3rd IAS Conference on HIV Pathogenesis and Treatment
24–27 July 2005, Rio de Janeiro, Brazil

Poster Number
TuFo0106

Abstract #
TuFo0106

Characterization of Anemia in HIV-infected (HIV+) Subjects Treated with Antiretroviral Therapy (ART) With and Without Zidovudine (+/- ZDV) in 54 Clinical Trials

Mark T. Edwards, Wayne Burkle, Amy Cutrell, Qiming Liao, Cindy Brothers and Jaime E. Hernandez

GlaxoSmithKline R&D, RTP, NC, USA

Introduction

Hematologic abnormalities have been described with HIV infection. The most common abnormality is anemia, which has been associated with advanced HIV disease and reported in 40% of untreated subjects and in 60 to 95% of treated subjects (1-5). Anemia has also been identified as a predictor of decreased HIV disease survival (6). Although HAART has been reported to improve HIV-related anemia, this complication remains relatively common and is associated with fatigue and decreased quality of life; with some studies showing improvement of these parameters after appropriate treatment.

Hematologic toxicity (mainly anemia and neutropenia) has been reported in HIV+ subjects, including those treated with ZDV. This ZDV-associated toxicity may be dose related. Approximately 3% of subjects have reported moderate to severe anemia (DAIDS 1992 grades 2 to 4) at the currently approved dose. To better characterize the incidence, severity and determinants of anemia in patients treated with HAART, we performed an analysis of data from 54 trials including more than 12,000 subjects treated with ART with and without ZDV.

Methods

- All GSK-sponsored clinical trials with at least 24 weeks of ART finished from January 1995 to January 2004 and with an authorized database were analyzed. Anemia was identified by hemoglobin (Hb) levels below normal, and classified with the DAIDS 1992 scale.
- Only subjects with hemoglobin data and a treatment start date were included in this investigation. Descriptive statistics were summarized for naïve and experienced subjects treated with and without ZDV.
- A retrospective analysis of risk factors for anemia in HIV clinical trials was also conducted. Univariate logistic regression models were fit to understand the individual predictive ability of each potential risk factor. Clinical characteristics used as potential risk factors were: BL demographics, BL CDC Class, BL plasma HIV-1 RNA, BL CD4+ cell count, presence/absence of ZDV in the regimen, BL hemoglobin, BL weight, BL ART status (ART-naïve or ART-experienced), and geographic region (US, Europe, Latin America, or rest of world [ROW]). Post BL hemoglobin results were also classified using the DAIDS 1992 scale; anemia was defined as a hemoglobin value that resulted in a grade 2 or higher classification. Two multivariable logistic regression models were finally constructed using stepwise selection.

Results

- Baseline demographics and characteristics were comparable between subjects treated with (5565 subjects) and without (7075 subjects) ZDV. 65% and 45% of subjects respectively were ART-naïve at BL (**Tables 1, 2**).
- The incidence of grade 2/4 anemia in ART-naive subjects was similar in those receiving ZDV (1.5%, 95%CI [1.1%,1.9%]) vs. those not receiving ZDV (1.1%, 95%CI [0.7%,1.5%]). In ART-experienced subjects, the incidence of anemia was higher, ($p<0.01$), in those receiving ZDV (1.8%, 95%CI [1.2%,2.4%]) vs. those not receiving ZDV (0.6%, 95%CI [0.4%,0.9%]). Severe anemia (grade 3/4) was seen in 1.0% of ART-naïve and in 0.9% of ART-experienced subjects taking ZDV vs. 0.6% and 0.3% of subjects not taking ZDV (**Table 3**).
- When subjects receiving ZDV were classified as receiving ZDV as a separate drug vs. as part of a fixed combination tablet (Combivir [COM, ZDV 300mg/ Lamivudine 150mg] or Trizivir [TZV, ABC 300mg/ Lamivudine 150mg/ZDV 300mg]) incidences of anemia were 2.0% (95%CI [1.5%,2.5%]) for ZDV and 1.2% (95%CI [0.8%,1.6%]) for COM/TZV (**Table 3**).

