NUKE-SPARING REGIMENS AS A MAIN SIMPLIFICATION STRATEGY AND HIGH LEVEL OF TOXICITY RESOLUTION AFTER ANTIRETROVIRAL SWITCH: THE SWITCHART STUDY

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P287 HIV Drug Therapy | 2-6 November 2014; Glasgow, UK

BACKGROUND

- The advent of combined antiretroviral therapy (cART) in the past decades has led to suppression of human immunodeficiency virus (HIV) replication in most cases, with the potential achievement of a normal life expectancy.[1] As cART cannot eradicate the infection, it must be prolonged lifelong and most patients need modifications of their antiretroviral regimens over time.
- Virological failure was the main reason for switching the cART a few years ago; however, the more effective and/or convenient antiretroviral drugs currently available may have affected the reasons for cART switch. Indeed, treatment simplification and toxicity seem to have gained importance in daily practice.
- Simplification strategies have emerged as a consequence of the use of new drugs and approaches to improve adherence, reduce pill burden and minimize side effects. However, the risk of drug resistance still remains –especially when treatment adherence is incomplete[2,3]–, which restrict the alternatives for HIV treatment.
- Despite the improvements achieved, cART is not devoid of adverse reactions such as central nervous system (CNS) symptoms in patients receiving efavirenz[4] or impaired renal function in those receiving tenofovir.[5,6] These reactions may compromise cART administration and may not be fully reversible after treatment cessation.

OBJECTIVE

- This study assessed the current reasons for switching the cART in daily clinical practice and the subsequent clinical evolution of toxicities leading to treatment switch.

METHODS

Study design

- This was a multicenter retrospective observational study conducted at 12 Spanish hospitals.
- Patients' information was retrieved from computerized medical charts at the moment of cART switch (baseline) and during the following year, including demographics, HIV-infection-related data, previous cART, reasons for cART switch, new cART and evolution of toxicities leading to cART switch.

Patient population

- The patient population included those patients meeting the selection criteria described in Figure 1 who accepted to participate in the study between September and November 2013.

Figure 1. Patient selection criteria

Inclusion criteria

- Patients aged ≥18 years.
- Diagnosis of HIV infection.
- Treatment with cART that was switched as per routine clinical practice between January 2011 and July 2012, and remained uncharged for at leats one year after the treatment switch.

Exclusion criteria

- cART switch consisting of the same active ingredients being administred in just one tablet of as co-formulated drugs instead of independently administred, and the other way around.
- Total or selective interruptions of their cART not indicated by any specialist doctor.

cART: combined antiretroviral therapy; HIV: human immunodeficiency virus.

RESULTS

- A total of 246 patients were included, whose main baseline characteristics are outlined in Table 1.

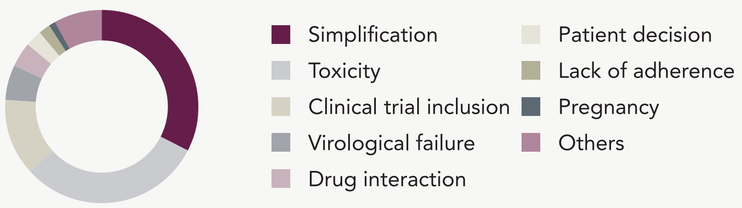
Table 1. Baseline patient characteristics (N=246)

Patient characteristics	Value
Age (years), median (IQR)	47 (42 - 52)
CD4 count (cells/µl), mean ± SD[a]	586 ± 306
HIV-RNA < 50 copies/ml, n (%)[a]	198 (81)
Number of previous regimens, mean ± SD[a]	5 ± 4
Time on previous cART (years), mean ± SD[b]	3 ± 2

cART: combined antiretroviral therapy; HIV: human immunodeficiency virus; IQR: interquartile range; SD: standard deviation. [a]Missing data, n=1; [b]Missing data, n=10.

