

Safety Profile of Viread and Truvada

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Overview

- Safety assessment in drug development
- Physiology 101
 - Renal
 - Bone
 - Liver
- Safety profile of VOICE products
- Safety assessment in VOICE



Safety Assessment in Drug Development

Phases of Safety Surveillance

Phase	Type	N
Preclinical	GLP	N/A
Phase 1	GCP +++	40
Phase 2	GCP ++	200
Phase 2B/3	GCP +	4200
Phase 4	?	?

Incidence of Adverse Events

	Number of participants needed to detect X cases of AE		
Incidence of AE	One Case	Two Cases	Three Cases
1:100	300	480	650
1:200	600	960	1,300
1:1000	3,000	4800	6,500
1:2000	6,000	9600	13,000
1:10,000	30,000	48,000	65,000

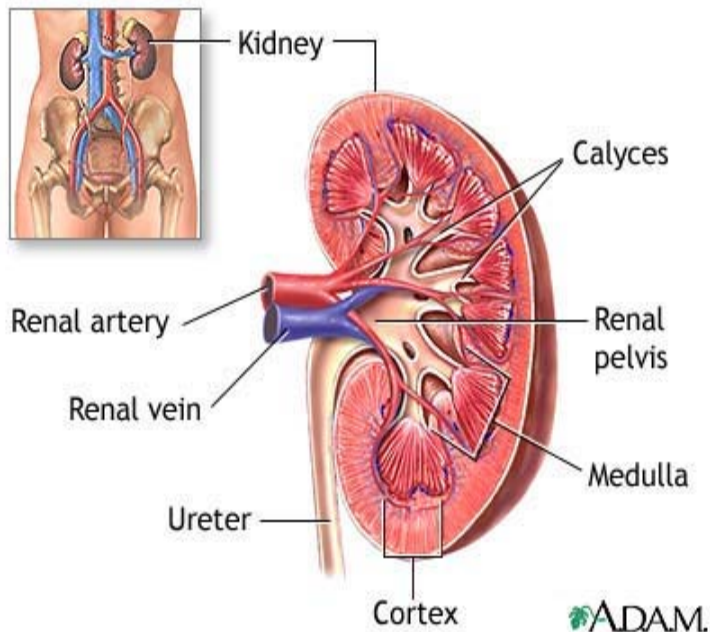
Physiology 101



Viread / Truvada Safety Issues

- Key safety issues
 - Renal toxicity
 - Reduced bone density
 - Liver problems
 - Lactic acidosis and hepatomegaly
 - Acute exacerbation of Hepatitis B
- Renal, bone, and liver AE important but rare

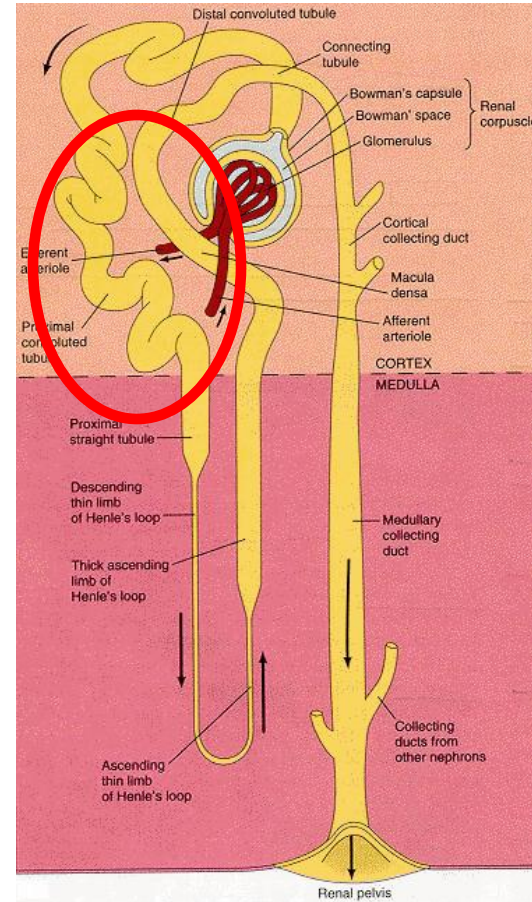
Renal



- We have two kidneys weighing about 400 g each.
- Filters about 160 L per day producing about 1.5 L urine per day
- Complex process of filtering and reabsorption of plasma:
 - Na^+ , bicarbonate, glucose, and amino acids

