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Severe neutropenia in HIV-infected people starting antiretroviral therapy in West Africa

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BACKGROUND

- During the last decade, access to antiretroviral treatment (ART) has substantially improved in sub-Saharan Africa. Facing the growing number of people initiating ART, an adapted monitoring of treatment-related toxicity is needed in order to inform WHO and national recommendations for the use of ART
- Adverse events related to ART are common and represent the first cause of treatment modification in HIV-infected people in sub-Saharan Africa. ART drugs with potential toxicity such as Zidovudine (AZT) are still massively prescribed in HIV-infected patients and little information is available on adverse drug reactions such as neutropenia in real-life conditions

Objective: To estimate the incidence of severe neutropenia and associated factors after ART initiation in five West African countries

METHOD

Study population and data collection

- Study design = retrospective cohort analysis within the multicenter and prospective international epidemiologic database to evaluate AIDS (IeDEA) collaboration in West Africa (http://www.iedea.org/regions/west-Africa)
- Study population = HIV-infected adults participating in IeDEA West Africa database who:
  - initiated between 2002 and 2014 an ART regimen that contained three or more drugs
  - had absolute neutrophil count (ANC) ≥750 cells/mm^3 at ART initiation (baseline)
  - had at least one follow-up ANC measurement in the first six months following ART initiation
- Severe neutropenia defined as ANC <750 cells /mm^3
- Characteristics studied: gender, age, HIV clinic, year of ART initiation, exposure to AZT and other regimens, clinical stage and CD4 count, hemoglobin level

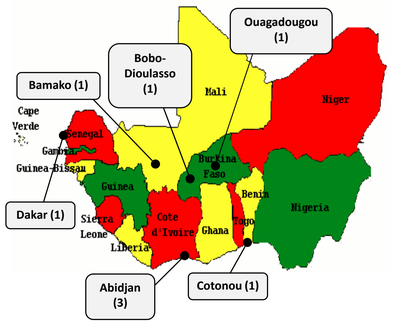


***Figure 1**. Participating HIV clinics*

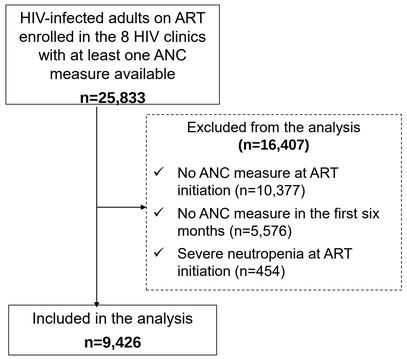


***Figure 2**. Study population flow chart*

Statistical analysis

- Incidence rate: number of patients with a first episode of severe neutropenia per 100 person-years (PY) of follow-up
- Univariate and multivariate Cox proportional hazards regression models for first events to assess the role of ART and other characteristics at baseline and time-updated
- Backward stepwise regression to keep only the most significant variables (p<0.05)

RESULTS

A total of **9,426** patients were included from Cote d'Ivoire (5,493), Burkina Faso (2,235), Benin (816), Mali (559) and Senegal (323)

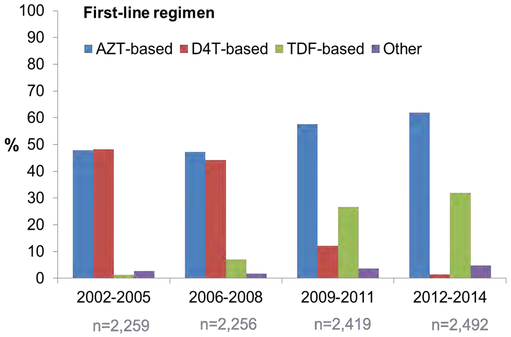
Baseline characteristics

- Median age = 37 years [Interquartile range (IQR) 31-44]
- Gender, women = 70.0%
- Median calendar year of ART initiation = 2009 [IQR 2006-2011]
- Median CD4 count = 174 cells/mm^3 [IQR 80-278]
- CDC stage 3 or WHO stage 4 = 16.5%
- Grade 1 neutropenia = 11.0% and grade 2 neutropenia = 4.8%
- Anemia (<10g/dL) = 31.2%
- Median haemoglobin = 10g/dL [IQR 9-12]
- ART regimen containing AZT = 53.9%

Incidence of severe neutropenia

- 888 cases of severe neutropenia identified (9,426 PY)
- Overall incidence rate = 9.1 per 100 PY (95% CI: 8.6-9.8)

***Figure 3.** First-line antiretroviral regimens prescribed according to calendar period, the IeDEA West Africa collaboration, 2002-2014 (N=9,426)*



