Les essais de phase II – M1

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Phases de développement du médicament

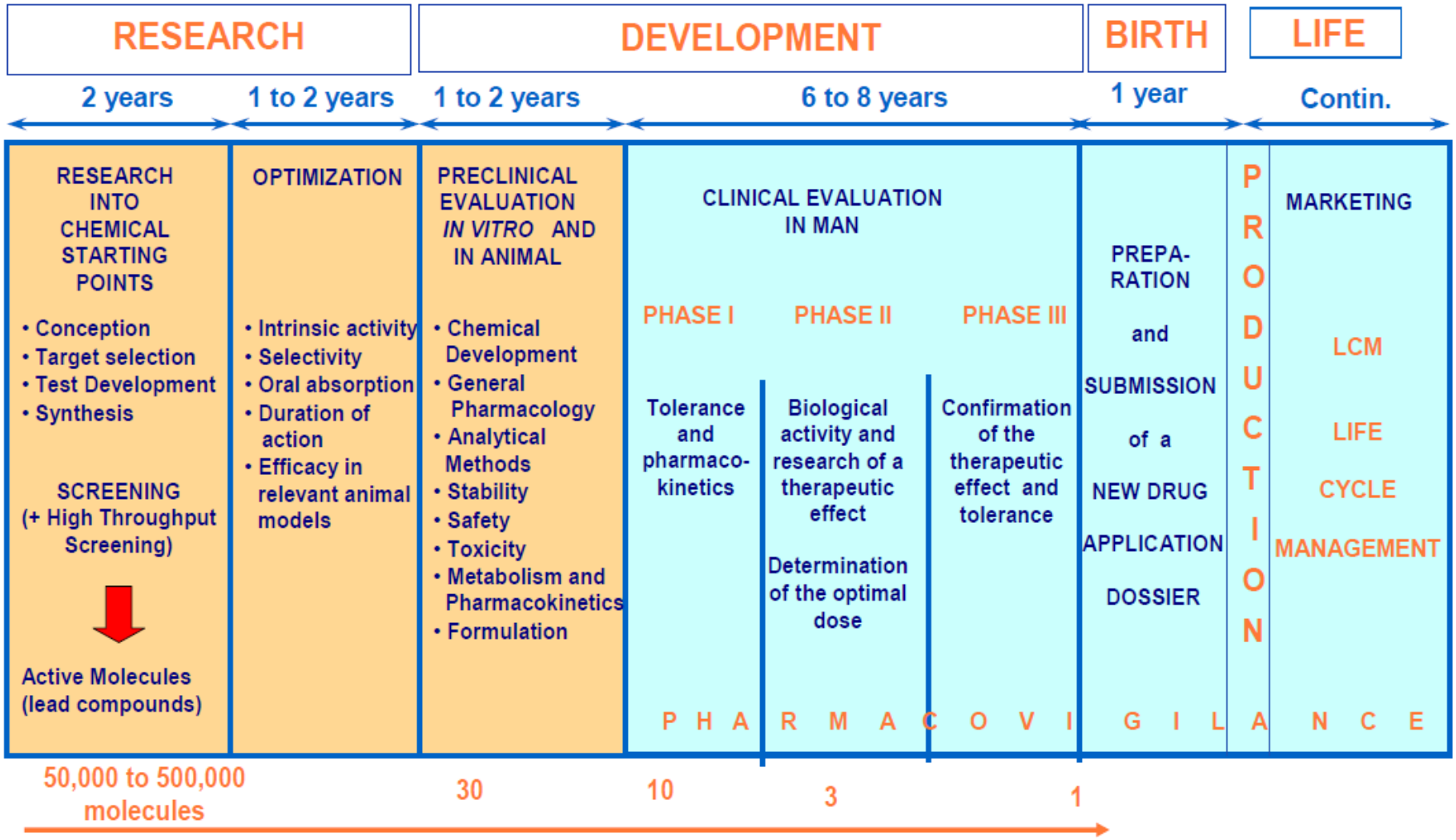
Nombre de produits par étape pour **arriver à 1 médicament sur le marché** (estimations) :

Phases de développement du médicament

Nombre de produits par étape pour **arriver à 1 médicament sur le marché** (estimations) :

- 1 000 molécules synthétisées
- 100 testées chez l'animal
- <10 testées chez l'homme
- **1 médicament qui obtient l'AMM**