The Nephron

- Functional unit of the kidney
- 1 million nephrons per kidney ($\pm 250,000$).
- Key elements
 - Glomerulus
 - Proximal tubule
 - Loop of Henle
 - Distal tubule
 - Collecting ducts





Glomerular Filtration Rate (GFR)

- The amount of filtrate formed per unit time.
- Normal value: 110 ml/min, 160 L/day
- Can be estimated by measuring creatinine clearance (eCR)
- eCR can be calculated using the Cockcroft-Gault formula
- GFR decreased in renal disease



Cockcroft-Gault Formula

$(140 - \text{Age}) \times \text{Mass (in Kilograms)} \times (0.85 \text{ if female})$

$72 \times \text{Serum Creatinine (in mg / dL)}$

Fanconi Syndrome

- ❑ Global dysfunction of the proximal tubule
- ❑ Leads to acidosis, bone disease, and electrolyte disturbance
- ❑ Mechanism: drug accumulation in proximal tubule



Bone

- Primarily made of collagen and hydroxyapatite
- About 206 bones in the human body
- Initial skeleton of cartilage in infants
- Replaced with bone by osteoblasts
- Always growing and breaking down
 - Osteoblasts – form new bone cells
 - Osteoclasts – break bone cells down
 - Osteocytes – mature bone cells





Definitions

- Osteopenia
 - Bone mineral density (BMD) that is lower than normal peak BMD but not low enough to be classified as osteoporosis
- Osteoporosis
 - BMD 2.5 standard deviations below peak bone mass
- Osteomalacia
 - Softening of the bones due to defective bone mineralization



Causes

□ Osteoporosis

- Pregnancy and breast feeding
- Menopause
- Steroids
- Chronic disease

□ Osteomalacia

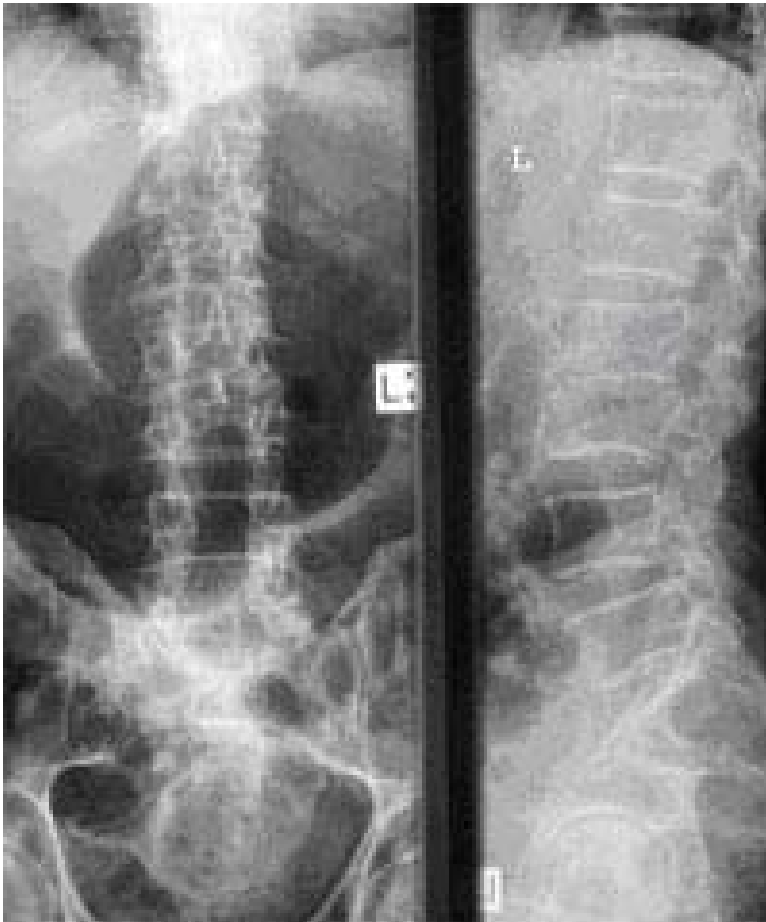
- Insufficient sunlight exposure,
- Insufficient nutritional quantities of vitamin D or phosphorus
- Renal tubular acidosis
- Chronic renal failure



