Néphrotoxicité du ténofovir

Olivier Epaulard, Grenoble

29 mars 2019

Ténofovir

- Prodrogue du ténofovir diphosphate
  - analogue structurel de la désoxyadénosine triphosphate

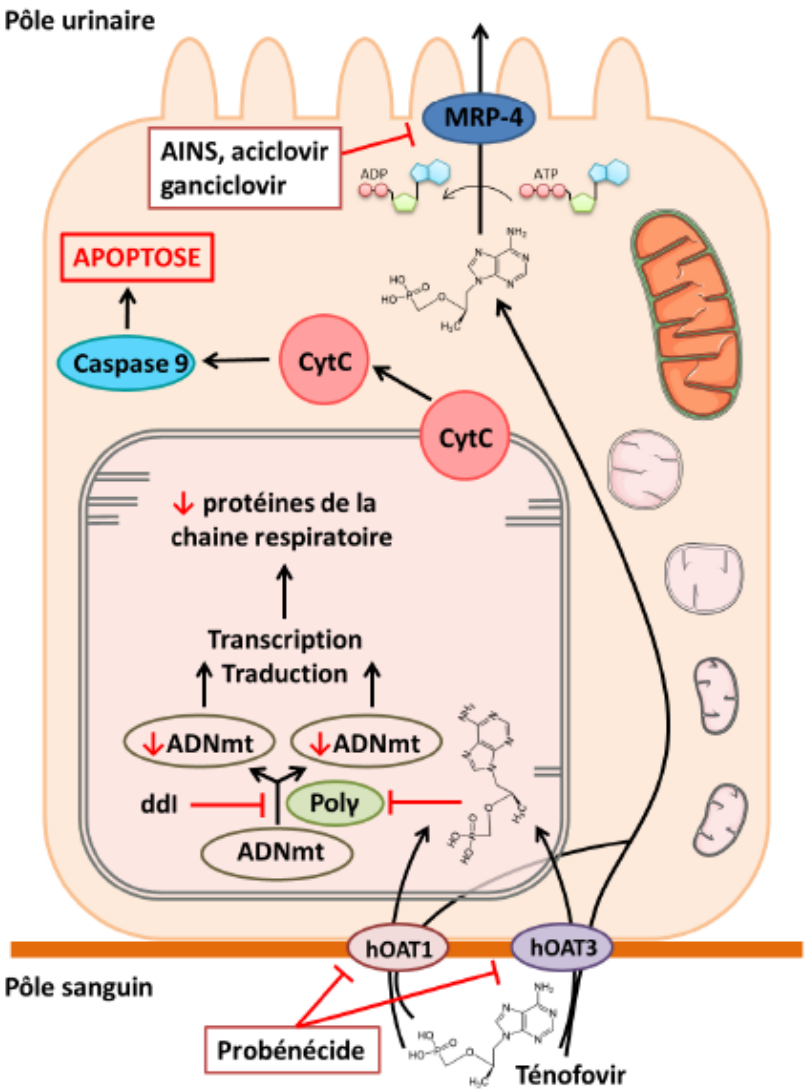
- Blocage de l'extension de la synthèse d'ADN par l'ADN-polymérase ARN-dépendante virale.

- Inhibiteur faible des ADN polymérases α et β de la cellule hôte et de la polymérase γ mitochondriale.

Fanconi Syndrome and Renal Failure Induced by Tenofovir: A First Case Report 2002

David Verhelst, MD, Matthieu Monge, MD, Jean-Luc Meynard, MD, Bruno Fouqueray, MD, PhD, Béatrice Mougenot, MD, Pierre-Marie Girard, MD, PhD, Pierre Ronco, MD, PhD, and Jerome Rossert, MD, PhD

- Syndrome de Fanconi complet :
  - acidose métabolique à trou anionique plasmatique normal
  - hypophosphorémie, hyperphosphaturie, hypokaliémie, hypo-uricémie
  - protéinurie tubulaire
  - glycosurie sans hyperglycémie
  - aminoacidurie



Isnard-Bagnis 2016

The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years

Mark R. Nelson[a], Christine Katlama[b], Julio S. Montaner[c], David A. Cooper[d], Brian Gazzard[a], Bonaventura Clotet[e], Adriano Lazzarin[f], Knud Schewe[g], Joep Lange[h], Christina Wyatt[i], Sue Curtis[j], Shan-Shan Chen[j], Stephen Smith[j], Norbert Bischofberger[j] and James F. Rooney[j] for the Tenofovir DF Expanded Access Team

2007

- plus de 10000 patients suivis pendant 4 ans
- effet indésirable sévère rénal : 0,5 % des cas, 1,5 pour 1000 patients-années.
- incidence
  - de l'IRA : 0,8 pour 1000 patients-années
  - du syndrome de Fanconi : 0,2 pour 1000 patients-années

MAJOR ARTICLE

Systematic Review and Meta-analysis: Renal Safety of Tenofovir Disoproxil Fumarate in HIV-Infected Patients

Ryan D. Cooper,[1] Natasha Wiebe,[1] Nathaniel Smith,[4] Philip Keiser,[5] Saraladevi Naicker,[6] and Marcello Tonelli[1,2,3]

MAJOR ARTICLE

Systematic Review and Meta-analysis: Renal Safety of Tenofovir Disoproxil Fumarate in HIV-Infected Patients

Ryan D. Cooper,[1] Natasha Wiebe,[1] Nathaniel Smith,[4] Philip Keiser,[5] Saraladevi

Diminution de la clairance de la créatinine de 4 ml/mn par an

(déclin physiologique : 0,4 ml/min par an)

