# 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.

### 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

### **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.

#### Data is manually curated from ∠ Clinical trials and their results

Annual scientific meetings *⊯* Patents

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

# **GVK**<sup>BIO</sup> Accelerating Research

## **Database Strengths**

#### Content

Clinical, Preclinical, and Exploratory biomarkers ✓ Therapeutic indication ∠ Utilities of biomarker **FDA/EMEA** approval data for biomarkers and associated assay methodologies

✓ Companion diagnostics - Approved, Development, Discovery

Analytical and Clinical qualification

∠ Drugs/Intervention details

Regulatory approved documents

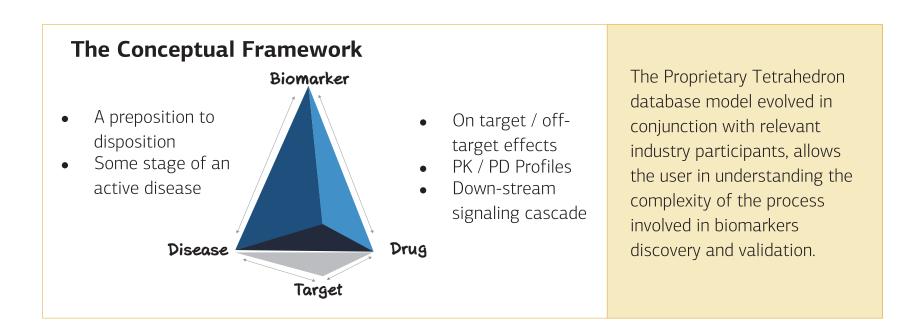
Approved Assays from 510K and PMA database

A large number of peer-reviewed journals

✓Other relevant web resources

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





#### 🖉 Endpoints observed Efficacy and Safety characteristics ✓ Clinical and Preclinical qualification ✓ Study population ∠ Drug-Induced organ toxicities *⊯* Drug resistance biomarkers

#### **Features & Support**

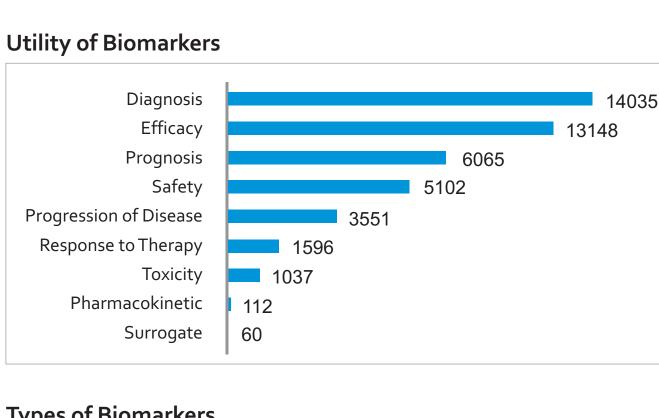
- Web-enabled search application for quick and easy access
- Controlled vocabulary through out
- ✓ Instant generation of 'biomarker report'
- ∠ Data export options in custom format to Excel, XML and PDF
- ✓ Intuitive User Interface with comprehensive search features
- ✓ "Alert a Colleague" option to share the data with otherusers
- ∠ Biweekly update with auto alert function

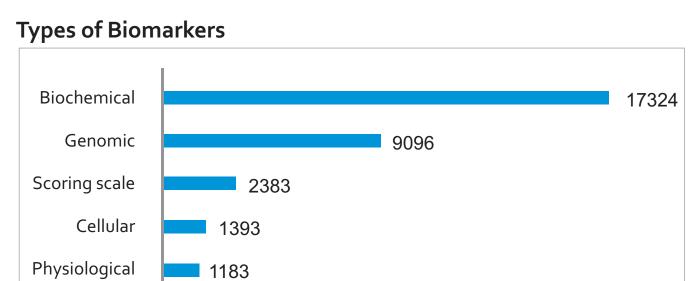
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- Custom alert by therapeutic area and biomarker name
- ∠ A dedicated server located in USA with backup server in India
- Provision of user-required data in their own formats

## **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	2159	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





## Methodology

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Advanced Search

**Biomarker Clinical Status** 

CREATININE

Biochemical

HIV Infection

Urinary system disorder

Evaluated Clinical
 Exploratory Clinical
 PreClinical

Biomarker Biomarker Name ? Biomarker Pathways ? Nature ? Biomarker Nature Type ? Application ? Biomarker Qualification ?

