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SOLTHIS : Evaluation of a Decentralized Program for Access to ARV in Ségou, Mali

Solthis
En partenariat avec l'Initiative Malienne d'Accès aux ARV (IMAARV)

B Jarrousse[1], A Doumbia[2], M Ba[3], E Klement[4], L Tégna[1], B Diarra Sonou[5], Z Traore[2], D Traore[6], B Touré[1], S Tchiombiano[1], B Dembélé[2], C Tétrel[4], A Maïga[2] , G Carcelain[7] , AG Marcelin[7], B Autran[4,7], C Katlama[4,7]

[1] SOLTHIS Ségou, Mali, [2] Hôpital Régional Ségou, Mali, [3] ONG Walé, Ségou, Mali, [4] SOLTHIS Paris, France, [5] Centre de Santé de Référence Ségou, Mali, [6] ONG APROFEM Ségou, Mali, [7] Hôpital de la Pitié-Salpêtrière, Paris, France

Abstract (updated):

SOLTHIS : Evaluation at 18 months of an integrated decentralized ARV treatment program in Ségou, Mali.

B Jarrousse[1], A Doumbia[2], M Ba[3], E Klement[4], L Tégna[1], B Diarra Sonou[5], Z Traore[2], D Traore[6], B Touré[1], S Tchiombiano[1], B Dembélé[2], C Tétrel[4], A Maïga[2], G Carcelain[7], AG Marcelin[7], B Autran[4,7], C Katlama[4,7]

[1]SOLTHIS Ségou, Mali, [2]Hôpital Régional Ségou, Mali, [3]ONG Walé, Ségou, Mali, [4]SOLTHIS Paris,France, [5]Centre de Santé de Référence Ségou, Mali, [6]ONG APROFEM Ségou, Mali, [7]Hôpital de la Pitié-Salpêtrière, Paris, France

Background: Solidarité Thérapeutique et Initiatives contre le SIDA (SOLTHIS) is a french medical NGO committed to HIV care whose main objective is to provide HIV care and antiretroviral therapy (ART) to patients in resource-limited countries. We report here the preliminary results of the first simplified HAART program implemented by SOLTHIS in Ségou rural district, Mali, supported by the Initiative Malienne d'Accès aux ARV (IMAARV) and the Ministry of Health.

Methods : Support included : training physicians in their use of ARVs, healthcare providers in adherence-focused activities; developing form-guided patient care protocols; support of pharmacy and lab; development of an electronic patient monitoring system.

Adults who started HAART between January 1st, 2004 and June 30, 2005 were included, except female patients enrolled in PMTCT program. Data were collected using FUCHIA monitoring software. Clinical assessment was planned at baseline then every month, immunological evaluation at baseline, month 6 then every six months. Virological evaluation was performed in a subgroup of 108 patients after six or twelve months of follow-up.

Results: 376 adult patients had been included: 61% were women, median age was 35 years. At baseline 94 % pts were WHO stage III or IV. Median weight was 48 kg (42 - 55 kg) . Median CD4 cell count was 112 cells/mm3; 98 % were ART-naive. The dominant regimen was stavudine/lamivudine/nevirapine (84%), used in fixed-dose combination (CIPLA, India) since October 2004. At follow up, 231 (61,4%) were still on HAART, 82(21,8%) had died (median time to death : 36.5 days). 57(15%) were lost to follow-up, 6 stopped treatment. Median weight increase was + 11 kg and median CD4 increase was + 177 cells/mm3 at six months in evaluable patients. In virological subtudy of 108 patients tested , 77.5% had a viral load below 200 copies/mlafter six months of treatment and 82.5% after 12 months of treatment.

Conclusion: Our preliminary data demonstrate 1/ that scaling-up HAART use for HIV- positive adults is feasible in African decentralized area 2/ that a simplified HAART strategy provides efficient clinical and immunological response. Increased early mortality, largely due to advanced HIV disease at HAART initiation rises the question of medical care organization and information of population regarding access to VCT in rural African setting. In next years, virological monitoring should be a critical issue for early detection of treatment failure.