Table 1. Baseline Demographics and Characteristics

Characteristic	ART with ZDV N=2616	ART with COM/TZV N=2949	ART without ZDV N=7075	Total N=12640
Age (year, median)	34	36	38	37
Female (%)	25	22	16	20
White (%)	55	56	60	58
ART-Naïve (%)	63	67	45	54
HIV-1 RNA Log_{10} copies/mL	4.5	4.5	4.7	4.6
CD4 + Cells/mm^3	426	394	290	342

- Baseline imbalances between the group of subjects with ZDV and those without ZDV were: Prior ART experience (34% ZDV, 55% no ZDV) and CD4 + cell counts (409 cells/mm^3 ZDV, 290 cells/mm^3 no ZDV). (**Table 1**).

Table 2. Prevalence and Severity of Anemia at BL

Hemoglobin	ART with ZDV N=2616	ART with COM/TZV N=2949	ART without ZDV N=7075	Total N=12640
Normal	99.1	99.0	98.3	98.6
Grade 1 (%)	0.6	0.5	1.2	0.9
Grade 2, 3 or 4	<1%	<1%	<1%	<1%

Table 3. Treatment Emergent Grade 2/4 Anemia

Hemoglobin **ART-naive**	**ART with ZDV** **N=1649**	**ART with COM/TZV** **N=1987**	**ART without ZDV** **N=3161**	**Total** **N=6797**
Grade ≥ 2 (%)	**1.8**	**1.2**	**1.1**	**1.3**
Grade ≥ 3 (%)	**1.3**	**0.7**	**0.6**	**0.8**
Experienced	**N=955**	**N=949**	**N=3910**	**N=5814**
Grade ≥ 2 (%)	**2.3**	**1.3**	**0.6**	**1.0**
Grade ≥ 3 (%)	**1.3**	**0.6**	**0.3**	**0.5**

Table 4. Determinants of Anemia in Univariate Models

Most Prognostic Explanatory Variables	Odds Ratio	p-value	% with Post-BL Anemia (# with ≥ Grade 2 Anemia / N per subgroup)
Asian descent	2.56	0.0031	2.8% (11/394)
Hispanic	1.67	0.0114	1.8% (32/1821)
Caucasian	0.52	<.0001	0.8% (62/7362)
Gender (M vs. F)	0.53	0.0004	1.0% (M; 101/10161) 1.9% (F; 46/2479)
CDC Class (Class C vs. Classes A + B)	2.37	<.0001	2.5% (class C; 27/1104) 1.1% (not class C; 92/8795)
Age (per 10 yrs)	0.99	0.0484	1.2% (<36; 69/5652) 1.1% (>36; 76/6980)
Regimen contained ZDV (Y vs. N)	1.86	0.0002	1.6% (Y; 87/5565) 0.9% (N; 60/7075)
Baseline Viral Load (Log_{10} HIV-1 PCR copies/mL)	1.75	<.0001	0.4% (<3.9 13/2958) 0.9% (3.9-4.6 29/3354) 1.3% (4.6-5.1 38/2983) 2.0% (≥5.1 63/3152)
Baseline CD4+ cell count (per 50 cells)	0.94	0.0021	1.9% (<200; 72/3891) 0.8% (200-350; 29/3461) 0.8% (>350; 42/5187)
Baseline hemoglobin (g/dL)	0.53	<.0001	1.0% (Normal or Grade 1; 129/12583) 64.0% (Grade 2 or higher; 16/25)
Baseline weight (per 10 kg)	0.75	<.0001	2.7% (<62 66/2420) 1.0% (62-<72 30/2912) 0.8% (72-<82 22/2793) 0.7% (≥82 19/2568)

- Among the 12640 subjects with hemoglobin data and treatment information, 80% were male, 99% had normal hemoglobin values at baseline, and 46% were ART-experienced (**Tables 1 and 2**). Global distribution was 49% US, 19% Europe, 3% Latin America, 30% ROW.
- There were 147 (1.2%) cases of post baseline grade 2-4 anemia as determined by the DAIDS 1992 scale; 12493 subjects served as controls.
- The results of the univariate logistic regression analysis are shown in **Table 4** while the results of the 2 multivariable models are shown in **Figures 1 and 2**.