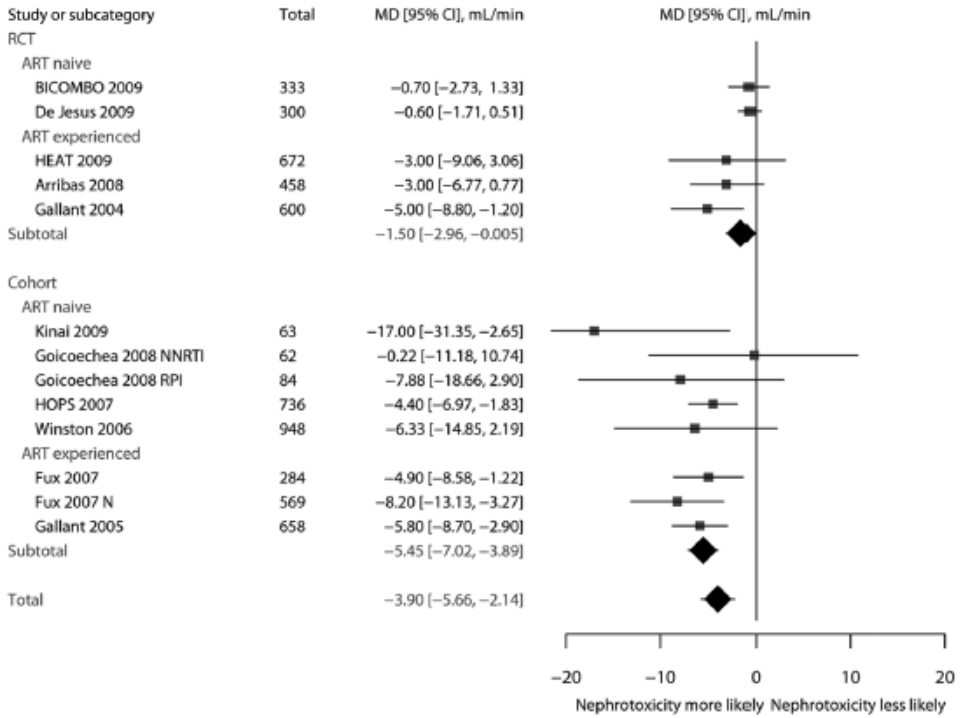


Figure 2. Change in glomerular filtration rate (in mL/min) calculated using the Cockcroft-Gault formulation (CG-GFR), for tenofovir disoproxil fumarate (TDF) therapy versus no treatment. BICOMBO 2009 refers to the study by Martinez et al [41], HEAT 2009 refers to the study by Smith et al [44], and HOPS 2007 refers to the HIV Outpatient Study by Young et al [20]. The other studies are indicated by first author and date of publication [16–19, 34, 37, 38, 40]. ART, antiretroviral treatment; CI, confidence interval; MD, mean difference; NNRTI, nonnucleoside reverse-transcriptase inhibitor; RCT, randomized controlled trial; RPI, ritonavir-boosted protease inhibitor.

Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study

2016

*Amanda Mocroft, Jens D Lundgren, Michael Ross, Christoph A Fux, Peter Reiss, Olivier Moranne, Philippe Morlat, Antonella d'Arminio Monforte, Ole Kirk, Lene Ryom, for the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) Study**

Incidence de DFG <70ml/mn : 5/1000 patients-années

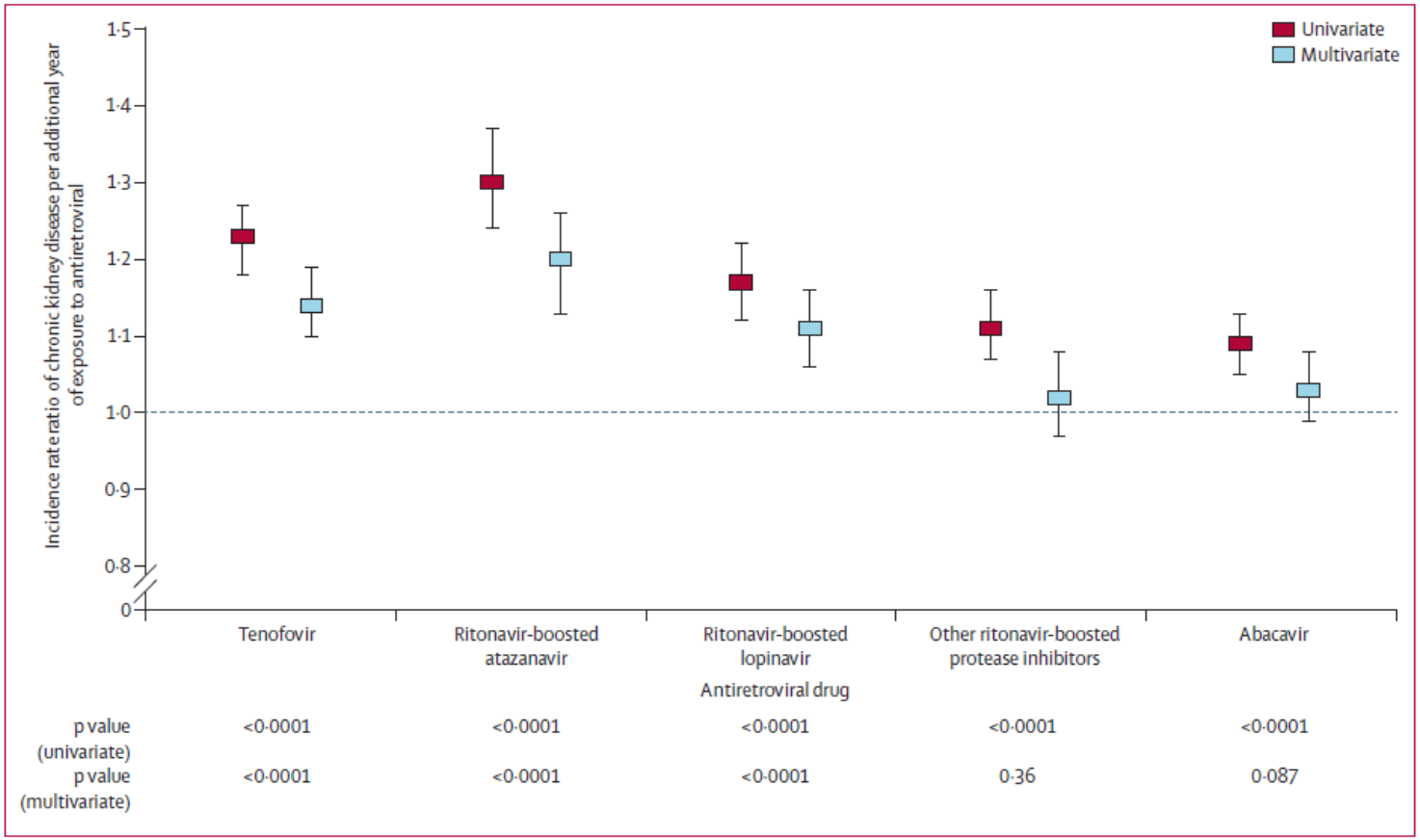


Figure 3: **Unadjusted and adjusted incidence rates of chronic kidney disease per year of additional exposure to potentially nephrotoxic antiretrovirals**

