MiniZID Study: A randomized controlled trial on safety of reduced dose (400mg) of zidovudine compared with standard Dose (600 mg) in HIV-infected patients starting antiretroviral therapy

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Background

In 2013 WHO recommendations recommended tenofovir as the preferred NRTI for first-line ART treatment. By 2017, 31% of adult patients are expected to be on AZT-based regimens, as a result of a switch to a second-line market (ref 1.)

A dose reduction of AZT from 600 mg to 400 mg daily would lead to a decrease from 89 USD to 60 USD cost per patient per year, saving 282-351 millions of USD based on 3 years global market forecasts (2012-14). (ref 2.)

In ressource-limited settings, the largest studies describing the hematologic toxicity of AZT-countaining ART regimen reported an incidence of severe anaemia (Hemoglobin<8g/dl) between 5% (ref 3.) and 12% (ref 4.)

A recent retrospective study in Thailand (ref 5.) found that dose reduction of AZT to 200mg BID in anemic patients under standard dose resulted in stable hemoglobin level with durable virological suppression during their 96 weeks follow-up.

Because reducing the dose may decrease adverse effects, the aim of our study is to compare the safety and efficacy of reduced dose zidovudine (200 mg twice a day) with standard dose zidovudine (300 mg twice a day) in treatment-naive HIV-infected adults.

Methods

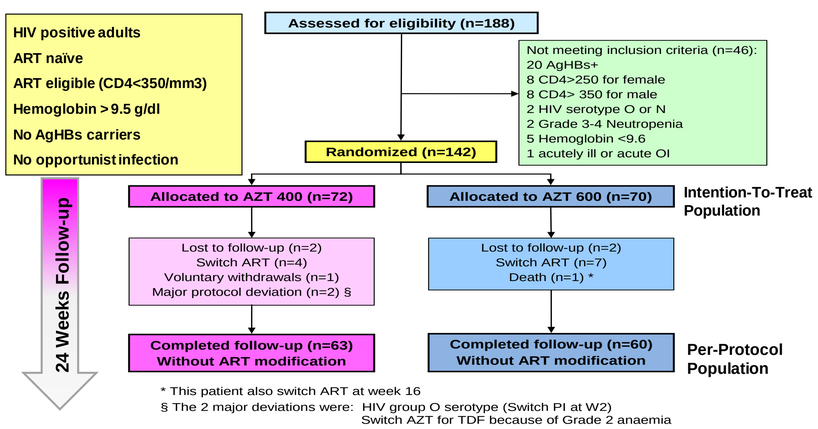
We conducted a prospective, randomized-control trial at one HIV clinic in Yaoundé, Cameroon (August 2011-December 2013). Adults eligible for treatment were randomized to receive 24 weeks of lamivudine plus nevirapine with either the standard dose (600 mg) or reduced dose (400 mg) of twice-daily zidovudine.

Baseline demographic, clinical, biological variables were summarized per treatment group using medians (interquartile range) and the Wilcoxon rank-sum test for quantitative variables; percentages and chi-squared test for qualitative variables.

The primary outcome was the difference in proportion of patients experiencing during the first 24 weeks of treatment a new grade 1 to 4 anaemia (OMS grading scale) or increasing their anaemia grade between the two dosing AZT using a Kaplan Meier method.

Secondary outcomes were: the probability at 24 weeks that patients experiencing/increasing to a severe (grade 3 to 4) anaemia in the entire cohort and in anaemic patients; proportion of patients at 24 weeks with a viral load ≤40 or ≤200 copies/mL, stratified by BMI (≤23 kg/m2 and >23 kg/m2) and by baseline viral load (≤100 000 copy/mL and >100 000 copy/mL). Comparison between the two dosing AZT regimen were done using a Wilcoxon rank-sum test with an alpha threshold of 5 %.

Figure 1. Trial Profile



* This patient also switch ART at week 16

§ The 2 major deviations were: HIV group O serotype (Switch PI at W2)
Switch AZT for TDF because of Grade 2 anaemia

Results

Table 1. Baseline Demographic and Clinical variables by treatment arm

	AZT 400 (n=72)	AZT 600 (n=70)	Total (n=142)
Sex, female n (%)	46 (64)	37 (53)	83 (59)
Age in years (IQR)	34 (30-39)	36 (30-44)	35 (30-42)
Weight in Kg (IQR)	64 (57-72)	67 (60-76)	65.5 (58-73)
BMI in Kg/m^2 (IQR)	22.8 (21-25)	23.8 (22-27)	23.2 (21-26)
WHO stage, n(%), Stage 3-4	36 (50)	29 (41)	65 (46)
Median (IQR) HIV-RNA Log_{10} cop/mL	5.5 (5.0-5.9)	5.4 (4.8-5.9)	5.4 (4.9-5.9)
Plasma HIV-RNA copies per mL			
VL<100'000, n (%)	18 (25)	20 (29)	38 (27)
VL>100'000, n (%)	54 (75)	50 (71)	104 (73)
Median (IQR) CD4 cell count cell/µL	162 (96-215)	180 (104-222)	163 (99-219)
Median (IQR) Hemoglobin g/dL	11.3 (10.7-12.6)	11.9 (10.9-13)	11.6 (10.8-12.8)
WHO Grade 1 anemia, n (%)	17 (24)	11 (16)	28 (20)
WHO Grade 1 neutropenia, n (%)	26 (37) §	32 (44) §	58 (41)
WHO Grade 2 neutropenia, n (%)	6 (9)	10 (14)	16 (11)
WHO Grade 3 neutropenia, n (%)	4(6) §	0 (0) §	4 (3)

