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

<table>
<thead>
<tr>
<th>Phase</th>
<th>Type</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>GLP</td>
<td>N/A</td>
</tr>
<tr>
<td>Phase 1</td>
<td>GCP +++</td>
<td>40</td>
</tr>
<tr>
<td>Phase 2</td>
<td>GCP ++</td>
<td>200</td>
</tr>
<tr>
<td>Phase 2B/3</td>
<td>GCP +</td>
<td>4200</td>
</tr>
<tr>
<td>Phase 4</td>
<td>?</td>
<td>?</td>
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</tbody>
</table>
## Incidence of Adverse Events

<table>
<thead>
<tr>
<th>Incidence of AE</th>
<th>Number of participants needed to detect X cases of AE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>One Case</td>
</tr>
<tr>
<td>1:100</td>
<td>300</td>
</tr>
<tr>
<td>1:200</td>
<td>600</td>
</tr>
<tr>
<td>1:1000</td>
<td>3,000</td>
</tr>
<tr>
<td>1:2000</td>
<td>6,000</td>
</tr>
<tr>
<td>1:10,000</td>
<td>30,000</td>
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</table>
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 (±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

\[
\frac{(140 - \text{Age}) \times \text{Mass (in Kilograms)} \times (0.85 \text{ if female})}{72 \times \text{Serum Creatinine (in mg / dL)}}
\]
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 (≥ 10%)*

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

*Based on 903 data – regimen included efavirenz
Truvada

- Combination of tenofovir disoproxil fumarate (300mg) and emtricitabine (200mg)
- Safety profile reflects this combination
- Pregnancy category B
Adverse Reactions (≥ 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:
  - ≥ G2 creatinine
  - ≥ G3 AST, ALT, Phosphorus

Peterson et al. PLOS Clinical Trials 2007
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

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>TDF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winston et al.</td>
<td>948</td>
<td>- 5.6 ml/min</td>
<td>- 1.3 ml/min</td>
</tr>
<tr>
<td>Gallant et al.</td>
<td>658</td>
<td>- 13.3 ml/min</td>
<td>- 7.5 ml/min</td>
</tr>
<tr>
<td>Mauss et al.</td>
<td>174</td>
<td>(97 ml/min)</td>
<td>(107 ml/min)</td>
</tr>
<tr>
<td>Nelson et al.</td>
<td>455,000</td>
<td>0.5% renal SAE</td>
<td>N/A</td>
</tr>
</tbody>
</table>
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