*AZT: Zidovudine; D4T: Stavudine; NVP: Nevirapine; TDF: Tenofovir

***Table 1**. Cox regression univariate and multivariate models estimating risk of severe neutropenia within two years after ART initiation. The IeDEA West Africa collaboration, 2002-2014 (N=9,426)*

	Univariate analysis		Multivariate analysis*	
	HR (95% CI)	p	aHR (95% CI)	p
Time-updated exposure to AZT (months)		**<10^{-4}**		**<10^{-4}**
Not exposed	1		1	
≤ 6	1.8 (1.5 – 2.1)		2.2 (1.8 – 2.6)	
> 6-12	1.8 (1.4 – 2.4)		2.1 (1.6 – 2.8)	
> 12	1.4 (1.0 – 1.9)		1.6 (1.2 – 2.2)	
Calendar year of ART initiation		**<10^{-4}**		**<10^{-4}**
2002-2005	1		1	
2006-2008	0.6 (0.5 – 0.7)		0.9 (0.7 – 1.1)	
2009-2011	0.5 (0.4 – 0.6)		0.7 (0.6 – 0.9)	
2012-2014	0.6 (0.5 – 0.7)		0.6 (0.4 – 0.7)	
Baseline neutrophils count (cells/mm^3)		**<10^{-4}**		**<10^{-4}**
≥1,300	1		1	
1,000-1,300	1.7 (1.4 – 2.1)		1.5 (1.3 – 1.8)	
750-1,000	2.7 (2.2 – 3.4)		2.5 (2.0 – 3.1)	
Baseline hemoglobin level (g/dL)		0.9		0.3
≥10	1		1	
<10	1.0 (0.9 – 1.2)		1.1 (1.0 – 1.3)	
Missing	1.1 (0.8 – 1.5)		0.9 (0.6 – 1.5)	
Baseline clinical stage (CDC 3 or WHO 4)		**<10^{-4}**		**<10^{-2}**
No	1		1	
Yes	1.4 (1.2 – 1.6)		1.2 (1.0 – 1.4)	
Missing	1.0 (0.9 – 1.2)		1.6 (1.1 – 2.3)	
Time-updated CD4 count (cells/mm3)		**<10^{-4}**		**<10^{-2}**
≥350	1		1	
<350	1.4 (1.2 – 1.7)		1.3 (1.1 – 2.2)	
Missing	1.1 (0.9 – 1.5)		1.6 (1.1 – 2.2)	

HR: Hazard ratio; aHR: Adjusted hazard ratio; CI: Confidence Interval; AZT: Zidovudine; CDC: US Centers for Disease Control; WHO: World Health Organization;
*Analyses were stratified by HIV clinics

DISCUSSION

Incidence of severe neutropenia

- The incidence rate of severe neutropenia within our study was higher than among patients living with HIV before access to ART as previously reported in other sub-Saharan African settings
- However, the incidence of severe neutropenia was lower than the one reported in a cohort in Cote d'Ivoire where the majority of patients were exposed to both AZT and cotrimoxazole (CTX) prophylaxis (Moh *et al*, Antivir Ther, 2005) ➔ A combined exposure to AZT-based regimens and CTX prophylaxis would lead to an increased risk of severe neutropenia

Associated factors

- Severe neutropenia was significantly higher in HIV-infected patients initiating an AZT-containing ART regimen and this risk persisted over time
- An advanced clinical stage and a more profound immune-deficiency were independent risk factors for severe neutropenia ➔ Consistent with previous findings and emphasizes the need of an early ART initiation (as per 2015 guidelines)
- Significant differences between HIV clinics point out site specificities potentially related to unmeasured parameters such as exposure to CTX over time that may have interacted with exposure to AZT in the development of severe neutropenia

Limitations

- Our sample is quite limited compared to our study population initially targeted in the 8 HIV clinics. However, these two groups were not statistically different with regards to age, gender, initial CD4 count and initial ART regimen
- Aside ART, no information was available on other medications so we were not able to assess the impact of CTX on the occurrence of severe neutropenia

CONCLUSION

- The incidence of severe neutropenia after ART initiation among HIV-infected adults in West Africa was high and associated with AZT exposure
- In addition, worsening HIV disease parameters as AIDS stage and low CD4 count were associated with an increased risk of severe neutropenia
- In a context where cytotoxic drugs such as AZT are still widely prescribed, future efforts are needed to scale-up access to less toxic drugs such as tenofovir and to initiate ART earlier with less immune-deficiency according to recent WHO recommendations

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