Phases de développement du médicament



Phases II

→ Estimation du **taux de réponse** (efficacité) d'une dose fixe

→ Etablir la **dose optimale**, meilleur effet thérapeutique avec le minimum d'effets indésirables

- Petit nombre de malade

- Non comparatifs
- Comparatifs

Phases II

- Durée: 1 à 3 ans (durée courte)
- **Première administration chez le malade**
- Pharmacodynamie/efficacité/mécanisme d'action
- Objectif: détermination des doses utilisées en Phase III

Phase II

Phase IIa

- Chez quelques patients rigoureusement sélectionnés
- Preuve de concept pharmacologique chez le patient (population cible)

Phase IIb

- Choix de la dose avec un bon bénéfice/risque
- Confirmation du potentiel « médicament »

Les études de phase IIa: l'exemple

Antiviral activity, safety, and pharmacokinetics/ pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults

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Exemple de méthodologie

Methods: In this study, INI-naive, HIV-1-infected adults currently off antiretroviral therapy were randomized to receive DTG (2, 10, or 50 mg) or placebo once daily for 10 days in an eight active and two placebo randomization scheme per DTG dose. Placebo patients were pooled for the purpose of analysis.

Exemple de méthodologie

Table 1. Demographics and baseline characteristics.

Characteristic	Dolutegravir once-daily dose			Placebo ($n=7$)
	2 mg ($n=9$)	10 mg ($n=9$)	50 mg ($n=10$)	
Male [*N* (%)]	9 (100)	9 (100)	10 (100)	7 (100)
Race [*N* (%)]				
African–American/African heritage	2 (22)	0	3 (30)	2 (29)
Caucasian/European heritage	7 (78)	9 (100)	7 (70)	5 (71)
Mean age [years (range)]	41 (20–55)	40 (32–45)	34 (22–53)	40 (21–54)
CDC classification				
Asymptomatic, lymphadenopathy, or acute HIV	8 (89)	8 (89)	9 (90)	6 (86)
Symptomatic, not AIDS	1 (11)	0	1 (10)	1 (14)
AIDS	0	1 (11)	0	0
Plasma HIV-1 RNA [$\log_{10}$ copies/ml, mean ± SD (min, max)]	4.40 ± 0.27 (4.03, 4.85)	4.58 ± 0.39 (4.25, 5.54)	4.47 ± 0.42 (3.85, 5.17)	4.25 ± 0.27 (4.03, 4.74)
Mean $CD4^+$ cell count [cells/μl (min, max)]	435 (175, 797)	398 (171, 509)	502 (232, 577)	427 (123, 1222)
Prior antiretroviral therapy [*N* (%)]	4 (44)	2 (22)	3 (30)	1 (14)
Any NRTI	4 (44)	2 (22)	3 (30)	1 (14)
Any NNRTI	2 (22)	0	2 (20)	1 (14)
Any protease inhibitor	1 (11)	1 (11)	3 (30)	0

CDC, Centers for Disease Control and Prevention; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; SD, standard deviation.

Exemple de méthodologie

Table 2. Change from baseline in plasma HIV-1 RNA levels on day 11 and proportion of patients with less than 400 and less than 50 copies/ml of plasma HIV-1 at nadir.

	Dolutegravir once-daily dose			
	2 mg ($n=9$)	10 mg ($n=9$)	50 mg ($n=10$)	Placebo ($n=7$)
Change from baseline on day 11				
Mean plasma HIV-1 RNA levels [$\log_{10}$ copies/ml (SD)]	−1.51 (0.58)	−2.03 (0.49)	−2.46 (0.35)	0.05 (0.26)
Adjusted mean difference[a] [$\log_{10}$ copies/ml (95% CI)]	−1.54 (−2.00 to −1.07)[b]	−2.04 (−2.52 to −1.55)[b]	−2.48 (−2.94 to −2.02)[b]	NA
Patients with plasma HIV-1 copies at nadir [*N* (%)]				
<400 copies/ml	5 (56)	5 (56)	9 (90)	0
<50 copies/ml	1 (11)	0	7 (70)	0

CI, confidence interval; NA, not applicable; SD, standard deviation.
[a]Active versus placebo.
[b]$P<0.001$.