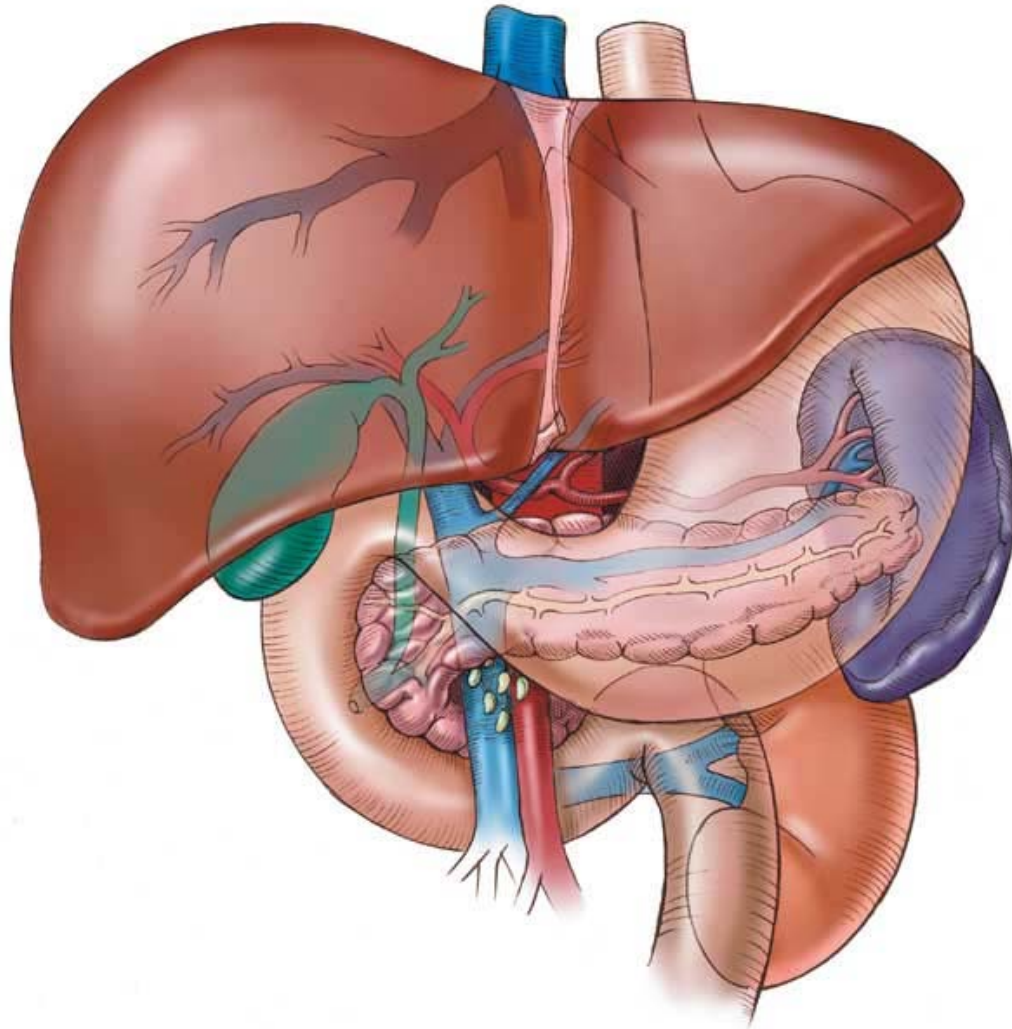
Diagnosis of Bone Disease

- Clinical
 - History of fractures
- Laboratory
 - Bone biomarkers
- Radiological
 - Plain radiographs
 - CT
 - Bone density (DXA)
 - Isotope bone scans