- The main reasons for cART switch were simplification (80 patients, 33%) and toxicity (77 patients, 31%), followed by clinical trial inclusion (32 patients, 13%), virological failure (15 patients, 6%), drug interaction (9 patients, 4%), patient decision (7 patients, 3%), lack of adherence (5 patients, 2%), pregnancy (2 patients, 1%) and others (19 patients, 8%) (Figure 2).

Figure 2. Reasons for combined antiretroviral therapy switch (N=246)



COMBINED ANTIRETROVIRAL THERAPY SWITCH DUE TO SIMPLIFICATION

- Eighty patients switched to a simpler regimen; baseline patient characteristics are outlined in Table 2.

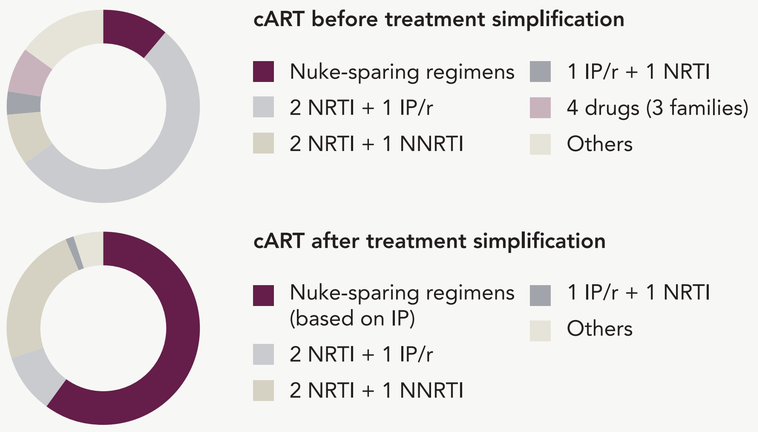
Table 2. Characteristics of patients with combined antiretroviral therapy switch due to simplification (N=80)

Patient characteristics	Value
Age (years), median (IQR)	48 (40 - 53)
CD4 count (cells/µl), mean ± SD	608 ± 265
HIV-RNA < 50 copies/ml, n (%)	71 (89)
Number of previous regimens, mean ± SD[a]	6 ± 5
Time on previous cART (years), mean ± SD[b]	3 ± 2

cART: combined antiretroviral therapy; HIV: human immunodeficiency virus; IQR: interquartile range; SD: standard deviation. [a]Missing data, n=1; [b]Missing data, n=2.

- Previous cART mostly included 2 nucleoside reverse transcriptase inhibitors (NRTI) plus 1 protease inhibitor (PI) boosted with ritonavir (PI/r) (43 patients, 54%), followed by nuke-sparing regimens (9 patients, 11%), 2 NRTI plus 1 non-nucleoside transcriptase inhibitor (NNRTI) (7 patients, 9%), 4 drugs (3 families) (6 patients, 8%), 1 IP/r plus 1 NRTI (3 patients, 4%) and others (12 patients, 15%) (Figure 3).
- The simplification strategy mainly contained nuke-sparing regimens (48 patients, 60%) (Figure 3) based on PIs (ritonavir-boosted darunavir: 38 patients, 48%): PI monotherapy in 37 (46%) patients, dual therapy in 10 (13%) patients (PI/r+maraviroc: 7 patients, 9%; PI/r+NNRTI: 3 patients, 4%) and triple therapy in another (1%) (PI/r+maraviroc+raltegravir).
- The second preferred option for simplification was 1 NNRTI plus 2 NRTI (19 patients, 24%) and all patients under a 4-drug treatment (3 families) (7 patients, 8%) also switched to fewer agents (3 drugs: 3 patients, 4%; 2 drugs: 3 patients, 4%) –mostly eliminating NRTI from their cART (4 patients, 5%).

Figure 3. Combined antiretroviral therapy before and after treatment simplification (N=80)



cART: combined antiretroviral therapy; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; PI/r: ritonavir-boosted protease inhibitor.

COMBINED ANTIRETROVIRAL THERAPY SWITCH DUE TO TOXICITY

- Seventy-seven patients switched due to toxicities; baseline patient characteristics are outlined in Table 3.

