

# Drug-induced nephrotoxicity analysis in HIV therapy; case study using creatinine biomarker data from GOBIOM database

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## Background

Antiretroviral therapy (ART), though made a significant impact on the mortality and morbidity of the patients with HIV infection, can cause severe nephrotoxicity which can lead to acute and chronic kidney diseases. Creatinine a breakdown product of creatine phosphate in muscle and a byproduct of muscle metabolism is an important indicator of renal health and often measured in HIV patients to assess the drug induced renal toxicity. Current research activities are focusing more on the identification of the biomarkers that might provide a more sensitive and rapid means of detecting acute kidney injury. Elevated levels of creatinine have been shown to be of value in diagnosing drug-induced nephrotoxicity.

## GOBIOM Database

GVK BIO Online Biomarker Database (GOBIOM) is a comprehensive database of validated and putative biomarkers providing insights into relationship between biomarker and disease. The user friendly interface facilitates analyzing and visualizing the biomarker data, which can aid in better understanding of biological processes involved in specific pathology, identification of new drug targets and accelerated drug discovery, development of personalized medicine strategies utilizing companion diagnostics, development/validation of diagnostic assay kits and monitoring the safety of experimental or marketed drugs. GOBIOM in a single platform provides clinical and preclinical information on biochemical, genomic, imaging, metabolite, clinical scoring scales and cellular markers spanning over 18 different therapeutic areas, covering 1064 therapeutic indications with its reported utilities like diagnosis, prognosis, monitoring disease progression, treatment response, surrogate, efficacy and toxicity.

## GOBIOM Statistics

Therapeutic Area	# Biomarkers	# Indications
Certain conditions originating in the perinatal period	7	5
Congenital malformations, deformations and chromosomal abnormalities	97	36
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	263	37
Diseases of the circulatory system	2717	166
Diseases of the digestive system	1185	56
Diseases of the ear and mastoid process	5	2
Diseases of the eye and adnexa	194	29
Diseases of the genitourinary system	814	40
Diseases of the musculoskeletal system and connective tissue	2459	50
Diseases of the nervous system	1656	79
Diseases of the respiratory system	1088	39
Diseases of the skin and subcutaneous tissue	748	23
Endocrine, nutritional and metabolic diseases	2388	136
Infectious and parasitic diseases	1139	66
Injury, poisoning and certain other consequences of external causes	460	19
Mental and behavioral disorders	1223	53
Oncology	14365	227
Others	3342	1
<b>Total :</b>	<b>31850</b>	<b>1064</b>

## Objective

Our objective was to evaluate the published information on all clinical studies to assess ART induced nephrotoxicity by tracking the levels of creatinine in HIV patients.

Analysis of following was done-

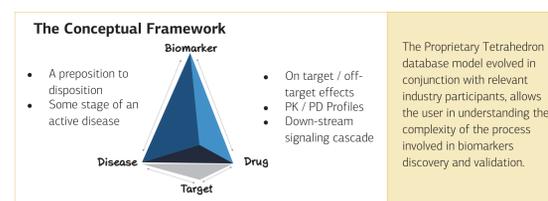
- ✦ Evaluation of biomarkers of ART induced nephrotoxicity in HIV patients
- ✦ Assessment of toxicity profiles of different anti-retroviral drugs by measuring creatinine levels
- ✦ Percentage difference of creatinine levels from baseline in HIV patients who underwent ART to assess the severity of the nephrotoxicity
- ✦ Incidence of drug induced nephrotoxicity as evaluated by increase in creatinine levels in HIV patients who were treated with ART

## Data is manually curated from

- ✦ Clinical trials and their results
- ✦ Annual scientific meetings
- ✦ Patents
- ✦ Regulatory approved documents
- ✦ Approved Assays from 510K and PMA database
- ✦ A large number of peer-reviewed journals
- ✦ Other relevant web resources

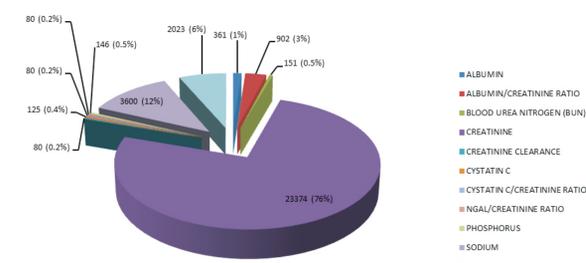
Database is developed in collaboration with a big pharma and USFDA.

A proprietary tetrahedron model is adopted in the framework of database by linking biomarkers, indication, drug, target and study population. This model simplifies the process of biomarker data analysis using GOBIOM



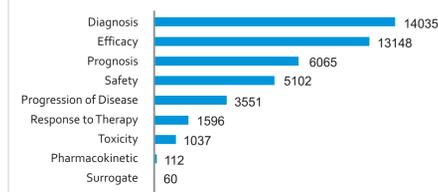
## Analysis

### Population statistics based on biomarkers analyzed for antiretroviral drug-induced nephrotoxicity in HIV infection

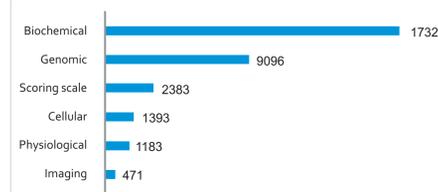


Of all the data available in GOBIOM database, 11 biomarkers were associated with ART induced nephrotoxicity in HIV of which, creatinine was evaluated in 23374 out of a total 30922 HIV patients. So, we analyzed the role of creatinine as a biomarker for ART induced nephrotoxicity in HIV patients.