Osteoporosis & Osteomalacia



Liver



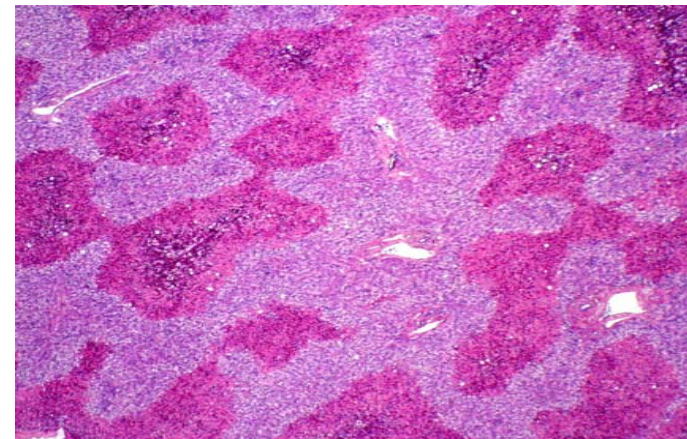
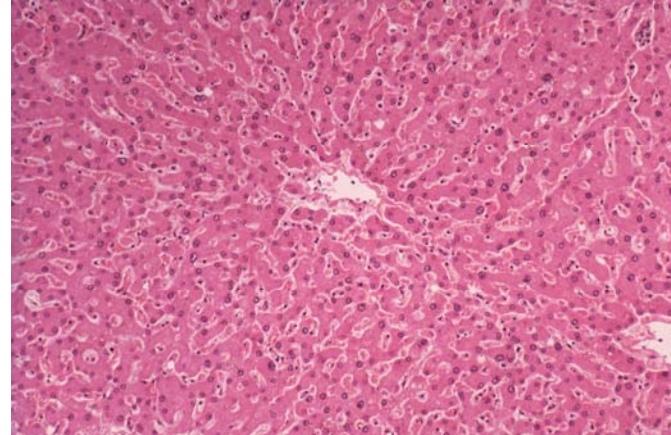


Liver

- The largest internal organ in the human body
- Plays a major role in metabolism and has number of functions in the body, including:
 - Glycogen storage
 - Decomposition of red blood cells
 - Production of bile
 - Plasma protein synthesis
 - Drug metabolism and detoxification

Liver Dysfunction

- Causes
 - Viral hepatitis
 - Drug toxicity
- Manifestations
 - Asymptomatic
 - Fulminant liver failure
- Diagnosis
- Clinical
 - Laboratory
 - Hepatitis serology
 - AST, ALT, bilirubin
 - Radiological / histopathological





Safety Profile of VOICE Products



Safety Profile of VOICE Products

- VOICE product safety data based on:
 - Preclinical data - non human primate studies
 - Clinical trial data
 - GS 903
 - GS 934
 - FHI Viread prevention study
 - Post-marketing surveillance
 - Case report literature
- Very limited data in HIV negative population

Viread





Viread

- Tenofovir disoproxil fumarate
- Approved in the US in 2001
- Oral bioavailability 25%
- Plasma half-life 17h
- *In vitro* half-life 60h
- Tenofovir excreted unchanged in urine
- PK not influenced by age, gender, or weight
- Pregnancy Category B



Adverse Reactions ($\geq 10\%$)*

- Rash
- Diarrhea
- Headache
- Pain
- Depression
- Asthenia
- Nausea

*Based on 903 data – regimen included efavirenz



Truvada™



200 mg emtricitabine-tenofovir disoproxil fumarate 300 mg



Truvada

- Combination of tenofovir disoproxil fumarate (300mg) and emtricitabine (200mg)
- Safety profile reflects this combination
- Pregnancy category B