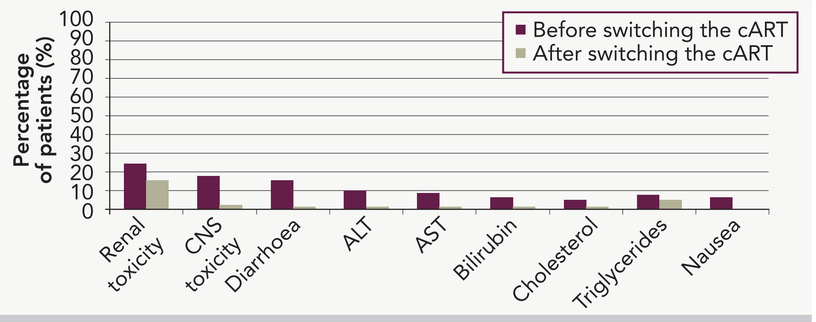
Table 3. Characteristics of patients with combined antiretroviral therapy switch due to toxicity (N=77)

Patient characteristics	Value
Age (years), median (IQR)	47 (43 - 53)
CD4 count (cells/µl), mean ± SD	606 ± 350
HIV-RNA < 50 copies/ml, n (%)	63 (82)
Number of previous regimens, mean ± SD	4 ± 3
Time on previous cART (years), mean ± SD[a]	3 ± 3

cART: combined antiretroviral therapy; HIV: human immunodeficiency virus; IQR: interquartile range; SD: standard deviation. [a]Missing data, n=3.

- The main reasons for cART switch were renal (19 patients, 25%) and CNS (14 patients, 18%) toxicities, followed by diarrhoea (12 patients, 16%), liver enzyme elevation (ALT: 8 patients, 10%; AST: 7 patients, 9%; bilirubin: 5 patients, 7%), lipid elevation (triglycerides: 6 patients, 8%; cholesterol: 4 patients, 5%), nausea (5 patients, 7%) and others (frequency ≤5%) (Figure 4).

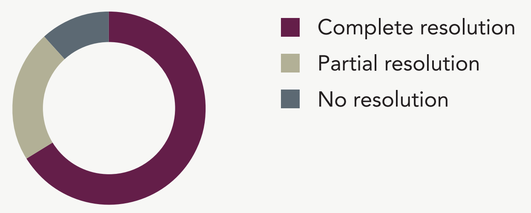
Figure 4. Main toxicities before and after switching the combined antiretroviral therapy (N=77)



ALT: alanine aminotransferase; cART: combined antiretroviral therapy; AST: aspartate aminotransferase; CNS: central nervous system.

- All patients with cART switch due to renal toxicity were receiving tenofovir (n=19); in most of these patients tenofovir was removed from the new regimen (18 patients, 95%), which mainly contained lamivudine/abacavir (9 patients, 50%) or were nuke-sparing (4 patients, 22%).
- Among patients with CNS toxicity (n=14), 11 (79%) patients were receiving efavirenz; the main new treatment was a second-generation NNRTI (etravirine) plus 2 NRTI (6 patients, 43%).
- Toxicities were completely resolved in 51 (66%) patients, partially resolved in 17 (22%) and not resolved in only 9 (12%) (Figure 5); the median time from cART switch to toxicity resolution was 4 (2-8) months.

Figure 5. Resolution of toxicities after switching the combined antiretroviral therapy (N=77)



CONCLUSIONS

- The most frequent reasons for switching the cART regimen in daily clinical practice are simplification and toxicities. Thus, therapy simplification has emerged as a main reason for cART switch and treatment toxicity still remains as major concern for therapy administration.
- The preferred simplification strategies are nuke-sparing regimens consisting of PI/r monotherapy or dual therapy, mainly based on ritonavir-boosted darunavir. The most prevalent toxicities leading to cART regimen switch are renal and CNS toxicities
- Although the occurrence of toxicities may limit cART administration over time, its switch enables toxicities to be completely resolved in most patients in the short term.

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Acknowledgements to Janssen for study funding.