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Initiation of ART based on Integrase Inhibitors increases the risk of IRIS

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Dat'Aids

Introduction: Immunocompromised HIV-infected patients frequently initiate ART based on integrase inhibitors (INSTI). Together with a low CD4 T cell count and a high likelihood of opportunistic infection, the sharp control of viral replication associated with INSTI-based ART might synergize the risk of immune reconstitution inflammatory syndrome (IRIS).

Objective: to determine the incidence of IRIS in exposed patients who initiated ART with or without INSTI as a third agent.

Methods: We selected from the Dat'AIDS cohort patients with a CD4 T cell count < 200/mm^3 starting from 01/01/2010 to 31/12/2015 ART based on 2 NRTIs associated with a bPI, a NNRTI or an INSTI, and admitted to hospital within 6 months. IRIS events were defined as symptoms consistent with an infectious or inflammatory condition associated with a drop of > 2 log_{10} copies/mL of HIV viral load, not explained by a newly acquired infection, the expected clinical course of a previous infection, or side-effects. Three physicians blinded to the ART regimen evaluated files and determined the classification by consensus. Characteristics associated with IRIS were analyzed in uni-and multivariate analysis.

Results: The study population included 2287 patients from 15 centers in France. Median age was 45 years (IQ_{25-75} 37-53), and 63% were men. The third agent was bPI in 65%, NNTI in 12%, and INSTI in 12%. At ART initiation, the median HIV viral load and CD4 T cell count were 5.2 log_{10} copies/mL (4,8-5,7) and 83/mm3 (31-146). IRIS occurred in 41 patients (1.8%) and was associated with tuberculosis (12 cases), atypical mycobacteria (10), JC virus (6), CMV (5), HHV-8 (4), *Toxoplasma* (2), *Cryptococcus* (1) and HBV (1). Patients receiving INSTI-based ART did not differ from those without INSTI regarding pre-ART HIV viral load and CD4 T cell count (table). IRIS occurred in 12/398 (3%) patients receiving INSTI-based ART, compared to 29/1889 (1.5%) patients without INSTI (OR 1.99 (1.1-3.5), p=0.04). Repartition of opportunistic infections did not differ according to ART regimen.

Conclusion: In conclusion, whilst relatively rare, the risk of severe IRIS requiring hospitalization appears greater in severely immunocompromised HIV-infected patients receiving INSTI-based regimens as first ART. This risk should be balanced with the benefit of these treatments in these patients.

The homogenous repartition of opportunistic infections among regimen groups argued against a bias of indication linked to mycobacterial infection and co-medication used, although we cannot preclude it formally. While effective control of HIV replication is key, initiation of ART based on INSTI in patients at high risk of IRIS deserves further studies.

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Introduction:

Integrase Strand Transfer Inhibitors (INSTI)-based regimen are now widely recommended as initial therapy for most patients, even in the setting of advanced HIV infection with opportunistic infections. The rapid decline of HIV viral load (VL) associated with INSTI-based ART in immunocompromised patients with a high likelihood of opportunistic infection might however synergize the risk of immune reconstitution inflammatory syndrome (IRIS).

Objective: to determine if IRIS incidence differs in immunocompromised patients who initiated ART containing or not an INSTI.

Methods:

- **The Dat'AIDS Cohort:**
  - French HIV medical centers that share the same electronic medical record system for the medical follow-up of HIV+ patients.
  - Merged database regularly updated for all patients from all the Dat'Aids centers => Dat'Aids cohort.
- **Patients:** All patients starting their first ART **between 01/01/2010 and 31/12/2015** with **CD4 cell counts below 200/mm^3** were classified as **INSTI+** if an INSTI was included in their regimen and **INSTI-** otherwise.
- **IRIS:** Medical charts of patients hospitalized within the first 6 months of ART were examined blinded to the choice of first ART (INSTI+ or INSTI-) by three HIV specialists (MD, GMB and PD). Unmasking and paradoxical IRIS events were defined as symptoms consistent with an infectious or inflammatory condition associated with a drop of > 2 log_{10} copies/mL of HIV VL, not explained by a newly acquired infection, the expected clinical course of a previous infection, or side-effects, according to adapted AIDS Clinical Trials Group IRIS criteria
- **Statistical analysis:** Continuous variables were described by medians, first and third quartiles, and compared between groups by Kruskal-Wallis rank sum test. Categorical variables were described by frequencies and compared between groups by Chi-Square test or Fischer exact when needed. Linear regression was use to estimate the OR of IRIS in INSTI+ patients.

