Second line failure and protease inhibitor resistance in a clinic in Johannesburg, South Africa

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ABSTRACT

Background: In resource limited settings, where few options exist for patients failing second line antiretroviral therapy (ART), programmatic approaches to treatment failure must be developed. We report on an approach to standardizing care for patients failing second line in South Africa.

Methodology: Retrospective study of 486 patients on second line protease inhibitor (PI) ART with a HIV-1 RNA >400 copies/ml at Themba Lethu Clinic in Johannesburg, South Africa between March 2012 and December 2013. Patients underwent adherence counselling and repeat viral load testing. Those with a repeat viral load after re-adherence of >1000 copies/ml underwent testing for HIV-1 drug resistance if adherence had improved.

Results: Of the 486 patients reviewed 459 were Themba Lethu Clinic (TLC) patients and 27 were referred from other sites for evaluation of second line failure. Of the TLC patients, 60% were female. The median age was 40.9 years (IQR 35.7 – 46.8), CD4 count was 333 cells/mm^3 (190 – 519) and viral load was 3104 copies/ml (1270 – 19000). The average length of time since ART initiation was 72.3 months (48.4 – 96.4). Of the 410 (84%) patients who had a ≥1 repeat viral load, 203 (55%) achieved viral re-suppression (<400 copies/ml) between three and six months after intervention. Among those that suppressed (79%), time to virolgical suppression was a median of 5.4 months (2.8 – 9.6).

Of the 72 HIV resistance tests conducted, 7 (11%) did not amplify, 18% (12/65) had no clinically significant resistance, 29% (19/65) had resistance to one of the thymidine analogues in clinical use (zidovudine or stavudine), 22% (14/65) had tenofovir resistance, and 26% (17/65) had resistance to one of three protease inhibitors in use in the South African public sector (atazanavir, lopinavir and darunavir).

Conclusions: Although most second line failures remain related to adherence and can be overcome with careful counselling, we found that 26% of patients who underwent HIV drug resistance testing had clinically significant protease inhibitor resistance.

BACKGROUND

- HIV treatment failure rates in Johannesburg on non-nucleoside reverse transcriptase inhibitor (NNRTI) based first line therapy are 11.9 after five years. (Fox et al, AIDS 2012; 26:14)
- Protease inhibitor (PI) based second line failure rates are much higher and approach 38% at 3 years in low and middle income countries. (Ajose et al, AIDS 2012; 26:8)
- In 2013 South Africa recommended patients failing 2nd-line undergo genotype testing and referral for 3rd-line drugs (darunavir, etravirine, raltegravir) which were previously not available in the public sector.
- We seek to describe the experience of an urban clinic in Johannesburg with 2nd-line failure and protease inhibitor resistance.

METHODS

Study design and population

- Retrospective study of 486 patients on second line protease inhibitor (PI) ART with a HIV-1 RNA >400 copies/ml at Themba Lethu Clinic in Johannesburg, South Africa between March 2012 and December 2013.
- Patients underwent second line failure intervention (see figure 1)
- Those with a repeat viral load >1000 copies/ml after re-adherence counselling underwent testing for HIV-1 drug resistance if the treating clinician believed the patient had good adherence
- Sequences were graded as intermediate or resistant using the Stanford University HIV Drug Resistance Database. Genotypes with intermediate or high level resistance were graded as 'resistant'

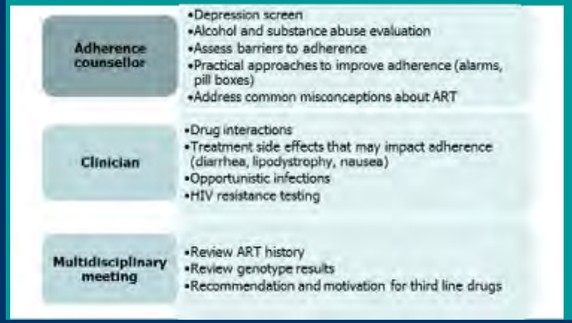
Statistical analysis

- Demographics and clinical characteristics were summarized using descriptive statistics.