Résumé (actualisé):

SOLTHIS : Evaluation à 18 mois d'un programme intégré d'accès décentralisé au traitement ARV à Ségou, Mali

B Jarrousse[1], A Doumbia[2], M Ba[3], E Klement[4], L Tégna[1], B Diarra Sonou[5], Z Traore[2], D Traore[6], B Touré[1], S Tchiombiano[1], B Dembélé[2], C Tétrel[4], A Maïga[2], G Carcelain[7], AG Marcelin[7], B Autran[4,7], C Katlama[4,7]

[1]SOLTHIS Paris,France, [2]Hôpital Régional Ségou, Mali, [3]ONG Walé, Ségou, Mali, [4]Centre de Santé de Référence Ségou, Mali, [5]ONG APROFEM Ségou, Mali, [6]Hôpital de la Pitié-Salpêtrière, Paris, France

Propos : Solidarité Thérapeutique et Initiatives contre le SIDA (SOLTHIS) est une organisation non gouvernementale (ONG) française de médecins engagés dans la lutte contre le VIH/SIDA dont l'objectif principal est de fournir un accès aux soins et aux médicaments antirétroviraux pour les patients infectés par le VIH dans les pays à ressources limitées. Nous rapportons les résultats préliminaires du premier programme d'accès aux ARV développé par SOLTHIS dans la région rurale de Ségou, au Mali avec le soutien de l'Initiative Malienne d'Accès aux ARV (IMAARV) et du Ministère de la Santé malien.

Méthodes : L'appui de SOLTHIS incluait : la formation des médecins à la prescription et au suivi des ARV ; la formation des soignants à l'éducation thérapeutique et à l'aide à l'observance ; le développement de guides de prescription ; le support technique de la pharmacie et du laboratoire ; le développement d'un système informatisé de suivi des patients.

Les adultes ayant initié des ARV entre le 1er janvier 2004 et le 30 juin 2005 ont été inclus, à l'exception des femmes enceintes incluses dans le programme PTME. Les données ont été recueillies en utilisant le logiciel de suivi FUCHIA. L'évaluation clinique était réalisée à l'inclusion, puis tous les mois, l'évaluation immunologique à l'inclusion, au sixième mois, puis tous les 6 mois. Une évaluation virologique a été réalisé dans un sous-groupe de 108 patients après six mois de suivi..

Résultats : 376 patients adultes ont été inclus : 61% étaient des femmes, l'âge médian était de 35 ans. A l'inclusion, 94 % des patients étaient au stade III ou IV de l'OMS. Le poids médian à l'inclusion était : 48 kg (42– 55 kg). Le taux médian de CD4 sanguins était de 112/mm3. 98 % des patients étaient naïfs de traitement. 84% des patients ont initié stavudine/lamivudine/névirapine (d4T3TC/NVP), utilisée sous formulation combinée à dose fixe (CIPLA, Inde) à partir d'octobre 2004. A la date d'analyse, 231(61,4%) adultes étaient suivis sous ARV, 82 (21,8%) étaient décédés (médiane de survenue : 36,5 jours), 57(15%) étaient perdus de vue, 6 en arrêt de traitement. Le gain pondéral médian était de 11 kg et le gain médian de CD4 était de + 177 cellules/mm3 chez les patients évaluables à 6 mois. Dans la sous-étude virologique de 108 patients testés, 77,5% présentaient une charge virale < 200 copies/ml après 6 mois de traitement, 82,5% après 12 mois de traitement..

Conclusion: Nos données préliminaires démontrent que 1) l'accès aux ARV des adultes infectés par le VIH est réalisable dans un contexte africain décentralisé 2) qu'une stratégie ARV simplifiée fournit une réponse clinique et immunitaire efficace. La mortalité précoce élevée, en grande partie due au stade avancé de l'infection VIH au moment de l'initiation des ARV, soulève la question de l'organisation des soins et de l'information de la population pour l'accès au conseil et au dépistage dans un contexte rural africain. Dans les prochaines années, la surveillance virologique pourrait devenir indispensable à la détection précoce de l'échec thérapeutique.

Correspondence to Bernard Jarrousse, SOLTHIS BP E 529, Ségou Mali
Tel:+22320320864, email:bernard.jarrousse@solthis.org

SOLTHIS Pavillon Laveran Hôpital de la Pitié-Salpêtrière,
47 bd. de l'Hôpital 75651 Paris Cedex 13 France
Tel:+33153610794, Fax: +33153610748, email: contact@solthis.org

Introduction

Solidarité Thérapeutique et Initiatives contre le SIDA (SOLTHIS)

- French medical non-governmental organization (NGO) committed to HIV care
- Main objective : to provide HIV care and ARV to patients in resource-limited countries.
- 3 programs in Mali, Niger and Benin : > 1200 HIV-infected patients included

We report here the preliminary results of the first simplified highly active antiretroviral therapy (HAART) program implemented by SOLTHIS in Ségou rural district, Mali, supported by the Initiative Malienne d'Accès aux ARV (IMAARV) and the Ministry of Health of the Republic of Mali.

