discovered with postmarketing data surveillance (spontaneous ADR reporting)	No subsequent drug approved
Nevirapine (Feb 1996)	(i) Apr 1999 (ii) Apr 2000 (iii) Feb 2004	(i+ii+iii) Severe skin/liver reaction	Changes in liver tests and rash in the first weeks of treatment High count of CD4+ cells is a risk factor	ADR was discovered with postmarketing data surveillance (spontaneous ADR reporting)	

a These DHPCs were excluded from the assessment of European Public Assessment Reports.

c.a. = approximately; **CYP** = cytochrome P450; **DDI** = drug-drug interaction; **DHPC** = Direct Healthcare Professional Communication; **MI** = myocardial infarction; **MoA** = Mechanism of Action; **PPI** = proton pump inhibitor.

contraindication in the SmPC valid in January 2011.[25-37]

Atazanavir's pH-dependent absorption, leading to lower plasma levels when co-administered with proton pump inhibitors (PPIs), was studied in appropriate pharmacokinetic interaction studies for the 'follow-on' drugs, i.e. tipranavir and darunavir. No discernable interaction was observed for concomitant administration of darunavir with a PPI and, as a consequence, no contraindication was included in the SmPC. An interaction study with an antacid but not with a PPI was performed for tipranavir. Based on the lowered plasma levels of tipranavir, a warning was included in the SmPC[29] to separate intake of antacids and tipranavir by 2 hours. Four of the seven 'older' drugs had a comment on acid-reducing agents but no comment on PPIs in the 'interactions' section of their original SmPC.[25,28,33,38] In the current January 2011 version of the SmPC, all drugs, except indinavir, had a comment on either acid-reducing agents or PPIs in their 'interactions' section.[35-37,39-41]

Intracranial haemorrhage was reported as a serious ADR of tipranavir. The 'follow-on' drug, darunavir, showed some effects on platelets in rats. It was claimed that this effect did not lead to bleeding and no further specific investigation of bleeding or the occurrence of intracranial haemorrhage was performed in clinical trials. For the eight 'older' drugs, none had any mention of haemorrhage or bleeding, except in patients with haemophilia, in neither the original SmPC[25-28,31-33,38] nor the version valid in January 2011.[35-37,39-43]

Regarding neuromuscular weakness that occurred with stavudine, a discussion on lactic acidosis (a precursory symptom) in clinical trials was present in the EPARs for both 'follow-on' drugs, tenofovir and emtricitabine, and a warning was included in their SmPCs.[44,45] Lamivudine, one of two 'older' drugs, had no mention of lactic acidosis or neuromuscular weakness in its original SmPC.[46] The original SmPC for abacavir was not available on the European Commission website, but there was a mention of lactic acidosis in its original patient information leaflet.[47] Both drugs have a discussion of lactic acidosis in the SmPC valid in January 2011.[48,49]

Table III. Evaluation of identified adverse drug reactions (ADRs) for study drugs in drug development and product information[a]

	Pre-clinical studies	Pharmacokinetic studies	RCTs	Warning or contraindication in SmPC
Protease inhibitors				
Indinavir (DDI with St Johns wort)	+	–	NA	No
amprenavir	+	+	NA	Yes
lopinavir/ritonavir	+	+	NA	Yes
atazanavir	+	+	NA	Yes
fosamprenavir	+	+	NA	Yes
tipranavir	+	–	NA	Yes
darunavir	+	–	NA	Yes
Atazanavir (DDI with omeprazole)	–	+	NA	Yes
tipranavir	+	+	NA	Yes
darunavir	–	+++	NA	No[b]
Tipranavir (intracranial haemorrhage)	++	–	++	Yes
darunavir	+	–	–	No
Nucleoside and nucleotide reverse transcriptase inhibitors				
Stavudine (neuromuscular weakness)	–	–	–	No
tenofovir	++	–	++	Yes
emtricitabine	–	–	++	Yes
Tenofovir (DDI with lamivudine/abacavir or lamivudine/didanosine)	++	+	+	No
emtricitabine	+++	NA	NA	Yes
Non-nucleoside reverse transcriptase inhibitor				
Nevirapine (liver/skin reaction)	+	–	++	Yes
etravirine	+	–	++	Yes

a Source: EPARs.

b EPAR has shown that a warning in SmPC is not required.