Incidence de DFG <70ml/mn : 5/1000 patients-années

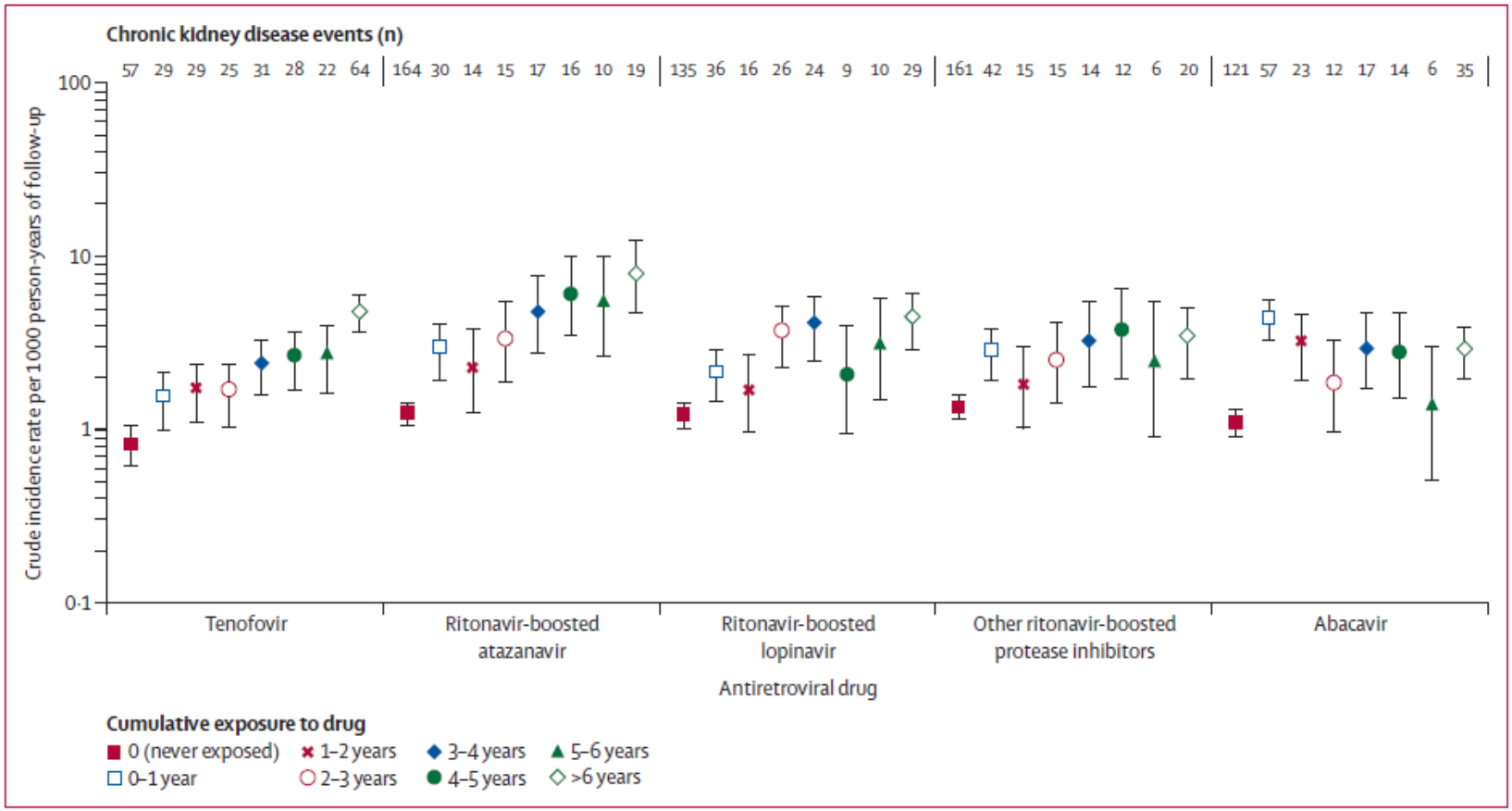


Figure 2: **Crude incidence rates of chronic kidney disease and cumulative exposure to potentially nephrotoxic antiretrovirals**

Conclusions des études chez les PVVIH

- Deux phénomènes :
  - Cas de syndrome de Fanconi aigus, rares
  - Altération chronique de la fonction rénale modeste mais détectable

- Influence des autres ARV prescrits (IP boostés en particuliers historiquement)

- « *Chez les patients ayant un DFG < 80 ml/min, l'utilisation du ténofovirDF nécessite une évaluation attentive du rapport bénéfice/risque. Lorsque le DFG est ≤ 50 ml/min confirmé sur deux prélèvements consécutifs, le ténofovirDF doit être évité. S'il est utilisé, il est recommandé d'effectuer un dosage plasmatique de ténofovir et de réduire la dose en cas de concentration élevée* »

Actualisation 2018 des recommandations Morlat

ORIGINAL ARTICLE

On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection

J.-M. Molina, C. Capitant, B. Spire, G. Pialoux, L. Cotte, I. Charreau, C. Tremblay, J.-M. Le Gall, E. Cua, A. Pasquet, F. Raffi, C. Pintado, C. Chidiac, J. Chas, P. Charbonneau, C. Delaugerre, M. Suzan-Monti, B. Loze, J. Fonsart, G. Peytavin, A. Cheret, J. Timsit, G. Girard, N. Lorente, M. Préau, J.F. Rooney, M.A. Wainberg, D. Thompson, W. Rozenbaum, V. Doré, L. Marchand, M.-C. Simon, N. Etien, J.-P. Aboulker, L. Meyer, and J.-F. Delfraissy, for the ANRS IPERGAY Study Group*

Table 2. Adverse Events.*

Adverse Events	TDF-FTC (N=199)	Placebo (N=201)	P Value
	no. of patients (%)		
Confirmed laboratory event			
Elevated plasma creatinine			
Any grade	35 (18)	20 (10)	0.03
Grade 1	35 (18)	19 (9)	
Grade 2	0	1 (<1)	
Proteinuria ≥2+	11 (6)	9 (4)	0.63
Glycosuria ≥2+	1 (1)	0	0.50

The Journal of Infectious Diseases

MAJOR ARTICLE

Low Risk of Proximal Tubular Dysfunction Associated With Emtricitabine-Tenofovir Disoproxil Fumarate Preexposure Prophylaxis in Men and Women

Kenneth Mugwanya,[1,2,10] Jared Baeten,[1,2,3] Connie Celum,[1,2,3] Deborah Donnell,[4] Thomas Nickolas,[5] Nelly Mugo,[2,11] Andrea Branch,[7] Jordan Tappero,[9] James Kiarie,[12] Allan Ronald,[13] Michael Yin,[6] and Christina Wyatt[8]; for the Partners PrEP Study Team[a]

Departments of [1]Epidemiology, [2]Global Health, and [3]Medicine, University of Washington, and [4]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; Department of Medicine, Divisions of [5]Nephrology, and [6]Infectious Diseases, Columbia University Medical Center, Department of Medicine, Divisions of [7]Liver Diseases, and [8]Nephrology, Icahn School of Medicine at Mount Sinai, New York, New York; [9]Division of Global Health Protection, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia; [10]Division of Disease Control, School of Public Health, Makerere University, Kampala, Uganda; [11]Kenya Medical Research Institute, and [12]Department of Obstetrics and Gynecology, University of Nairobi, Kenya; and [13]Department of Medicine, University of Manitoba, Winnipeg, Canada

