Poster Number

954

Scan this QR code to link to this poster and to download a PDF copy.

You will be prompted to enter the following passcode: 954

Long-Term Safety and Efficacy of Tenofovir DF Therapy in HIV-Infected Children Through Week 336

X Saez-Llorens[1] , JG Deville[2], A Mirza[3], JS Chen[4], A Gaur[5], M Rathore[3], D Hardin[6], Y Liu[7], E Quirk[7]

[1]Hospital del Niño, Panama City, Panama, [2]University of California Los Angeles (UCLA), Los Angeles, CA, USA,
[3]University of Florida Center for HIV/AIDS Research Education and Service (UF CARES), Jacksonville, FL, USA, [4]Drexel University College of Medicine, Philadelphia, PA, USA,
[5]St Jude Children's Research Hospital, Memphis, TN, USA, [6]Eli Lilly, Indianapolis, IN, USA, [7]Gilead Sciences Inc., Foster City, CA, USA

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Phone: (650) 574-3000
Fax: (650) 578-9264

22nd Conference on Retroviruses and Opportunistic Infections
February 23-26, 2015
Seattle, Washington

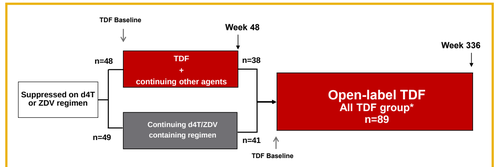
Background

- An estimated 3.3 million children (< 15 years of age) are living with HIV infection[1]
- Tenofovir disoproxil fumarate (TDF, Viread®)[2]
  - TDF 300 mg approved in adolescents (12 to <18 years) in US and EU
  - Pediatric formulations (150, 200 and 250 mg tablets and a 40 mg/g powder) approved in children aged 2 years and older
- Extensively characterized safety profile in adults[3,4]
- Long-term TDF safety data in children are limited (including renal and bone)
- Tenofovir exposure achieved in pediatric subjects taking TDF powder or tablet was similar to exposures achieved in adults receiving once-daily doses of TDF 300 mg.[5]

Methods

- GS-US-104-352: Phase 3, randomized, open-label non-inferiority study comparing the safety and efficacy of switching stavudine (d4T) or zidovudine (ZDV) to TDF versus continuing d4T or ZDV
- Population:
  - HIV infected children ages 2 to < 16 years
  - Virologic suppression to < 400 copies/mL on a d4T or ZDV containing regimen
- Primary Endpoint:
  - Maintenance of virologic suppression (< 400 copies/mL) at Week 48
  - 15% non-inferiority margin
  - Missing = failure analysis

Figure 1. GS-US-104-352 Study Schema



*All TDF group: included all subjects who received TDF in the randomized phase, and subjects who switched from d4T orZDV in the randomized phase to open-label TDF in the extension phase. The latter subjects had their baseline reset, and only data from the date of the subject's first dose of TDF in the extension phase were included.

Table 1. Study Drug Dosing

TDF Dosage Form	Body Weight (kg)	Once Daily Dosing
Oral Powder	≥ 10	Up to 300 mg
Tablets	17 to < 22	150 mg
	22 to < 28	200 mg
	28 to < 35	250 mg
	≥ 35	300 mg

- Compared to adults the mg/kg dose is ~2X in children
- Pediatric dose tablets were introduced in 2012

- Study Visits:
  - Randomized Phase: Weeks 2, 4, 8 and every 8 weeks until Week 48
  - Extension Phase: every 12 Weeks through Week 336
- General Safety Assessments: Adverse events (AE) and Clinical laboratories (CBC, chemistries, urinalysis)
- Efficacy Assessments:
  - HIV-1 RNA (Roche COBAS Amplicor or Taqman)
  - Efficacy endpoints: HIV-1 RNA <50 copies/mL, <400 copies/mL, (missing = failure); 95% CIs of the point estimate were calculated from the Exact method.
- Resistance Testing:
  - Performed upon discontinuation due to virologic failure (2 consecutive HIV-1 RNA >1000 copies/mL not attributed to non-adherence)
    or
  - had HIV-1 RNA ≥ 400 copies/mL at Week 48, 96, 144, 192, 240 and every 48 weeks thereafter or at early discontinuation

Methods (cont'd)

Renal and Bone Mineral Density (BMD) Assessments

- Renal:
  - Renal Labs:
    - serum creatinine, phosphate, glucose
    - urine protein, glucose
    - eGFR (Schwartz)
  - Renal events
- Bone:
  - Dual-energy x-ray absorptiometry (DXA) scans every 24-48 Weeks
    - lumbar spine and total body minus head (TBMH)
    - Hologic and GE Lunar scanners
      - Identical scanner used for longitudinal assessments in individual subjects
      - Categorical analysis of subjects with ≥4% decrease from baseline
  - BMD Z-scores adjusted for height-age
    - Age where 50th percentile corresponded to the subject height per US CDC growth chart
    - Categorical analysis above and below BMD Z-score of -2.0