DDI = drug-drug interaction; **EPAR** = European Public Assessment Report; **NA** = not applicable; **RCTs** = randomized controlled trials; **SmPC** = Summary of Product Characteristics; **–** indicates not mentioned in the EPAR or SmPC; **+** indicates evidence is present, but discussion is poor or follow up on the evidence is not performed; **++** indicates discussion present on evidence of the ADR or evidence that suggests the ADR is not likely; **+++** indicates a good discussion on the ADR, either that the ADR is possible or not at all likely.

For tenofovir, where a pharmacodynamic interaction with lamivudine/abacavir or lamivudine/didonasine was observed, the 'follow-on' drug, emtricitabine, was tested *in vitro* for resistance of the known mutation type virus but only for lamivudine alone and not for the combination of lamivudine with abacavir or didonasine. The SmPC mentions that combination therapy with lamivudine cannot be recommended as specific interaction studies have not been performed.[45] For the three 'older' drugs, there was no mention of the mutated virus strain in the SmPC of stavudine and lamivudine,[46,50] while it could not be determined for abacavir since the original SmPC was not available. The mutated virus strain is discussed in the January 2011 version of the SmPC for lamivudine and abacavir, but not stavudine.[48,49,51]

Following the severe skin and/or hepatic reaction of nevirapine, rash was reported in clinical trials of the 'follow-on' drug, etravirine, and hepatic events were slightly more frequent than for placebo. Rash was included as a common adverse effect in the SmPC.[52] For efavirenz, the single 'older' drug, a rash was listed as a possible adverse effect in both the original and January 2011 versions of the SmPC.[53,54]

Three safety issues could not be paired to a 'follow-on' drug and were only assessed for 'older' drugs, already on the market when the DHPC was issued. All three safety issues were for

nucleoside and nucleotide reverse transcriptase inhibitors.

For the drug hypersensitivity associated with abacavir and described in table II, all four 'older' drugs did have a contraindication for the use of the drug when the patient was known to have hypersensitivity to the drug in both the original and January 2011 versions of their SmPC.[44-48,50,51,55,56]

For the MI associated with abacavir, and described in table II, none of the four 'older' drugs had any discussion on MI or precursory symptoms in either the original or January 2011 version of their SmPC.[44-48,50,51,55,56]

For the renal disorder associated with tenofovir and described in table II, three of the 'older' drugs had no mention of renal disorders in the 'undesired effect' section of either the original or January 2011 version of their SmPC.[45,46,48,50,51,56] For abacavir, the original SmPC could not be accessed and its patient information leaflet had no mention of renal disorders in the 'adverse effect' section.[47] Abacavir did have renal failure listed as a possible undesired affect in the SmPC valid in January 2011.[49]

Size of Safety Population

Less than 1500 subjects (patients and healthy volunteers) were included in the clinical development programme of six (two 'index', one 'follow-on' and three 'older') HIV drugs in our study. The programme of two 'follow-on' drugs (amprenavir and fosamprenavir) included more than 1000 subjects, but for these two we could not assess properly whether the number exceeded 1500 subjects (table IV). Two of the 'index' drugs did not have the required long-term population of 100 patients treated for at least 48 weeks. Both drugs were licensed under exceptional circumstances. For one 'follow-on' drug the information in the EPAR was not sufficient to assess the number of the long-term participants. One 'older' drug did not have the required long-term population of 100 patients treated for at least 48 weeks and for two 'older' drugs the information in the EPAR was not sufficient to assess the number of the long-term participants. For the remaining 12 drugs, the EPARs indicated that at least 100 patients were treated for 48 weeks with the new HIV drug.

Eleven (61%) of the 18 HIV drugs were approved under Exceptional Circumstances or Conditional Approval; four were 'index', four were 'follow-on' and three were 'older' drugs. These drugs were more likely (81.8%) than the regularly approved drugs (28.6%; $p = 0.024$) to be non-compliant with the guidelines on safety population and long-term population (table IV).