Figure 1. Determinants of Anemia in Multivariable Model 1 Stepwise Logistic Regression (N=12640, n=0 missing)

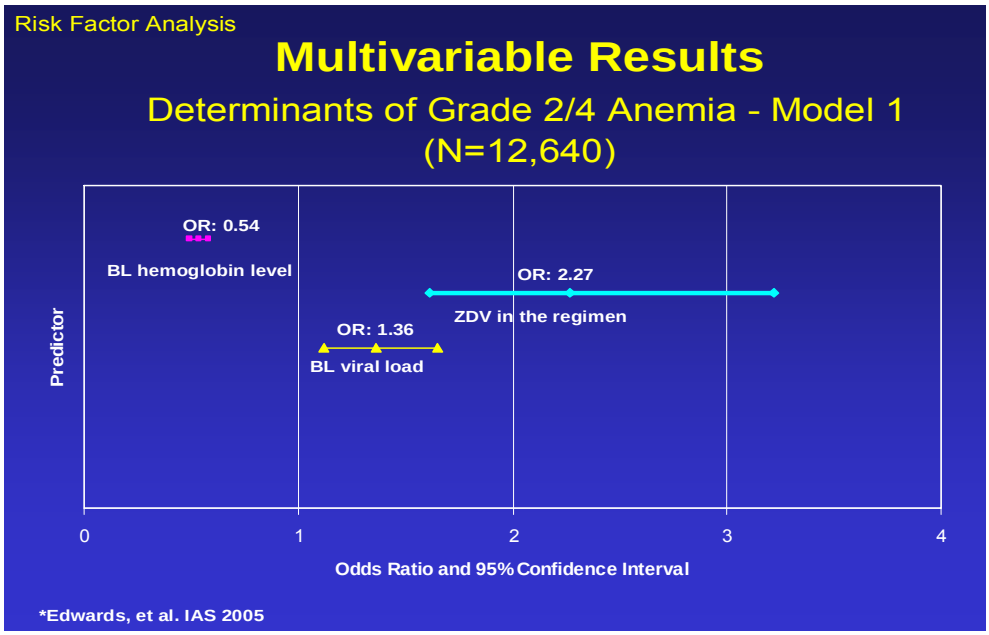
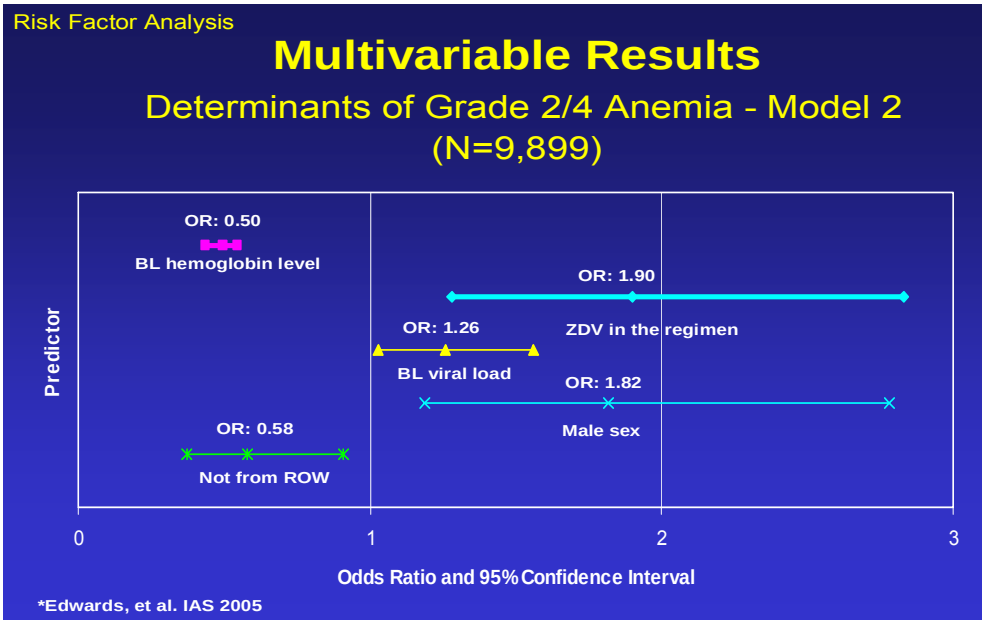