Results

- **Efficacy:**

Table 2. Subjects with Plasma HIV-1 RNA < 400 copies/mL at Week 48, Randomized Phase (n, %)

Subjects with Plasma HIV-1 RNA < 400 copies/mL at Week 48 (n, %)	TDF N=48	d4T or ZDV* N=49	p-value	Difference (95% CI)
Missing = Failure				
At Week 48	40/48 (83.3%)	45/49 (91.8%)	0.23	–8.5% (–21.5% to 4.5%)

- **Resistance:**
  - The resistance development was consistent with current therapy or archived mutations
  - K65R was observed at Week 4 in 1 subject in the TDF group which was consistent with the subject's current therapy but may also been archived from previous therapies
- **Safety:**
  - No deaths or SAEs considered related to study drug were reported and no subjects discontinued due to an AE in the randomized phase

Table 3. Demographics and Baseline Characteristics

Characteristic		TDF N=48	d4T or ZDV* N=49	All TDF** n= 89
Age	Years, mean (range)	**7** (2-15)	**7** (2-14)	**8** (2-15)
Age Group	2 to < 6 years 6 to <12 years 12 to < 18 years	16 28 4	**14** **34** **1**	**24** **59** **6**
Sex	Male, n (%)	**21** (43.8)	**29** (59.2)	**44** (49.4)
Race	Mestizo (Indian and Hispanic) Black White Other	**29** (60.4) **13** (27.1) **3** (6.3) **3** (6.3)	**37** (75.5) **6** (12.2) **6** (12.2) **0**	**65** (73.0) **15** (16.9) **6** (6.7) **3** (3.4)
Weight	kg, mean (SD)	**25.9** (12.0)	**24.1** (7.8)	**25.9** (10.4)
Body Mass Index	kg/m^2, mean (SD)	**17.59** (3.7)	**16.59** (1.8)	**17.1** (3.0)
eGFR (Schwartz)	mL/min/1.73m^2, Median (Q1, Q3)	**163.69** (143.4, 189.8)	**150.81** (138.6, 160.9)	**163.6** (145.2, 184.8)
Baseline HIV-1 RNA	< 50 copies/mL, n (%) 50 - < 400 copies/mL ≥ 400 copies/mL	**36** (75.0) **11** (22.9) **1** (2.1)	**41** (83.7) **6** (12.2) **2** (4.1)	**70** (78.7) **15** (16.9) **4** (4.5)
Baseline CD4 Count	cells/µL, median (range)	**1061**(500-3671)	**1149** (407-2313)	**1095** (387-3671)

* Original clinical baseline
** TDF baseline

Results (cont'd)

Figure 2. Disposition

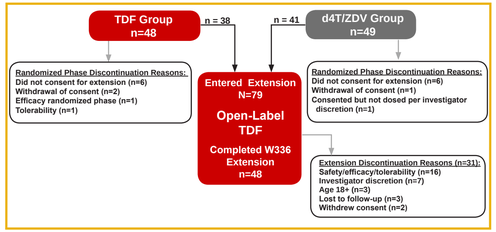


Table 4. Virologic Response Rates in the All TDF Group By Visit, Extension Phase (Missing=Failure)

Study Visit	Subjects with HIV-1 RNA <50 c/mL		Subjects with HIV-1 RNA <400 c/mL	
	n/N (%)	95% CI	n/N (%)	95% CI
Week 48	61/89 (68.5%)	57.8%, 78.0%	76/89 (85.4%)	76.3%, 92.0%
Week 96	57/79 (72.2%)	60.9%, 81.7%	66/79 (83.5%)	73.5%, 90.9%
Week 144	54/78 (69.2%)	57.8%, 79.2%	63/78 (80.8%)	70.3%, 88.8%
Week 192	53/74 (71.6%)	59.9%, 81.5%	57/74 (77.0%)	65.8%, 86.0%
Week 240	51/71 (71.8%)	59.9%, 81.9%	52/71 (73.2%)	61.4%, 83.1%
Week 288	45/64 (70.3%)	57.6%, 81.1%	47/64 (73.4%)	60.9%, 83.7%
Week 336	32/40 (80.0%)	64.4%, 90.9%	33/40 (82.5%)	67.2%, 92.7%

Note: denominator based on the number of subjects who consented to extension. Week 336 includes n=12 Taqman values.