Adverse Reactions ($\geq 10\%$)*

- Diarrhea
- Nausea
- Fatigue
- Dizziness
- Depression
- Insomnia
- Abnormal dreams
- Rash

*Based on 934 data – regimen included efavirenz



FHI Viread Prevention Study

- Phase 2 randomized , double blind placebo controlled trial
- Conducted between June 2004 and March 2006 in Ghana, Cameroon, and Nigeria
- N = 936 HIV negative women
- Primary endpoints:
 - \geq G2 creatinine
 - \geq G3 AST, ALT, Phosphorus



FHI Safety Data

- Premature closure of Cameroon and Nigeria sites diminished data sets
- 428 person-years of laboratory testing
- Drug was used for approximately 69% of all study days
- Person-years of safety follow-up:
 - TDF: 210.2
 - Placebo: 217.6
- No significant difference between TDF and placebo



Tenofovir Renal Issues

- Administration of nucleotide drugs associated with renal toxicity
 - Cidofovir > adefovir > tenofovir
- Key manifestations
 - Fanconi syndrome
 - Mild renal insufficiency
 - Acute renal failure
- Renal issues uncommon in patients without pre-existing renal disease or use of nephrotoxic drugs



Tenofovir Induced Nephrotoxicity

□ Preclinical

- Prolonged administration (> 8 months) of s.c. tenofovir (30 mg / kg / day) in macaques results in Fanconi syndrome

□ Clinical Trials

- GS 903: No difference in renal function after 144 weeks
- GS 934: After 48 weeks modest changes in GFR
 - Truvada + EFV - 1 ml/min
 - AZT + 3TC + EFV + 6 ml/min

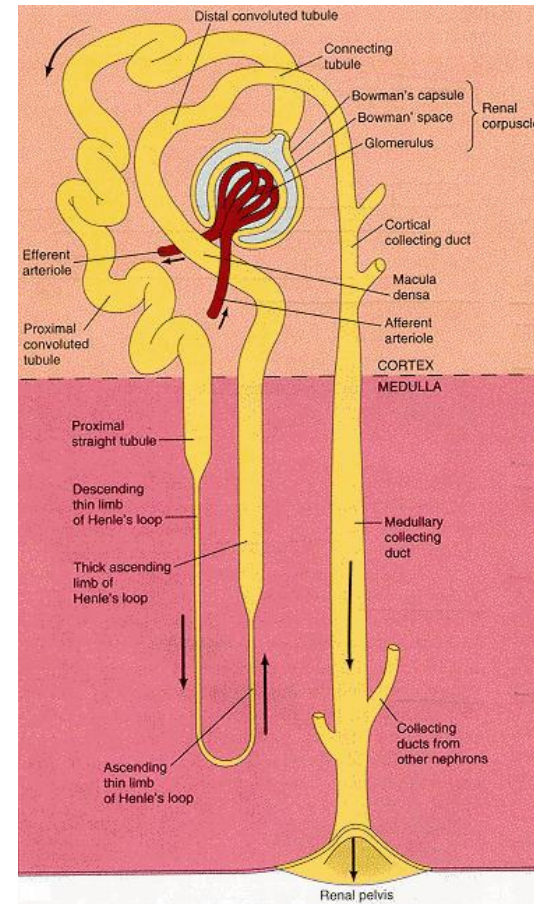
Observational Studies

	N	GFR	
		TDF	Control
Winston <i>et al.</i>	948	- 5.6 ml/min	- 1.3 ml/min
Gallant <i>et al.</i>	658	- 13.3 ml/min	- 7.5 ml/min
Mauss <i>et al.</i>	174	(97 ml/min)	(107 ml/min)
Nelson <i>et al.</i>	455,000	0.5% renal SAE	N/A

Safety Assessment in VOICE

Renal

- Exclusion criteria:
 - Serum creatinine greater than the site laboratory ULN for women
 - Calculated creatinine clearance less than 60 mL/min by the Cockcroft-Gault formula
 - Abnormal urinalysis
 - Protein
 - Glucose
- Lab monitoring