Clinical Development Times

The median time from patent application to marketing authorization approval for all study drugs was 8.4 years, ranging from 2.7 to 15.8 years. No significant difference was shown in the median time from patent application to marketing authorization approval between the 'older' drugs and 'index' drugs (median 6.7 years, interquartile range [IQR] 4.6–9.2) and their 'follow-on' drugs (median 8.8 years, IQR 7.1–12.8; $p = 0.689$). Clinical development time (years) did significantly increase over time for the studied HIV drugs per year of market approval, on average by 0.49 years per calendar year (95% CI 0.04, 0.93; $p = 0.033$) [table IV].

Discussion

Our study shows that in the clinical development for the majority of new HIV drugs, attention is paid to previously identified ADRs of drugs approved earlier in the same pharmacological class without significantly affecting drug development time. The ADRs are discussed in the EPARs and, if appropriate, relevant information is included in the SmPC. For drugs already on the market, the occurrence of a safety issue for a drug of the same drug class seems to result in a re-evaluation of the safety information in the SmPC for most of the 'older' drugs.

In our study, we show that EMA guidelines for development of HIV drugs, requiring that ADRs that have been observed for earlier-approved drugs are evaluated in clinical development programmes of new HIV drugs, were followed.[7,17,18]

Pre-marketing clinical trials are generally considered insufficient to establish the full safety profile of a drug. Furthermore, when ADRs have been identified they are not translated into clear warnings or usable knowledge for the healthcare professional.[5] However, we find the latter is not the case for the class-related safety issues we studied. All but one of these ADRs were generally carefully evaluated pre-approval and resulted in appropriate warnings in the SmPC.[7] In the case of intracranial haemorrhage, identified with tipranavir, this issue was not discussed in the EPAR of darunavir, the only subsequently approved protease inhibitor in our study.[57] We cannot rule out that evaluation of class-related safety issues was triggered by something other than the DHPC. A general effect of acid-reducing agents was described for four of seven 'older' protease inhibitors, but none specifically mentioned PPIs. Most of the SmPCs valid in January 2011 do mention PPIs specifically as is the issue evaluated in pharmacokinetics programmes of the 'follow-on' drugs.

Most SmPCs of 'older' drugs did change to include class-related safety issues at sometime between approval and January 2011. This suggests that a re-evaluation of the safety of 'older' drugs is performed and SmPCs change as a result. However, there were exceptions. No change to the SmPC of indinavir was made, despite evidence that the absorption of indinavir is also dependent on the pH.[58] Since all other protease inhibitors do have a comment on possible interaction with

Table IV. Evaluation of population exposed to study drugs and the duration of drug development

Drug	Population		Time from patent to MA (y)	Approval type	Year of approval
	long-term population[a]	safety population[b]			
Protease inhibitors					
Ritonavir (O)	Inadequate information[c]	374	2.7	EC	1996
Saquinavir (O)	>180	574	5.8	EC	1996
Indinavir (I)	~100	~2 000	3.4	Regular	1996
Nelfinavir (O)	24	819	3.3	EC	1998
Amprenavir (F)	>100[d]	>1 000	7.1	EC	2000
Lopinavir/ritonavir (F)	Inadequate information[c]	2 000	7.2	EC	2001
Atazanavir (I)	>200	2 244	6.9	EC	2004
Fosamprenavir (F)	>470	>1 000	6.3	Regular	2004
Tipranavir (I)	57	3 195	10.5	EC	2005
Darunavir (F)	1056	1 783	13.5	CA	2007
Nucleoside and nucleotide reverse transcriptase inhibitors					
Stavudine (I)	>100[d]	>13 000	8.4	Regular	1996
Lamivudine (O)	Inadequate information[c]	18 889	6.5	Regular	1996
Abacavir (O)	147	4 400	10.0	Regular	1999
Tenofovir (I)	75	1 050	15.8	EC	2002
Emtricitabine (F)	1348	2 136	12.8	Regular	2003
Non-nucleoside reverse transcriptase inhibitor					
Nevirapine (I)	~450	906	7.6	EC	1998
Efavirenz (O)	408	2 437	5.8	Regular	1999
Etravirine (F)	279	1 041	8.8	CA	2008

a Number of patients exposed to the drug for at least 1 year.

b Number of patients and healthy volunteers exposed to the drug.

c EPAR did not provide sufficient information to estimate the population.

d Information in EPAR is unclear and the population was estimated.