Table 5. AEs Leading to Study Drug Discontinuation

AE Leading to Study Drug DC* n (%)	All TDF (n=89)
Hypophosphatemia	3 (3.4)
Arthralgia	2 (2.2)
Proteinuria	2 (2.2)
Glycosuria	1 (1.1)
Brain neoplasm	1 (1.1)

* 9 AEs occurring in 8 subjects

Table 6. Common AEs (Grades 1-4)

Adverse Event* n (%)	All TDF (n=89)
Nasopharyngitis	56 (62.9)
Dental caries	21 (23.6)
Cough	19 (21.3)
Diarrhea	19 (21.3)
Gastroenteritis	18 (20.2)

* ≥ 20%

Table 7. Grade 3 and 4 Laboratory Abnormalities

Grade 3-4 Lab Abnormality n (%)	All TDF (n=89)
Hyperamylasemia	8 (9.0)
ALT > 5 X ULN	7 (7.9)
Hypophosphatemia	3 (3.4)
Glycosuria	2 (2.3)
Hypouricemia	1 (1.1)
Hyperglycemia	1 (1.1)
Hypomagnesemia	1 (1.1)
Lipase* > 3X ULN	1 (3.6)
Hypocalcemia	1 (1.1)
AST > 5X ULN	1 (1.1)
Thrombocytosis	1 (1.1)

*Reflex test performed when Amylase is ≥1.5xULN on n=28; ULN = upper limit of normal

Renal and BMD Safety Analysis

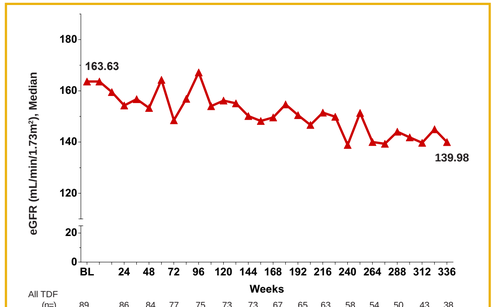
Renal:

- 6 subjects discontinued for renal AEs:
  - hypophosphatemia (n=3); proteinuria (n=2); glycosuria (n=1)
    - 4 of the 6 subjects had clinical features consistent with proximal renal tubulopathy (hypophosphatemia, proteinuria, normoglycemic glycosuria)
    - 1 additional subject had features of proximal renal tubulopathy but did not discontinue TDF due to AE

BMD:

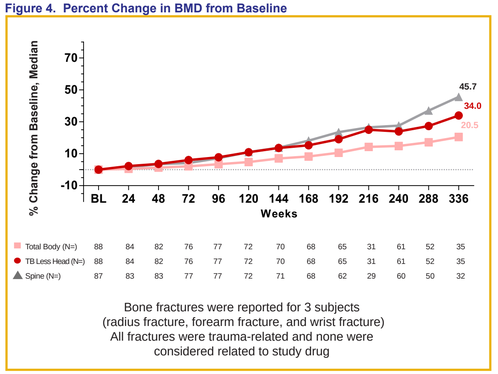
- Overall, 13/86 subjects (15.1%) had ≥ 4% decline in spine or total body less head BMD at one post baseline visit
  - 3 subjects had ≥ 4% decline in BMD at > 1 visit

Figure 3. eGFR by Visit



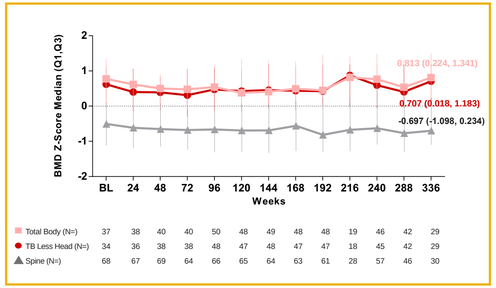
Median change of -28.68 mL/min/1.73 m²

Figure 4. Percent Change in BMD from Baseline



Bone fractures were reported for 3 subjects
(radius fracture, forearm fracture, and wrist fracture)
All fractures were trauma-related and none were considered related to study drug

Figure 5. BMD Z-Score (Height- Age Adjusted)



Conclusions

Among pediatric patients aged 2 to < 16 years with HIV-1 infection treated with TDF-containing ARV regimens:

- **High rates of virologic suppression through 336 weeks of treatment**
  - **80% of subjects with HIV-1 RNA < 50 copies/mL at Week 336 (missing=failure analysis)**
  - **One subject developed K65R at Week 4, suggesting it may have been archived from previous therapy**
- **TDF was generally well tolerated**
  - **BMD increased over time**
  - **eGFR decreases through Week 336 were consistent with normal changes in an aging pediatric population**
  - **6 out of 89 subjects discontinued due to AEs related to renal toxicity**
- **TDF can be considered as a once-daily component of ARV therapy in HIV-infected children**

References

1. UNAIDS Global report 2013. Available at www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/epidemic. Accessed Jan 2015
2. Gilead Sciences. Viread (tenofovir disoproxil fumarate) US prescribing information. Available at: http://www.gilead.com/pdf/viread_pi.pdf
3. Gallant JE et al.; Study 934 Group. N Engl J Med. 2006;354:251–260.
4. Gallant JE et al.; 903 Study Group. JAMA. 2004;292:191–201.
5. Saez-Llorens et al. Pediatr Infect Dis J. 2015 (accepted Dec 2013)

Acknowledgments

- Our Investigators, their patients and families
- The Gilead GS-US-104-0352 Study Team
- The Gilead Pediatric HIV and Viread teams