- Étude Partner
- 1549 sujets (776 sous FTC-TDF, 773 sous placebo)
- Même fréquence de tubulopathie : 1,7% et 1,3% sur 2 ans

Table 3. Frequency of Markers of Proximal Tubular Dysfunction in Cohort Analysis Comparing FTC-TDF to Placebo

Outcome Definition	Participants, No. (%)		OR (95% CI)	*P* Value[a]
	FTC-TDF (n = 776)	Placebo (n = 773)		
Primary analysis: ≥2 markers of proximal tubular dysfunction				
Fractional tubular resorption of phosphate <82%, urine glucose ≥10 mg/dL with serum glucose ≤126 mg/dL, urine total protein–urine creatinine >200 mg/g with urine albumin–total protein ratio <0.4, fractional excretion of uric acid >15%	13 (1.7)	10 (1.3)	1.30 (.52–3.33)	.68
Sensitivity analysis for composite outcome				
Fractional tubular resorption of phosphate <95% with serum phosphate <2.6 mg/dL; all other criteria as in primary analysis	9 (1.2)	8 (1.0)	1.12 (.38–3.36)	>.99
TmP/eGFR <0.8 mmol/L; all other criteria as in primary analysis	15 (1.9)	11 (1.4)	1.36 (.58–3.31)	.56
Fractional tubular resorption of phosphate <95% with serum phosphate <2.6 mg/dL, fractional resorption of glucose <100%; all other criteria as in primary analysis	8 (1.0)	5 (0.7)	1.60 (.45–6.24)	.58
Individual markers of proximal tubular dysfunction				
Phosphate handling				
Fractional tubular resorption of phosphate <82%	20 (2.6)	21 (2.7)	0.95 (.51–1.76)	.86
Fractional tubular resorption of phosphate <95% with serum phosphate <2.6 mg/dL	14 (1.8)	8 (1.0)	1.76 (.73–4.21)	.21
TmP/GFR <2.6 mg/dL	34 (4.4)	33 (4.3)	1.03 (.63–1.68)	.91
Glucose resorption				
Urine glucose ≥10 mg/dL with serum glucose ≤126 mg/dL	84 (10.8)	96 (12.4)	0.86 (.63–1.17)	.32
Fractional tubular resorption of glucose <100%	10 (1.3)	7 (0.9)	1.43 (.54–3.77)	.63
Proteinuria				
Tubular proteinuria: urine total protein–urine creatinine >200 mg/g with urine albumin– total protein ratio <0.4	57 (7.3)	31 (4.0)	1.90 (1.21–2.97)	<.01
Urine total protein–urine creatinine >200 mg/g	62 (8.0)	34 (4.4)	1.89 (1.23–2.90)	<.01
Uric acid excretion				
Fractional excretion of uric acid >15%	27 (3.5)	10 (1.3)	2.27 (1.32–5.72)	.001

Abbreviations: CI, confidence interval; FTC, emtricitabine; OR, odds ratio; TDF, tenofovir disoproxil fumarate; TmP/eGFR, ratio of maximum rate of tubular phosphate resorption to glomerular filtration rate.

[a] *P* values from unadjusted χ^2 or Fisher exact test, where appropriate, for the randomized comparison of participants assigned to FTC-TDF versus placebo. Multivariate analyses including sex, baseline age, eGFR, indicator for elevated systolic blood pressure, and body mass index yielded similar results.

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J Acquir Immune Defic Syndr. 2018 February 01; 77(2): 206–211. doi:10.1097/QAI.0000000000001575.

Frequency of monitoring kidney function in HIV-uninfected persons using daily oral tenofovir disoproxil fumarate pre-exposure prophylaxis

Kenneth K. Mugwanya, MBChB, MS, PhD[1,2], Jared M. Baeten, MD, PhD[1,3,4], Christina Wyatt, MD, MS[5], Nelly R. Mugo, MBChB, M.Med., MPH[1,6], Connie L. Celum, MD,MPH[1,3,4], Allan Ronald, MD[7], John Kiarie, MBChB, M.Med., MPH[8], Elly Katabira, MBChB, FRCP[9], Renee Heffron, MPH, PhD[1,3,*], and for the Partners PrEP Study and Partners Demonstration Project Teams[*]

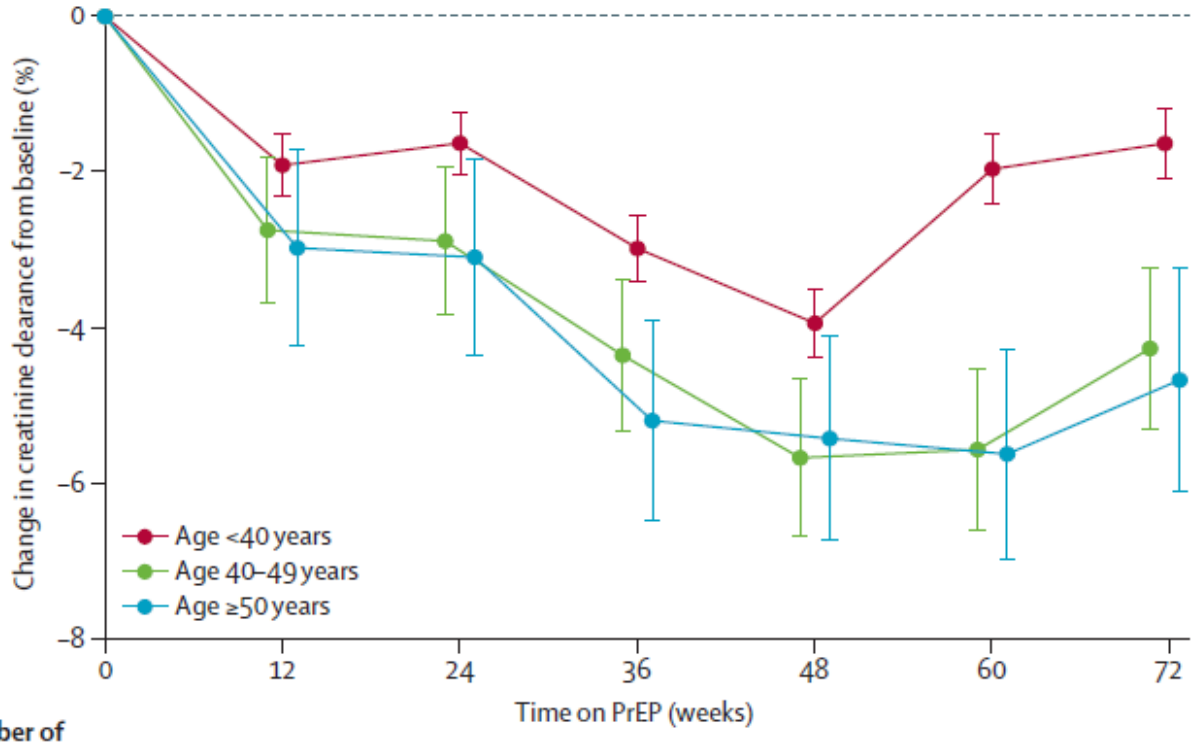
- Enjeux : alléger le contrôle de la fonction rénale dans des pays dont le niveau sanitaire rend complexe un suivi rapproché
- 5358 PrEPeurs de 2 études Partners
- **52 cas de Clair. Créat.<60ml/mn** sur 24 mois : <1%
- Pas de différence selon la fréquence du suivi
- Associé à âge >45 ans, poids <55 kg, Cl. Créat initiale < 90/ml/mn

