The extent and limitations of the European regulatory perspective on antiretroviral agents – focus on the aging population

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The evidence base for the approval of antiretroviral agents in Europe

- **Two or more pivotal trials with efficacy endpoints at 48 (Treatment naive) or 24 (treatment experienced) weeks of therapy**
- **Virological endpoint, based on the ”surrogacy of viremia” (suppression of viral replication prevents progression of immune deficiency, AIDS and AIDS-related death)**
- **Study duration (treatment naive) at least 96 weeks to gather safety information**
- **Approximately 1000-1500 patients exposed at the time of approval**
- **Study participants tend to be male and mostly between 30-40 years of age. Example: Among more than 600 patients treated with rilpivirine in the pivotal trials, 4 were above 65 years**

Specific concerns about drug therapy in older subjects

Pharmacokinetic differences (the way the body handles the drug):

- **Reduced renal function (However, this can readily be estimated and doses adjusted)**
- **Comorbidities – polypharmacy – drug-drug interactions**
- **Reduced hepatic elimination of drugs in the absence of liver disease mainly relevant for the very elderly**

Pharmacodynamic differences (the effects of the drug on the body):

- **Less tolerance for CNS effects**
- **Lower bone mineral density**
- **Higher cardiovascular risk**

The risk management plan (RMP)

- **All drugs that are approved have an RMP**
- **Risks to be covered are drug specific, not disease specific**
- **Always includes ”routine pharmacovigilance” (spontaneous reporting of adverse events from clinical practice)**
- **Specific identified safety concerns may lead to post-marketing commitments from the company (specific studies to be conducted)**
- **In the absence of specific concerns, lack of data in subgroups such as the elderly may be defined as ”missing information” in the RMP**
- **Regulators identify the specific concerns (e.g., bone events for products containing Tenofovir disoproxil Fumarate); it is up to the company, however, to propose the means to address the concern, in a way that is acceptable to regulators (e.g., a particular post-marketing study)**
- **Regulators cannot force a company to use a specific means to cover an identified risk, if the company comes up with an alternative deemed scientifically acceptable**

Example: From Stribild® RMP

Bone events due to proximal renal tubulopathy/loss of bone mineral density	TDF	Routine pharmacovigilance activities including monitoring and review in PSURs. Clinical studies (GS-99-903, GS-US-236-0103, GS-US-174-0102, GS-US-174-0103, GS-US-174-0115, GS-US-174-0121, GS-US-104-0321, GS-US-104-0352) Planned clinical study in HBV infected pediatric patients (GS-US-174-0144) Planned cross-sectional study to assess bone mineral density (BMD) in HIV-1 infected patients of interest who include those over 50 years of age, particularly women, and who have been exposed to TDF for at least 3 years (GS-US-104-0423). Clinical study of STB in HIV-1 infected women (GS-US-236-0128) Planned post-authorization safety study of HIV-1 infected pediatric patients

Example: the D:A:D study

- **Academia-industry collaboration requested by the EMA and agreed by companies to meet concerns about the cardiovascular safety of HIV drugs in late 1990s**
- **Subsequently expanded to investigate renal-, liver- and malignancy events in relation to antiretroviral drug exposure**
- **A very significant long term follow-up cohort of patients with HIV infection – and therefore of a population aging with HIV infection**
- **For some products, the D:A:D study was/is cited in the RMP as a means to cover specific concerns; in other cases, D:A:D did not match any specific identified risk for the product**
- **The legal obligation of the company is to adress the safety concern in a scientifically satisfactory way; not to conduct a specific study**
- **It is not within the legal remit of EMA to specifically demand that the companies continue support for the D:A:D study**

Drug-drug interactions in the guideline for development of antiretrovirals

- **“Focus on the safe and effective co-administration of drugs for HCV, HBV, invasive fungal and bacterial infections including mycobacterial diseases, hormonal contraceptives, drugs for the treatment of metabolic abnormalities such as hyperlipidaemia, gastro-oesophageal reflux and drugs used in the management of substance dependence”**
- **The focus is not on the common morbidities of the elderly**
- **Numerous relevant drugs are used to treat age-related comorbidities; impossible to specifically study all of these – importance of the mechanistic understanding of the DDI potential**

Drug development outside the antiretroviral treatment paradigm

- **Drug development for HIV not directly aiming at suppression of HIV replication forms a specific challenge where there is little regulatory experience**
- **Examples include various approaches to HIV cure, as well as attempts to target stipulated indirect effects of HIV infection (e.g., chronic inflammation with consequences such as cardiovascular events)**
- **The ultimate goals of therapy may be long-term and not easily captured in a clinical trial context; requires the establishment of credible surrogate markers of efficacy.**
- **Treatment approaches may pose identified risk to trial participants (e.g., carcinogenicity, reproductive toxicity)**