Methods

- **Support provided by SOLTHIS** :
  - Training physicians in their use of ARVs and therapeutic counselors in adherence-focused activities
  - Developing form-guided patient care protocols
  - Technical support of pharmacy
  - Technical support of laboratory by training biologist and laboratory assistants to CD4 measurement
  - Development of an electronic patient monitoring system
  - Provision of clinical care oversight
- **Standardized first-line drug regimen**: **Generic d4T + 3TC + NVP**
- **Alternative regimens for contra-indication, intolerance, TB, HIV-2**
  - Generic AZT ddI EFV IDV RTV
- **Eligibility criteria for initiation of HAART:**
  - All WHO stage IV or III
  - WHO stage I or II and CD4<200/mm3
- **Cotrimoxazole prophylaxis** in all symptomatic patients or CD4< 350/mm3

Adults who started HAART between January 1st, 2004 and June 30, 2005 were included, except female patients enrolled in PMTCT program.

- Collection of data using FUCHIA[a] monitoring software (Epicentre, Paris, France).
- Clinical and adherence assessment at baseline then every month
- CD4 measurement (BD FACSCount[a]) at baseline, month 6 then every 6 months
- Virological evaluation (Roche Amplicor assay) performed after 6 or 12 months by the laboratory of Virology, Hôpital de la Pitié-Salpêtrière, Paris
- Reverse transcriptase genotyping performed for viral load > 1000 copies/mL

Statistical analysis was performed using Epi Info for Windows, version 3.3.2 software.
Outcome measures include survival, weight gain, CD4 and virological response to HAART.

Results

- **Initial training** settled by SOLTHIS in January 2004
  - 15 physicians
  - 3,5 healthcare providers
- **4 HIV care centers** :
  - Ségou district hospital, *Hôpital Régional Nianankoro Fomba*
  - Ségou public health outpatient clinic, *Centre de Santé de Référence Famory Doumbia*
  - 2 community-based NGO : *Walé, APROFEM.*

Between January and April 2004, these four centers initiated free ART services. The ARVs were first provided by SOLTHIS, then by the Malian Government.

376 adult patients included (results updated for presentation)

Baseline characteristics (Table 1)

- Predominance of women
- WHO stage III or IV : 94%
- Pulmonary tuberculosis : 19 patients (5%)
- Median CD4 cell count : 112 cells/mm3
- **HIV-1 : 94.3 %** **HIV-2 : 5.7 %**

Treatment (Table 2)

- **HAART-naïve** : 98%
- **Dominant regimen** : d4T+3TC+NVP 84%
- **Used in generic formulations** (Stavir, Lamivir, Nevimune, CIPLA, Mumbai, India)
- **Generic fixed-dose combination** (Triomune, CIPLA) since October 2004.

TABLE 1 : Baseline characteristics of the Ségou cohort (376 patients)

	Baseline values (%)
Demography	
Sex [n (%)]	
Female	226 (60.1)
Male	150(39.9)
Age (y)	
Median	35
IQR	28 – 42
Clinical Presentation	
Stage of infection (WHO classification) [n (%)]	
- stage I	
- stage II	3 (0.8)
- stage III	17 (4.7)
- stage IV	211 (58.6)
	129 (35.8)
Body weight (kg)	
Median	48
IQR	42 – 55
Initial presentation [n (%)]	
Wasting syndrome	
New or on-going opportunistic infections	84 (22.4)
	292 (77.6)
Degree of Immunodepression	
CD4 cell count (/mm3)	
Median	
IQR	112
CD4 stage [n (%]	36 - 199
<50	
50-200	80 (29.3)
200-350	127 (46.5)
>350	49 (17.9)
	17 (6.3)

TABLE 2 : First- line ARV drug regimens used in the Ségou cohort

	n (%)
d4T+3TC+NVP	**316 (84.1)**
d4T+3TC+EFV	20 (5.3)
AZT+3TC+NVP	9 (2.3)
AZT+3TC+EFV	9 (2.3)
d4T+3TC+IDV*	16 (4.3)
AZT+3TC+IDV*	3 (0.8)
ddI+3TC+NVP	1 (0.3)
AZT+3TC+rtv/IDV	1 (0.3)
AZT+ddI+ rtv/IDV	1 (0.3)

* boosted by ritonavir after May 2005 (IDV 400 mg/RTV 100 mg bid)

Patient Disposition

- **At follow-up** (median duration= 5.8 months, IQR 1.3 to 12.7)
  - **231** (61.4%) **alive and still on HAART**
  - **82** (21.8%) **died**
  - **57** (15.2%) **lost to follow-up**
  - **6** (1.6%) **stopped treatment**.