Bone

- Exclusion criteria:
 - Pathologic bone fracture not related to trauma
 - Serum phosphate level below site laboratory LLN for women
- VOICE B Study
 - DXA
 - Bone biomarkers
 - Bone turnover
 - Bone mineral metabolism



Bone Density



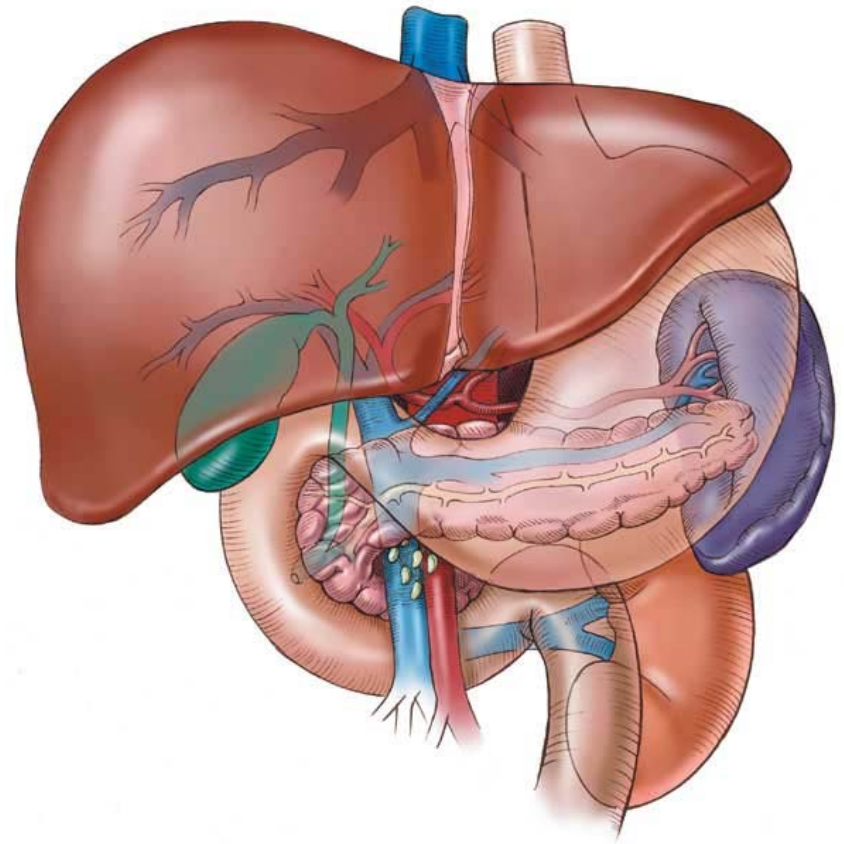


BMD Assessment

- T-score (VOICE participants ≥ 30 years)
 - BMD compared with what is normally expected in a healthy young adult of your sex.
- Z Score (VOICE participants < 30 years)
 - BMD compared with what is normally expected for participant's age, sex, weight, and ethnic or racial origin.

Liver

- Exclusion criteria:
 - AST or ALT greater than 1.5 x site laboratory ULN
 - Positive for HBsAg test result
- Laboratory monitoring





VOICE Toxicity Management

□ Renal

- Proteinuria / glycosuria
- Creatinine
- Phosphate

□ Bone

- Fractures

□ Liver

- AST/ALT
- Lactic acidosis
- Hepatitis B infection



Pharmacovigilance

- The pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines



Pharmacovigilance Meeting

- To review MTN approach to safety monitoring in VOICE study
- Key stakeholders
 - MTN safety physicians
 - DAIDS Medical Officers
 - SCHARP/FHI
- Input from Gilead Sciences safety team on best practices



Conclusions

- VOICE will generate a significant increase in laboratory and clinical AE
- Need to develop best practices for VOICE pharmacovigilance
- Site staff will require enhanced safety training



Thank You