2016

Association of age, baseline kidney function, and medication exposure with declines in creatinine clearance on pre-exposure prophylaxis: an observational cohort study

Monica Gandhi, David V Glidden, Kenneth Mayer, Mauro Schechter, Susan Buchbinder, Beatriz Grinsztejn, Sybil Hosek, Martin Casapia, Juan Guanira, Linda-Gail Bekker, Alexander Louie, Howard Horng, Leslie Z Benet, Albert Liu, Robert M Grant

- iPrEx – OLE
- 1445 participants
- Plusieurs pays et continents



Number of participants in each age strata							
Age <40 years	953	832	780	727	640	594	566
Age 40–49 years	166	151	147	134	128	118	118
Age ≥50 years	105	99	98	94	88	78	66

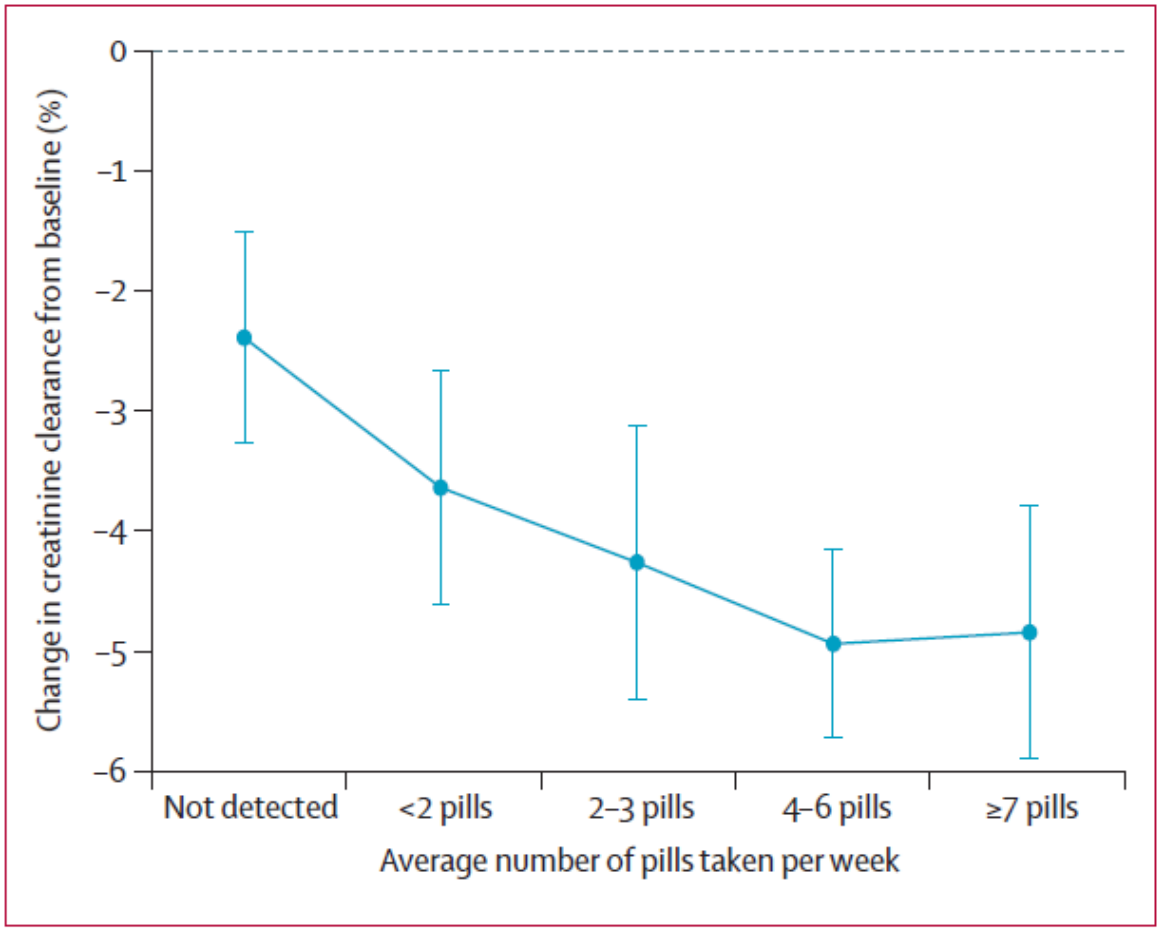
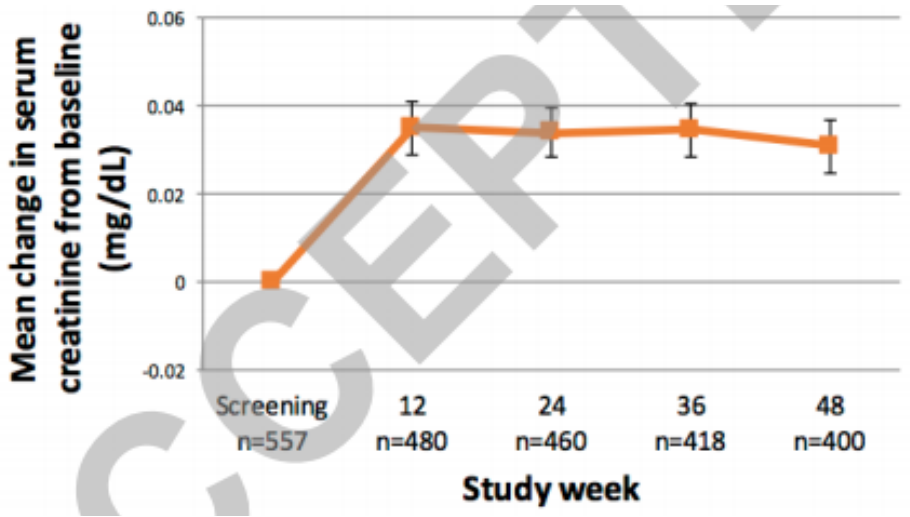