## Utility of Biomarkers



## Types of Biomarkers



## Methodology

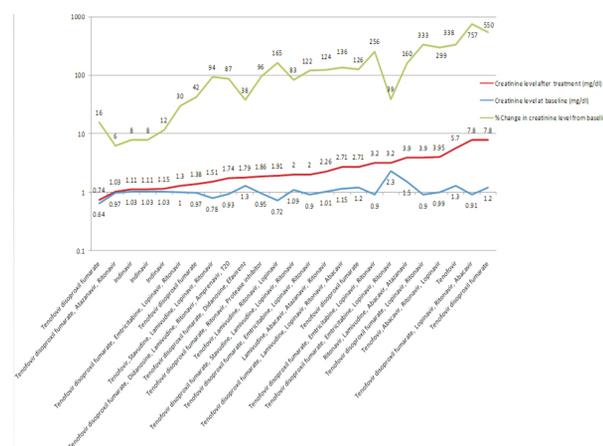
Following steps were carried out in the analysis

- ✦ Entire published information on creatinine and its association with drug-induced nephrotoxicity in HIV infection was extracted from GOBIOM database
- ✦ Information from 51 references (including journals, patents, scientific conferences) was present in GOBIOM database as on 18th March 2014

Following are the snapshots from the GOBIOM database for the search criteria employed in the present analysis

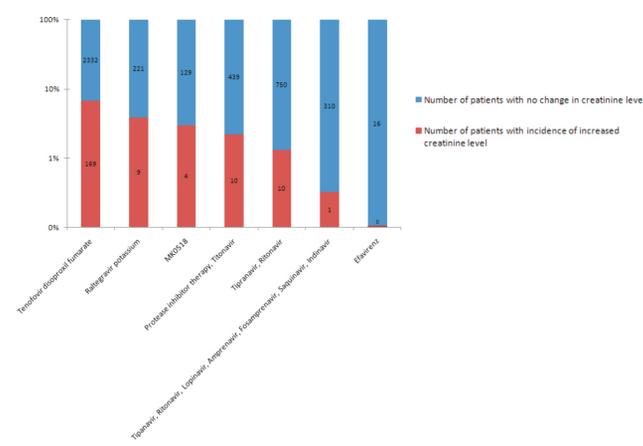


### Alteration in creatinine level from baseline in HIV patients treated with different antiretroviral drugs



Total number of studies = 16

### Percentage incidence of drug induced nephrotoxicity as evaluated by increase in creatinine levels in HIV patients treated with antiretroviral drugs



Total number of studies = 9  
Number of patients analyzed = 4400

## Conclusion

- ✦ Creatinine is concluded as a good safety marker in 25 studies, with a total sample size of 4789 patients with a clear association with drug-induced nephrotoxicity in HIV patients
- ✦ Of all the antiretroviral drugs used to treat HIV, Tenofovir either as a monotherapy or in combination with other drugs induced nephrotoxicity as evaluated by the increase in creatinine levels
- ✦ Evaluation of creatinine levels in blood could be an effective strategy to monitor drug-induced nephrotoxicity in HIV patients treated with ART especially Tenofovir

## Database Strengths

### Content

- ✦ Clinical, Preclinical, and Exploratory biomarkers
- ✦ Therapeutic indication
- ✦ Utilities of biomarker
- ✦ FDA/EMA approval data for biomarkers and associated assay methodologies
- ✦ Companion diagnostics - Approved, Development, Discovery
- ✦ Analytical and Clinical qualification
- ✦ Drugs/Intervention details
- ✦ Endpoints observed
- ✦ Efficacy and Safety characteristics
- ✦ Clinical and Preclinical qualification
- ✦ Study population
- ✦ Drug-Induced organ toxicities
- ✦ Drug resistance biomarkers

## Features & Support

- ✦ Web-enabled search application for quick and easy access
- ✦ Controlled vocabulary throughout
- ✦ Instant generation of 'biomarker report'
- ✦ Data export options in custom format to Excel, XML and PDF
- ✦ Intuitive User Interface with comprehensive search features
- ✦ "Alert a Colleague" option to share the data with other users
- ✦ Biweekly update with auto alert function
- ✦ Custom alert by therapeutic area and biomarker name
- ✦ A dedicated server located in USA with backup server in India
- ✦ Provision of user-required data in their own formats
- ✦ Easy integration with client proprietary data
- ✦ Alert service on new marker addition or updates of existing markers
- ✦ On-demand service for any biomarker addition into the database
- ✦ Competitive intelligence analysis
- ✦ On-demand training sessions

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