

BACKGROUND

- Triple-class treatment-experienced patients with extensive viral drug resistance is increasing worldwide
- Usage of salvage regimens with at least 2 fully active drugs have led to high rates of maximal sustained virological suppression among these patients
- New antiretroviral agents (ARV) with expanded activity (XA-ARV) in existing (tipranavir, darunavir, enfuvirtide and etravirine) and novel classes (raltegravir and maraviroc) are commonly the cornerstone of successful salvage therapy in heavily-experienced patients.
- Expert care is essential in the interpretation of resistance tests, in the design of effective salvage regimens and to preclude the emergence of resistance to the new agents.
- In Mexico an ARV universal free-access program has been consolidated and most of the providers, in the Ministry of Health Program, are general physicians.
- A national committee was created by the Ministry of Health in 2008 to aid Mexican physicians in the prescription of an optimal ARV regimen, based on history and resistance testing, in heavily treatment-experienced patients with virologic failure, and to optimize the use of the new XA-ARV drugs.

OBJECTIVE

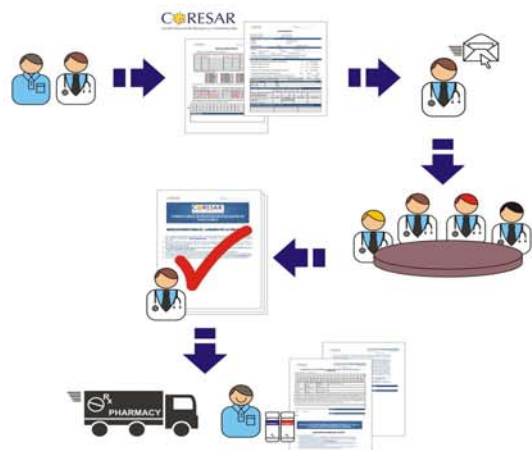
To assess the impact (early viral response and mortality) of a national advisory board run by the Ministry of Health in Mexico, to aid physicians in the prescription of an optimized salvage ARV regimen (based on history and resistance testing) in heavily treatment-experienced patients with virologic failure.

METHODS

Study design: Single arm open clinical trial.

Eligibility criteria: Patients with a history of 2 or more ARV regimens, and viral failure, whose physician received a recommendation of a new optimized regimen through a national advisory board.

Intervention: Following the physician's request individual eligible cases were analyzed by a panel of 10 specialists with sound experience in ARV therapy. Based on the history of previous ARV exposure and resistance testing (HIV genotype in all patients and virtual phenotype in some) a salvage regimen (with at least 2 fully active and one or more partially active drugs) was designed by consensus of the board members. This regimen was recommended to the practitioner caring the patient and, if acceptance of the advice was obtained from the physicians, darunavir, raltegravir and/or etravirine were sent to the health care center. These XA-ARVs were under the caution and regulation of the board's pharmacy and were not available by ways other than through the advisory board. Other ARV drugs included in the recommended regimen were dispensed through the regular federal ARV free-access system.



Surveillance of these patients was done through electronic registries and interviews with their clinicians.

Primary outcome measures: Physician's adherence to the recommended therapy, patient's plasma viral load and mortality after the initiation of the optimized salvage regimen

Statistical analysis: Descriptive: percentages, median and interquartile range (IQR); Comparisons: Mann-Whitney U Test for continuous variables and chi-square test for categorical and ordinal variables.

RESULTS

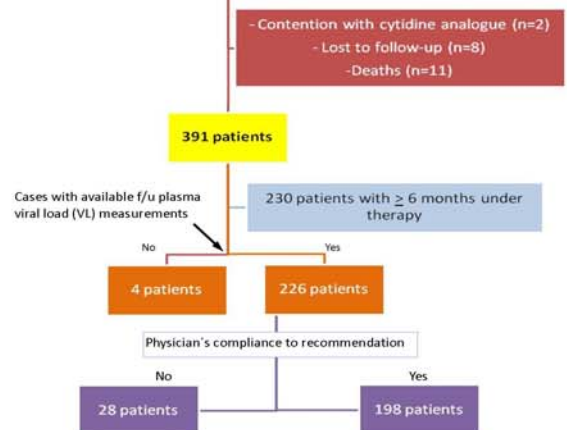
We present the data of 412 pts, 336 (82%) male, with ARV treatment failure receiving a therapeutic recommendation by the Advisory Board.

Feature	Median	Interquartile range
Age: years (n = 378)	39.9	33.5 – 46.6
Time since HIV diagnosis: years (n = 348)	9.1	6 - 12
Time since start of first ARV regimen: years (n = 377)	7.7	4.7- 10.1
Number of previous ARV regimens (n = 393)	4	3 - 5
T-CD4 cell count (nadir): cells/ml (n = 341)	55	22-122
T-CD4 cell count (before assessment by the Advisory Board): cells/ml (n = 399)	182	79-346

Undetectable VL according to historical data



412 patients with ARV treatment failure receiving a therapeutic recommendation by the Advisory Board



213/226 (94%) pts with available VL at f/u reached < 400 copies/mL after a median time of salvage therapy of 25 weeks (IQR 14.9,40.8). The median increase of CD4 count (n=223) was 94 cel/mm³ (IQR -2,198), and viral rebound occurred in 29/226 (13%) cases. The median time of follow-up was 41.3 wk (IQR 27.8, 54.25).

VIRAL OUTCOMES IN 214 PATIENTS WITH 6 OR MORE MONTHS OF FOLLOW-UP

Type of analysis:	PERCENTAGE OF PATIENTS			
	VL less than 400 copies/ml	2,000 copies/ml > VL > 400 copies/ml	VL = > 2,000 copies/ml	Rebound
Intention-to-treat (n = 237)*	77	2	9	12
Per-protocol (n=198)	82	2	4	12

* In patients lost to follow-up and in those with missing data, the outcome was defined as "VL = > 2,000 copies/ml". Includes patients in whom his/her physician did not comply with the recommendation

DISCUSSION

- There is a high level of compliance by the Ministry of Health physicians to prescribe the recommended ARV salvage therapy by the advisory board.
- Cases assessed by the advisory board were characterized by a history of frequent lack of drug compliance to previous regimens, a high exposure to ARV (50% of patients with 4 or more previous regimens, mostly failing therapies), with genotypes showing multiple resistance mutations to the 3 main ARV classes, and the unavailability to XA new ARV's. It was thus expected that very often new salvage therapy designed by the practitioner would not reach the goal of maximal and sustained viral suppression.
- It seems possible to achieve this goal through a strategy of experienced professionals providing a carefully thought and consensual advice to physicians and through the regulation of access to new XA-ARV's.
- A longer and more comprehensive follow up of patients from this cohort is still needed to assess the actual long-term success of this strategy.
- It is of interest to investigate the determinants of viral failure among cases from our cohort, including poor drug adherence and the advice of suboptimal regimens by the advisory board.
- As more than half of our patients apparently have never had an undetectable plasma HIV viral load, it is expected that cases achieving this aim after our intervention will lead to a dramatic decrease in morbidity, mortality and health care costs.