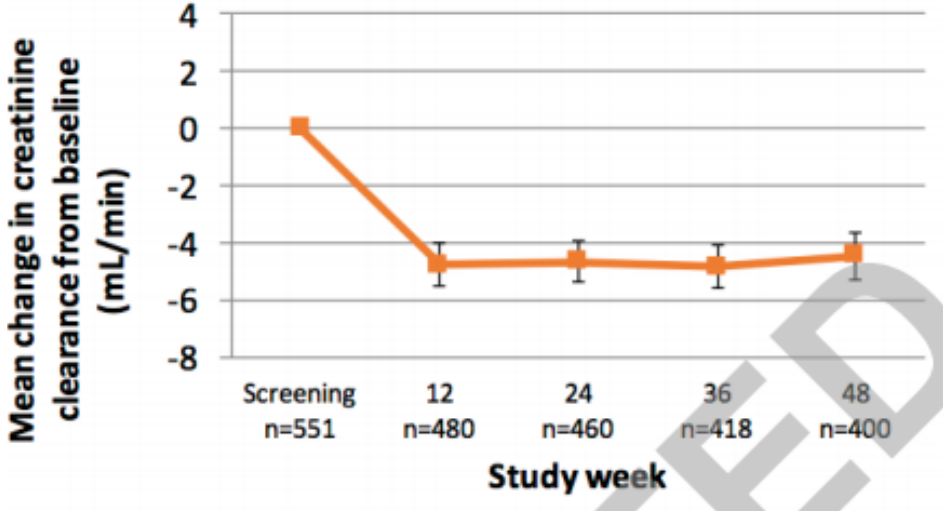
Figure 2: **Change in creatinine clearance based on number of pills taken per week**
Average number of pills taken per week was established from hair concentrations of tenofovir. Bars show SE.

Changes in Kidney Function Associated with Daily Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Preexposure Prophylaxis Use in the United States Demonstration Project

JAIDS 2017

Authors:
Eric C. Tang, MD, MPH, Residency Program in Internal Medicine, Kaiser Permanente San Francisco Medical Center; Residency Program in General Preventive Medicine and Public Health, University California, San Francisco; San Francisco, USA





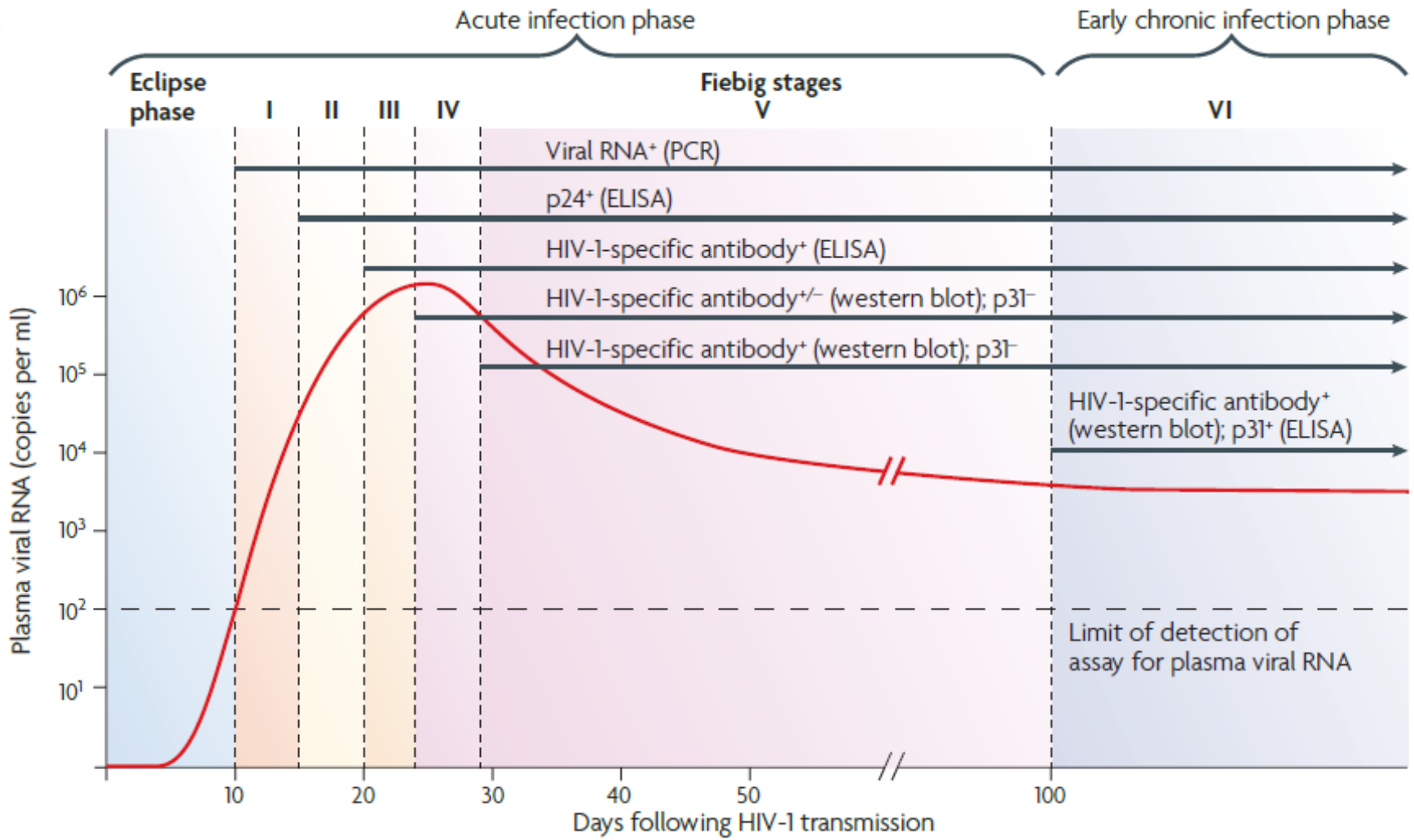
En conclusion

- Rares syndromes de Fanconi aigus
- Diminution modérée et avec peu d'impact de la créatininémie au long cours… et surtout à la phase initiale

- Bilan initial et à 1 mois
  - Quid de ceux dont le DFG est <70 ml/mn ?
    - Privilégier à la demande ?
    - Surveillance rapprochée
  - Attention si co-prescription d'un néphrotoxique au long cours (IEC, …)

- Suivi régulier nécessaire
  - L'hypophosphorémie apparaitra avant l'augmentation de la créatininémie
  - Réversibilité dans la plupart des cas

PrEP : initiation et primo-infection



McMichael 2010

… d'où les recommandations

- Sérologie à 2 reprises séparées d'un mois
  - Dans les faits : sérologie à 6 semaines du dernier RSNP
  - Place de la CV de dépistage dans certaines situations ?
- Sérologie à 1 mois puis tous les 3 mois
  - Pour s'assurer qu'il n'y a pas de séroconversion (par malobservance essentiellement)

- Primo-infection à l'initiation du traitement :
  - iPrEx, Proud : 2 patients dans chaque ont ainsi développé une résistance au ténofovir
  - Étude TDF2 : 1 patient concerné