Clinical Response (Figure 1)

- **Median weight** at month 6, 12 and 18 versus baseline

  highly significant **p<0.0001**
- **Patients with new opportunistic infections after 6 months : 6.8%**

Immunological Response (Figure 2)

- **Remarkable increase of CD4 cell counts in most of the patients**
- **Median changes from baseline**:

  + 177 cells/mm3 at month 6 (± 1)
  + 247 cells/mm3 at month 12 (± 1) **M6,M12,M18 vs BL**
  + 308 cells/mm3 at month 18 (± 1) **p<0.0001**

Figure 1 : Evolution of median body weight on HAART

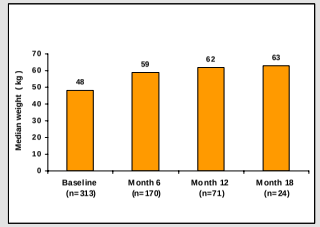


Figure 2 : Immunological response observed on HAART

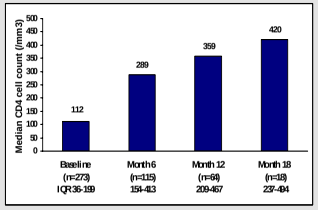
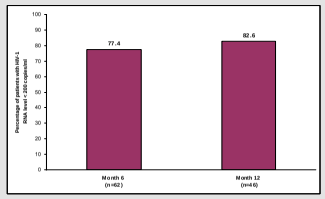


Figure 3 : Virological response observed under first-line HAART regimen



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Virological Response (Figure 3)

- **62 patients tested at month 6 :** **48 (77.4%) patients below 200 copies/mL**
  14 patients with detectable viral load
  Median HIV1 RNA : 2455 copies/mL (IQR 452 to 7740)
- **46 other patients tested at month 12 :** **38 (82.6%) patients below 200 copies/mL**
  8 patients with detectable viral load
  Median HIV1 RNA : 5115 copies/mL (IQR 712 to 28750)
- **Viral genotyping** (n = 16) : NRTI mutations : K70R =1, M184V = 4, K219E = 1
  NNRTI mutations : K103N = 1 ,Y181C/I = 3, G190A = 1, K101E = 1, K101N/K = 1
  Wild type : 8 patients
  Not amplifiable : 1 patient
  Resistance to **3TC** : 1 patient Resistance to **3TC and NNRTI** : 3 patients Resistance to **NNRTI**: 1 patient

Adherence **85% of patients highly adherent** (≥ 95% of drug intake between each clinic visit)

Tolerance

- **First-line regimen well tolerated**
- **Transient mild to moderate side-effects** (grade 1/2 WHO toxicity) : **65 (17.2%) patients**
- **Stopping treatment:**
  - **Stavudine** (peripheral neuropathy) : 7 patients (2.0 %/exposed)
  - **Nevirapine** (rash) : 6 patients (1.8 %/exposed)
  - **Indinavir** (GIT intolerance) : 1 patient

Figure 4 : Survival probability under HAART according to initial CD4 level

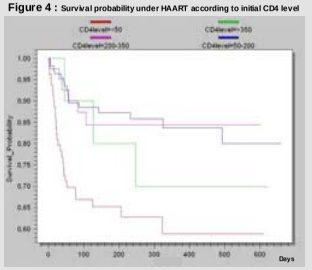
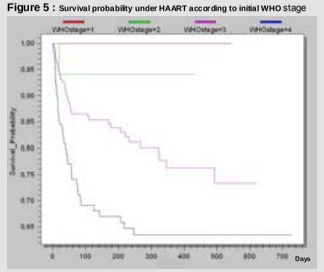


Figure 5 : Survival probability under HAART according to initial WHO stage



Outcome

- **Probability of survival** (i.e., alive and still in follow-up) **73.3% at 12 months (95% CI 68.8% to 77.4%)**
- **57 patients lost to follow-up** (15.2%)
  - Most of them highly symptomatic at baseline
  - one third lost to follow-up within two months after initiation of HAART
- **82 deaths** related to HIV: 72 other causes: 4 not specified: 6 patients
- **Median time to death** : **36.5 days** (IQR 13 to 77)
- **Mortality strongly associated with baseline CD4 level**
  Baseline **CD4<50**: 33.7 % died Baseline **CD4 200-350**: 14.3% died p=0.006
- Difference of **survival probability** depending **on initial CD4 level** (**Figure 4**) highly significant (Log-Rank=17.2988, p=0.0006)
- Difference of **survival probability** depending **on initial WHO stage** (**Figure 5**) also highly significant at 12 months :
  stage 1=100% stage 2=94.1% stage 3=76.3% stage 4= 63.4%,
  Log-Rank=12,6351, p=0,0055

Conclusion

- Based on our preliminary cumulative data :
  - Scaling-up HAART use for HIV- positive adults is feasible in African decentralized area
  - A simplified and affordable HAART strategy provides efficient clinical and immunological response.
- Increased early mortality, largely due to advanced HIV disease at HAART initiation rises the question of medical care organization and information of population regarding access to VCT in rural African setting.
- The development of a database for monitoring is a key issue to evaluate the effectiveness of implementing access to HAART
- In next years, virological monitoring should be a critical issue for early detection of treatment failure.