CA = Conditional Approval; **EC** = Exceptional Circumstances; **EPAR** = European Public Assessment Report; **F** = 'follow-on' drug; **I** = 'index' drug; **O** = 'older' drug; **MA** = Marketing Authorization.

acid-reducing agents, this seems clearly a class-related safety issue. On the other hand, no 'older' drug had a comment on intracranial haemorrhage in their January 2011 SmPC, and since the 'follow-on' drug did not have investigation on intracranial haemorrhage in its EPAR this suggests that the safety issue is regarded as idiosyncratic rather than class-related. The MI associated with abacavir could also be regarded as idiosyncratic,[24] thus explaining the lack of SmPC changes for 'older' drugs. Where the safety issue is already included in the original SmPCs of 'older' drugs, e.g. in the case of hypersensitivity of abacavir, it could be that there is always a hypothetical possibility of the safety issue and the comment is added as routine.

Development time of the 'follow-on' drugs – drugs sharing the same pharmacological class – did not significantly increase compared with the 'index' drugs and 'older' drugs. There was one exception; indinavir had a shorter development time than all its 'follow-on' drugs, although slightly longer than the 'older' drug ritonavir. Indinavir and ritonavir were two of the first protease inhibitors to be approved. They opened up the route for new potent treatment combinations that became known as highly active antiretroviral therapy (HAART).[59] Thus, indinavir and ritonavir were regarded as an important breakthrough in the treatment of HIV and this may have led to their very short clinical development time. As for other drugs, development times over the studied years are observed to be increasing.[60]

Our research showed that HIV drugs are likely to be licensed under Exceptional Circumstances or Conditional Approval and are more likely to receive a DHPC than other centrally approved drugs.[6,61] This finding suggests that because of the complex nature of the disease or the pressure put on regulators to approve the marketing applications quickly,[12,62,63] HIV drugs are more at risk of safety issues arising post-approval. The size of the safety population was, in the majority of the study drugs, in line with the regulatory guidelines.[18] Licensing under Exceptional Circumstances or Conditional Approval creates the possibility of including fewer subjects in clinical trials, and we found that the size of the safety population did significantly correlate with the type of marketing authorization of HIV drugs. In general, drugs licensed under Exceptional Circumstances and Conditional Approval are less likely to fulfil the requirements of more than 1500 subjects exposed. However, in another study, we showed that for all centrally approved drugs in the EU, drugs approved through these procedures were no more likely to receive a DHPC than were drugs approved through the standard procedure.[34] Furthermore, in this study, we did not find a correlation between evaluation of safety issues for drugs approved through the Exceptional Circumstances/Conditional Approval versus standard procedure.

Limitations of the Study

We collected most of our data from EPARs that do not provide access to confidential data. However, one may assume that all relevant clinical efficacy and safety data are present in the EPARs; the available data should therefore be sufficient to draw conclusions. The use of patent application dates is a weak proxy for clinical development time. The time from patent application to the beginning of pre-clinical or clinical research can vary depending on several issues, but generally companies do apply for patents before requesting ethics approval of their clinical trials.[23] We are not aware of a central database of clinical trial applications covering our study period; therefore, time from first patent application to marketing authorization was the best available proxy for clinical development time. The study evaluated only HIV drugs and cannot be extrapolated to other types of drugs. However, we could expect comparable results for other drug classes. Regulatory guidelines for clinical development of various drug classes or disease areas acknowledge class-related adverse effects. Finally, we only had access to DHPCs issued after 1 January 1999[6] and cannot evaluate if any DHPCs were issued for HIV drugs between 1995 and 1998 and how this was followed up.

Conclusion

We found that in the case of HIV drugs, knowledge on ADRs gained from earlier-approved

drugs has been used in the development of new drugs in the same class. We were not able to demonstrate that this affects clinical development times.

Acknowledgements

The authors would like to thank Margje Monster-Simons for her help with the EPAR assessment. This study was performed in the context of the Escher project (T6-202), a project of the Dutch Top Institute Pharma. The funder did not have any role in the design or execution of the study. The authors have no conflict of interest to declare.

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