OPEN

The effect of oral preexposure prophylaxis on the progression of HIV-1 seroconversion

Deborah Donnell[a,c], Eric Ramos[b], Connie Celum[c,d,e], Jared Baeten[c,d,e], Joan Dragavon[b], Jordan Tappero[g], Jairam R. Lingappa[c,e,f], Allan Ronald[h], Kenneth Fife[i], Robert W. Coombs[b], for the Partners PrEP Study Team*

Primo-infection sous PrEP :

- Charge virale plus basse

- Délai plus long entre positivité de l'ARN et positivité du WB

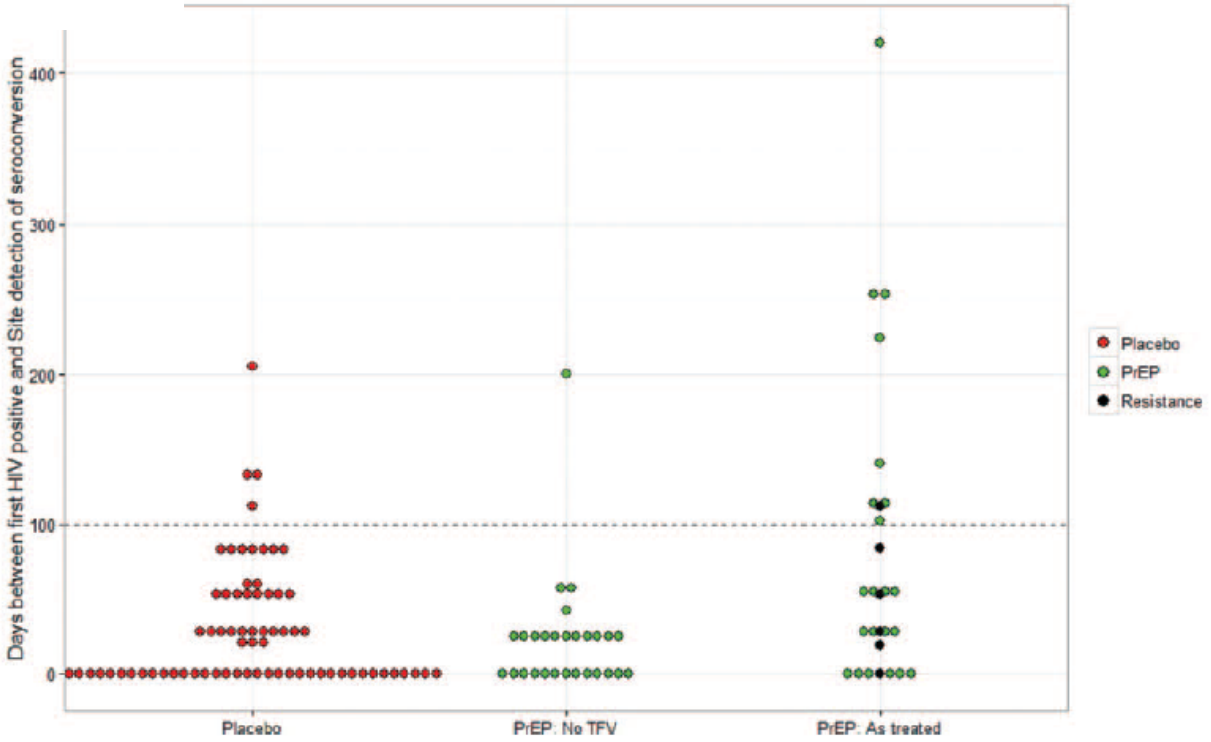
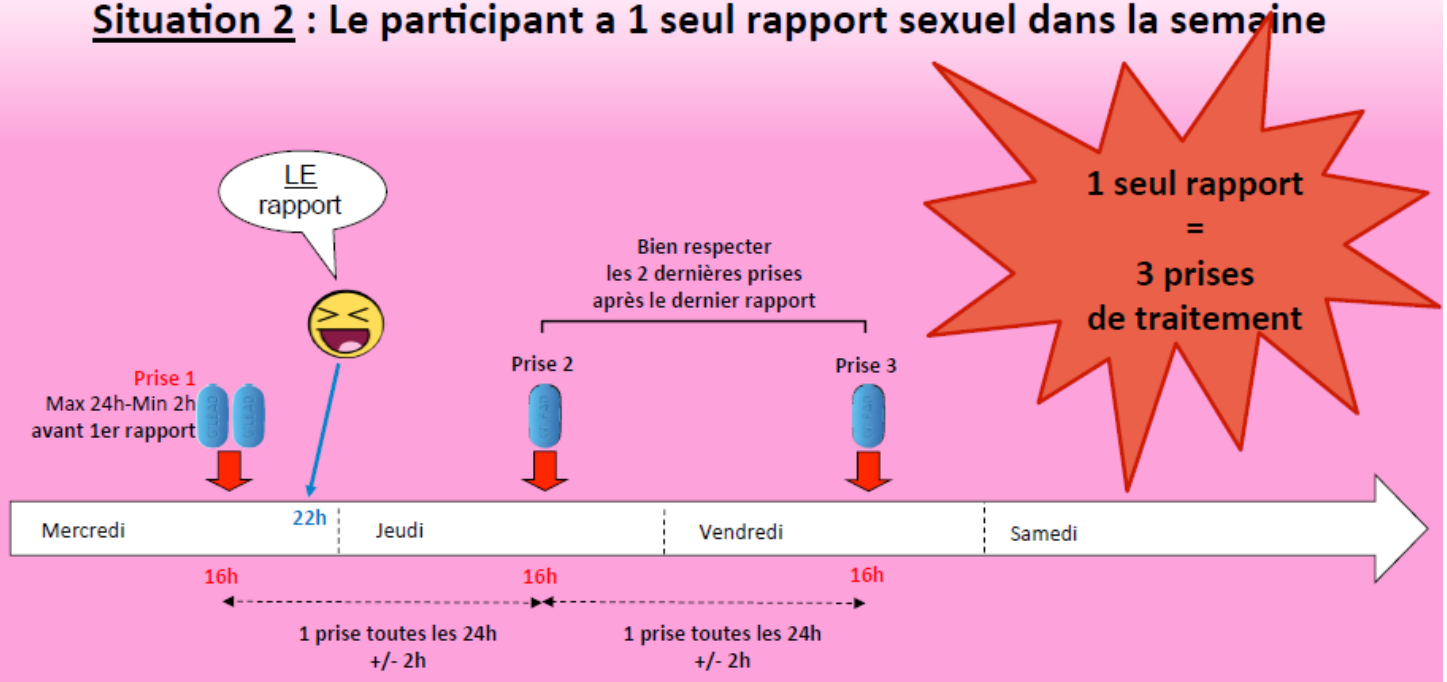