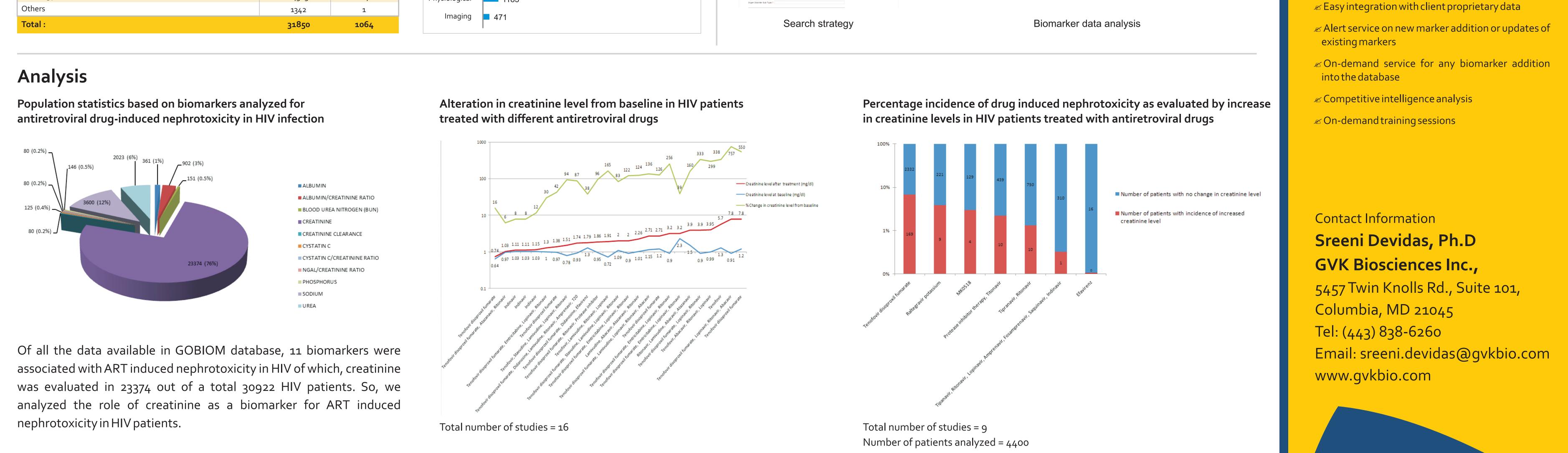
Therapeutic Area ? Therapeutic Area ? Indication ? Associated With ? Disease Stage ? Disease Grade ?

PreClinical Cell Line ? Model ?

Safety / Toxicity Organ Disorder ?

- 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

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PreClinical     Contains      Starts with	Please enter """ in the text box to view the entire list or type at least two (2) characters to get the matching list. Type and submit t o retrieve the complete data.	> Application > Drugs > Pathways > Therapeutic Area	BIOMARKER NAME STATUS CREATININE CREATININE Clinical	JS DISEASE NAME TYPE FE al HIV Infection Biochemical No	A BM CLASS Safety/Toxicity	Filter By	Filter Applied
	Please use "Ctrl" + "Moure click" to select m ultiple values. Please select all the multiple v to the already made selection, you would have to select all the values	<ul><li>Year of Publication</li><li>Biomarker with below data</li></ul>				GOVERATION      GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION     GOVERATION	Apply Filter
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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

#### Continue 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