§ P < 0.05

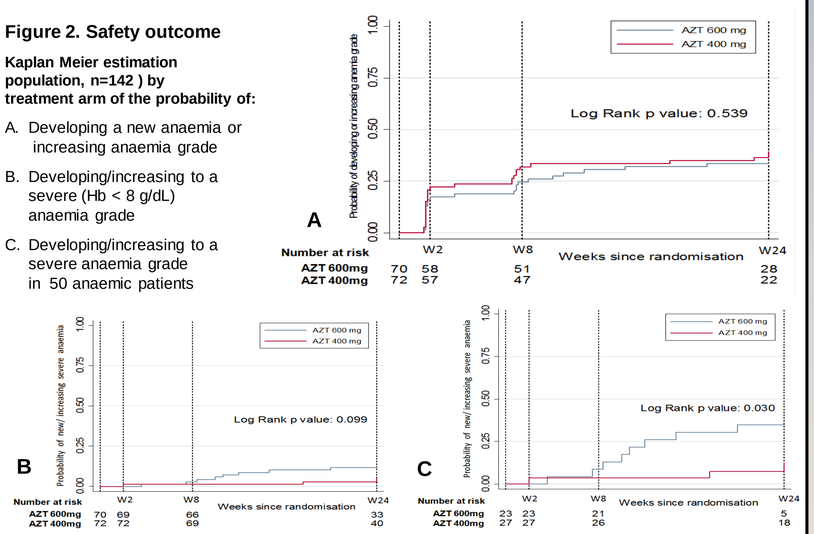
Figure 2. Safety outcome

Kaplan Meier estimation population, n=142) by treatment arm of the probability of:

A. Developing a new anaemia or increasing anaemia grade

B. Developing/increasing to a severe (Hb < 8 g/dL) anaemia grade

C. Developing/increasing to a severe anaemia grade in 50 anaemic patients



Results

Overall, 50 participants (35%) experienced a new anaemia or increased their anaemia grade during the 24 weeks follow-up. There was no statistically significant difference between the AZT 400 mg and AZT 600 mg arm: 38% vs 33% in the ITT analysis (p=0.56, figure 2A).

Fewer patients in the AZT400 arm required a switch to tenofovir (1.4% vs 11.4%; p=0·017) or a blood transfusion (2.8% vs 5.7%, p=0.44) because of AZT-attributable anemia.

Among the 50 anaemic patients, fewer patients in the AZT400 arm experienced severe (< 8g/dL) anaemia (11.1% vs 34.8%, p=0.03, figure 2C).

The two treatment groups showed similar virological response at week 24 (Table 2).

Median CD4 T-cell count increases: AZT400: +117 cells/µL, IQR 75-155
AZT600: +126 cells/µL, IQR 77-161 (p=0.48)

Four patients with plasma HIV-RNA > 400 copies/mL had NRTI and NNRTI drug resistance mutations (M184V, K103S, E138EQ, V90IV, 106AV, 181CY), two in each treatment arm.

Table 2. Proportion of patients (%) with plasma HIV RNA < 200 (<40) cop/mL at W24

Population/analyses	AZT 400	AZT 600	P- value
ITT (n=142):	88 (57)	86 (69)	0.755 (0.152)
ITT modified (n=142): Switch/Missing = Failure	79 (51)	79 (63)	0.931 (0.168)
Per Protocol Population (n=123):	91 (59)	92 (73)	0.817 (0.088)
VL > 1log5 (baseline)	89 (51)	88 (63)	0.818 (0.243)
VL ≤ 1log5 (baseline)	94 (81)	100 (95)	0.269 (0.221)
BMI ≤ 23 Kg/m2	84 (53)	91 (74)	0.447 (0.118)
BMI > 23 Kg/m2	97 (65)	92 (73)	0.394 (0.452)

Conclusions

Although we observed no difference in overall anemia rate, reduced dose zidovudine demonstrated improved safety, with fewer patients necessitating switch antiretroviral and blood transfusion because of severe anaemia.

Virological efficacy at week 24 seemed similar, though our sample size was not powered to demonstrate non-inferiority between the two dosing regimen.

In ressource-limited countries, the safety of the second-line regimen is a major concern. We recommend a larger phase 3 non-inferiority clinical trial using reduced zidovudine-based ART as a second-line regimen.

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Acknowledgments

Funding: the study has been supported with a grant from theBill and Melinda Gates Foundation (OPP1026207), by a grant from the University Hospital of Geneva (CI 71414 and 73404) as well as the Canton de Genève (CI 75432).

We thank the local study nurses for their involvment and enthusiam: Edwige Majolie Megne Tiche, Daniel Eroum, Geneviève Lamare.

We also thank the CNPS hospital staff of Emergency Ward and Centre de Traitement Agréé.

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