Fig. 1. Time between first HIV-infected sample and site detection of seroconversion ($N = 129$). Each c

PrEP à la demande : schémas de prise

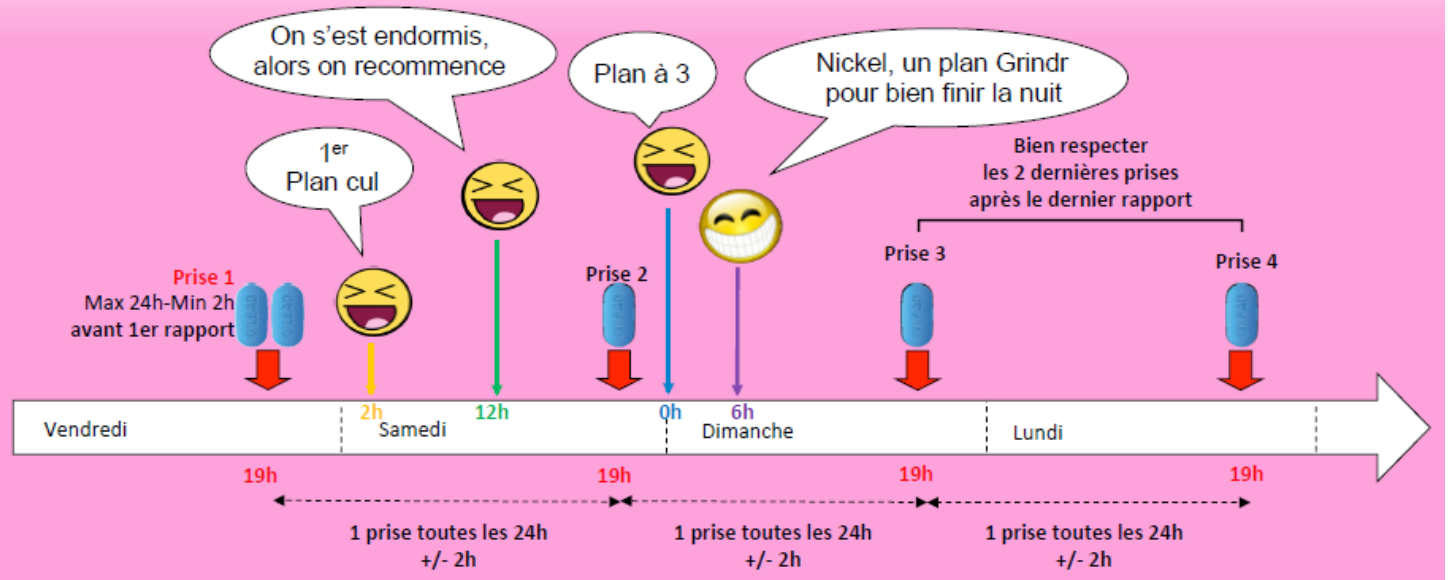
Comment se prend une PreP dans l'essai IPERGAY ?

<u>Situation 2</u> : Le participant a 1 seul rapport sexuel dans la semaine



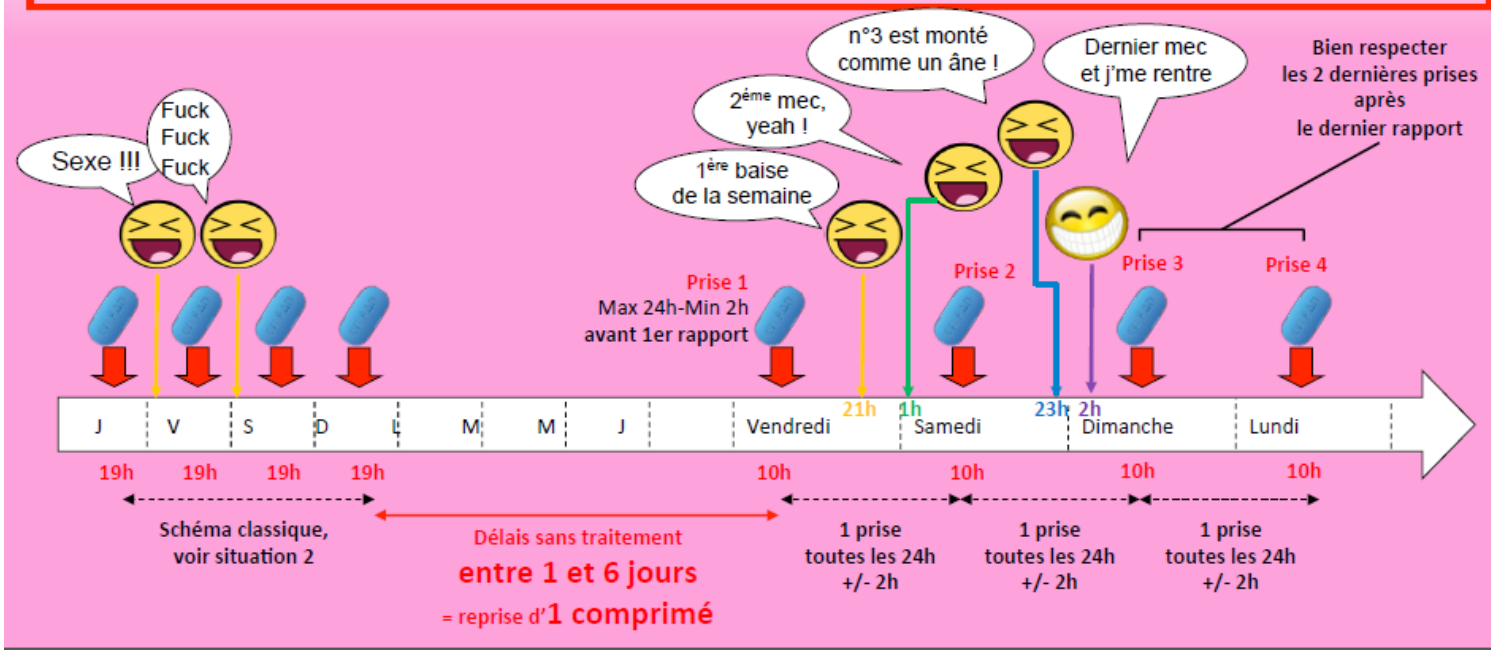
Comment se prend une PreP dans l'essai IPERGAY ?

<u>Situation 1</u> : Le participant a plusieurs rapports sexuels le week-end



Comment se prend une PreP dans l'essai IPERGAY ?

<u>Situation 3</u> : Le participant reprend une activité sexuelle et il a pris son <u>dernier comprimé il y a moins de 6 jours</u>



Comment se prend une PreP dans l'essai IPERGAY ?

Diapos Jessica Berdougo & Stéphane Morel