Figure 2. Determinants of Anemia in Multivariable Model 2 Stepwise Logistic Regression (N=9899, n=2741 missing)



Discussion

Despite significant advances in the treatment of HIV infection, the need for drugs with better long term tolerability and toxicity has been identified. Although effective HAART has been associated with improvement of hematologic complications including anemia, this toxicity remains relatively common. Therefore, comparative safety data in patients treated with HAART with and without ZDV and identification of risk factors for the development of anemia are particularly pertinent.

In this analysis using data from more than 12,000 patients participating in 54 controlled clinical trials and with varied characteristics, we were able to demonstrate a low prevalence of anemia at BL and a relatively low incidence of HAART-associated anemia. Although the risk of developing anemia was higher for subjects receiving ZDV-containing HAART, this incidence was also low and appeared lower when COM or TZV were used. Reasons for this finding are not known but may include variability in the BL characteristics that were identified as risk factors for the development of anemia.

To identify potential risk factors for the development of anemia in this large cohort, two multivariable models correcting for confounders were constructed. The first model was designed to maximize the number of subjects in the model while the second maximized the number of variables for consideration in the model. Interestingly, both models identified the presence of anemia and a higher viral load at BL as risk factors for subsequent development of anemia regardless of the use of ZDV or not. Ssali et al, recently reported risk factors for the development of severe anemia after ZDV treatment in patients in Africa (7) and also describe BL Hb levels as a determinant; one of our multivariable models identified sex as a potential risk factor but unlike the DART analysis, the risk was higher for males in our cohort. This may be explained by another finding in the same model, namely that subjects from areas similar to those analyzed in DART had a higher risk of anemia vs. other geographic areas.

In conclusion, the vast majority of patients treated with HAART +/- ZDV in this cohort did not develop anemia; several risk factors were identified that could be useful when considering ZDV-containing HAART.

Conclusion

- **The overall incidence of anemia in this cohort was low (1%).**
- **Subjects treated with ZDV had a higher incidence of anemia compared to subjects not treated with ZDV.**
- **This incidence, however, was also low and appeared to be lower when COM/TZV were used.**
- **Multivariable logistic regression models selected ZDV use, high baseline viral load, and male gender as determinants of increased risk.**
- **As expected, higher hemoglobin values at baseline generally suggest a decreased risk of developing anemia.**

References

1. Coyle T, Med Clin of North Am 1987;81:449-470
2. Sullivan PS, et al. Blood 1998;91:301-308
3. Moore RD and Forney D, J Aquir Immune Defic Synd 2002;19:54-57
4. Semba RD, et at, J Aquir Immune Defic Synd 2001;26:315-319
5. Servais, et al, J Aquir Immune Defic Synd 2001;28:221-225
6. Saah AJ, et al, J Aquir Immune Defic Synd 1994;7:287-295
7. Ssali T, et al, Conference on Retroviruses and Opportunistic Infections, Boston USA 2005.

Acknowledgements

We would like to thank the patients who volunteered to participate in this study and the investigators and coordinators for their support in conducting the study.