Ethical Approval

- Ethical approval was granted by the Human Research Ethics Committee at the University of the Witwatersrand. Analysis of

Figure 1 – Second line failure intervention



RESULTS

Table 1 Patient characteristics at start of second line failure intervention (n=486)

Variable	TLC (n= 459)	Referral (n=27)*
Age	40.9 (35.7 – 46.8)	38.0 (31.2 – 41.5)
Female (N, %)	275 (60%)	13/19 (68%)
CD+ T cells/mm^3	333 (190 – 519)	64 (22 – 581)
HIV-1 RNA (copies/ml)	3104 (1270 – 19000)	3387 (932 – 99142)
Total time on first-line (months)	22.8 (12.7 – 41.6)	-
Total time on second-line until failing (months)**	15.6 (6.4 – 33.9)	-
Never suppressed < 400 copies/ml while on second-line	186/449 (41%)	10/19 (53%)
Time since second line failure intervention (months)	11.5 (7.6 – 14.8)	10.6 (5.8 – 13.9)
Time from intervention to switch to third line(months)	3.6 (1.5 – 6.7)	0.6 (0.2 – 1.5)
Total time on ART (months)	72.3 (48.4 – 96.4)	15.0 (9.2 – 18.7)

*Referral defined as a first visit date less than 12 months before third-line clinic start date
**Defined as VL > 400 copies/ml

Figure 2 – Flow of patients through second line failure intervention

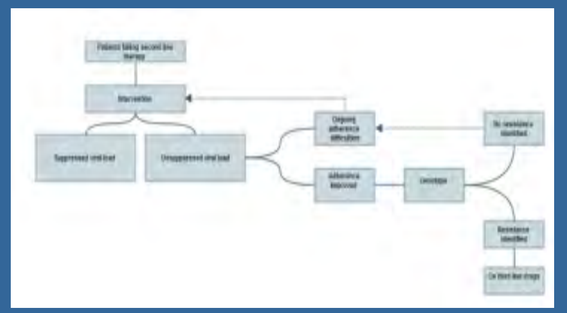


Table 2: Outcomes

Variable	N (%)
Total patients with second line failure	486
Had a repeat viral load	410/486 (84%)
Achieved virologic suppression (<400copies/ml) at 3-6 months Viral load ≥1000 copies/ml at 3-6 months	203/372 (55%) 129/372 (35%)
Time to re-suppression (<400copies/ml) (months)	5.4 (2.8 – 9.6)
No of patients referred for HIV genotype testing	72/486 (15%)
Patients on third line therapy *	33
Virologic suppression (< 400copies/ml) after 3 months of third line therapy Viral load >1000copies/ml after 3 months on third line	18/23 (78%) 3/23 (13%)

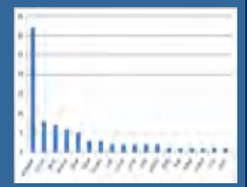
* Third line drugs include darunavir, etravirine, raltegravir

Table 3: HIV resistance testing results

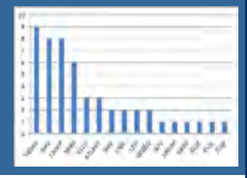
HIV resistance tests	N = 72
Did not amplify	7 / 72 (11%)
Wild type virus	12 / 65 (18%)*
Thymidine analogue resistance**	19 / 65 (29%)
Tenofovir resistance	14 / 65 (22%)
Thymidine analogue and tenofovir resistance	14 / 65 (22%)
1st generation NNRTI***	43 / 65 (66%)
2nd generation NNRTI ****	8 / 65 (28%)
Protease inhibitor resistance*****	17 / 65 (26%)
Atazanavir	16 / 65 (25%)
Lopinavir	12 / 65 (18%)
Darunavir	2 / 65 (3%)

* Percentage of resistance tests that were successfully amplified
** Thymidine analogues in clinical use in South Africa include zidovudine and stavudine
*** Nevirapine, efavirenz
**** Etravirine, rilpivirine

NRTI Mutations



PI Mutations



CONCLUSIONS

- The majority of patients in this cohort (55%) had a suppressed viral load within 6 months of intervention demonstrating that most second line failures remain related to adherence and can be overcome with careful counselling
- We found that 26% of patients who underwent HIV resistance testing had clinically significant protease inhibitor resistance.

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