Characteristics at ART initiation and evolution compared between patients receiving INSTI (INSTI+) and patients not receiving INSTI (INSTI-).

		ART with INSTI N=398	ART without INSTI N=1889	p
Age, median (years, [IQ25-75])		45 [37 ; 55]	45 [37 ; 53]	0.3
Gender (% of men)		65.8	61.9	0.3
Route of infection (%)	Heterosexual	53.0	53.6	0.9
	Men with men	30.7	30.6	
	Blood products /IVDU	2.5	2.4	
	Other/Unknown	13.8	13.4	
Pre-ART CD4 cell count, median cells/mm3 ([IQ25-75]		34 [16-85]	84 [32-146]	0.06
Pre-ART Vial Load, median log_{10}.copies/ml ([IQ25-75])		5.3 [4.8-5.7]	5.2 [4.7-5.6]	0.06
Viral load after 3 months of ART, median log_{10}.copies/ml ([IQ25-75])		1.7 [1.4-2.1]	2.1 [1.6-2.5]	<0.001
ART regimen	2 NRTI + 1 bPI	0	79.0	
	2 NRTI + 1 NNRTI	0	14.5	
	2 NRTI + 1 INSTI	70.6	0	
	Other (more than 3)	29.4	6.5	
IRIS Cases, N(%)		**12 (3.0)**	**29 (1.5)**	**0.05**
OR [95% CI]		**1.99 [1.09-3.47]**	**Ref.**	**0.04**
IRIS related to	M. tuberculosis	5 (42%)	7 (58%)	0.81
	M. avium	2 (20%)	8 (80%)	
	Progressive Multifocal Leukoencephalopathy	1 (16.7%)	5 (83.3%)	
	CMV	2 (40%)	3 (60%)	
	Kaposi sarcoma	2 (50%)	2 (50%)	
	C. neoformans	0	1	
	Toxoplasmosis	0	2	
	Hepatitis B	0	1	

Discussion:

- A sharper control of HIV replication by more potent ART regimens, as reported for INSTI-based regimens, may increase the risk of IRIS in immunodeficient patients at high risk of opportunistic infections.
- Using a prospectively collected multi-center cohort, we found that IRIS events requiring hospitalization, mainly related to mycobacterial infections, were twice more frequent among patients with CD4 cells below 200/mm^3 who initiated INSTI-based ART regimen.
- The lower HIV VL observed after 3 months of ART in the INSTI+ group experiencing more IRIS events supports our hypothesis.
- In patients with extensive opportunistic infections at high risk of IRIS, achievement of viral replication control is obviously instrumental and highly desirable. Nevertheless using an **INSTI may enhance the risk of IRIS** in this population. Strict clinical monitoring during the 3 to 6-month period usually associated with IRIS occurrence is highly recommended.
- The relatively low frequency of IRIS events in our study (1.8%) may be explained by the strict definition of IRIS we used and by our exclusive focus on severe IRIS events requiring hospitalization and treatment, avoiding thereby less relevant IRIS events such as darts or *Herpesviridae*-related IRIS.
- Because of known interactions between protease inhibitors and rifampicin, it is possible that in case of a pre-existing mycobacterial disease, patients were more prone to receive an INSTI-based regimen. As shown in the table, we could not show that this was the case, but we may lack power to find any significant difference in the choice of first ART in IRIS cases.

Conclusion:

In conclusion, whilst relatively rare, the risk of severe IRIS requiring hospitalization appears greater in severely immunocompromised HIV-infected patients receiving INSTI-based regimens as first ART. This risk should be balanced with the benefit of these treatments in these patients.