Exemple de méthodologie

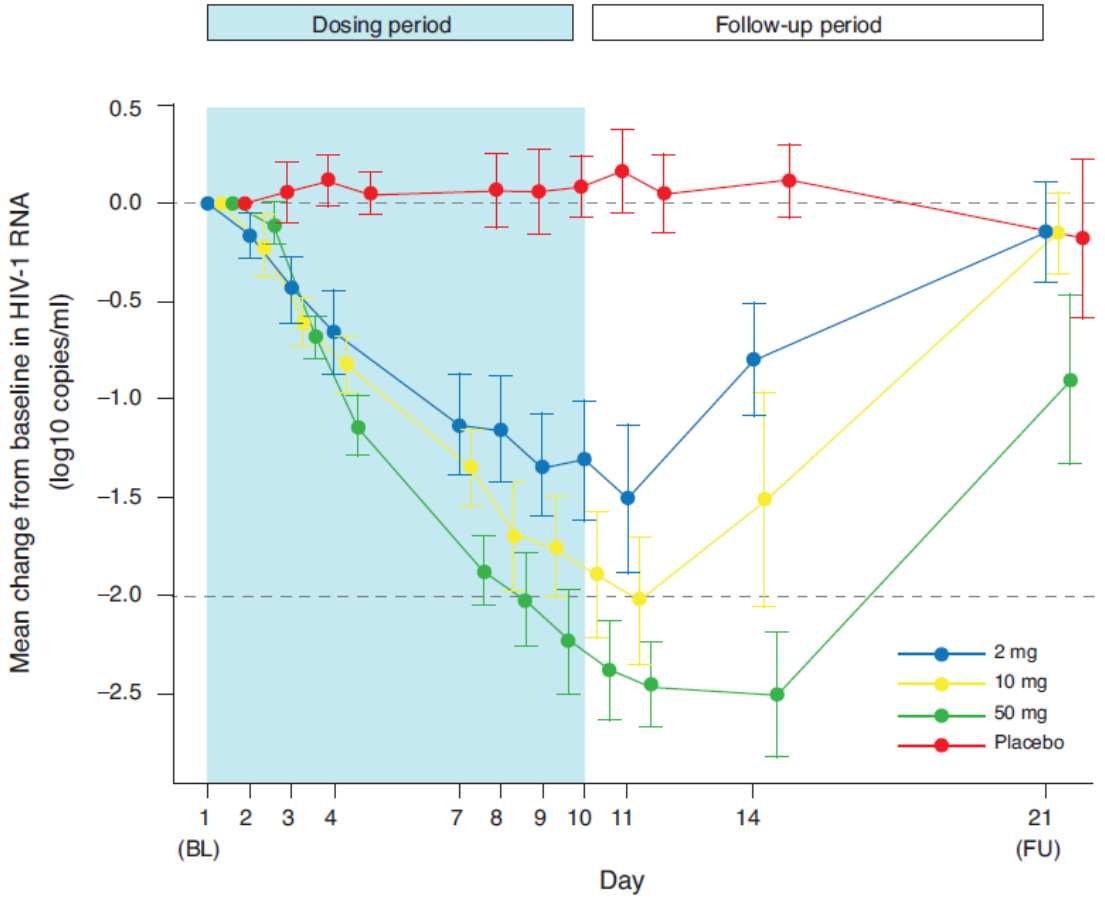

Fig. 1. Mean change from baseline in HIV-1 RNA. BL, baseline; FU, follow-up.

Exemple de méthodologie

Table 3. Steady-state pharmacokinetics on day 10.

DTG dose	*n*	C_{max} (μg/ml)[a]	t_{max} (h)[b]	$AUC_{0-\tau}$ (h∗μg/ml)[a]	$t_{1/2}$ (h)[a]	C_{τ} (μg/ml)[a]
2 mg	9	0.22 (25)	1.00 (0.42–3.00)	2.56 (29)	11.1 (24)	0.04 (50)
10 mg	7	0.80 (23)	1.48 (0.50–3.00)	10.1 (20)	11.6 (21)	0.19 (25)
50 mg	10	3.34 (16)	2.00 (0.97–4.00)	43.4 (20)	12.0 (22)	0.83 (26)

$AUC_{0-\tau}$, area under the plasma concentration–time curve during one dosing interval; C_{τ}, concentration at the end of dosing interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; DTG, dolutegravir; $t_{1/2}$, terminal elimination phase half-life; t_{max}, time of occurrence of C_{max}.

[a]Geometric mean (CV %).

[b]Median (range).

Exemple de méthodologie

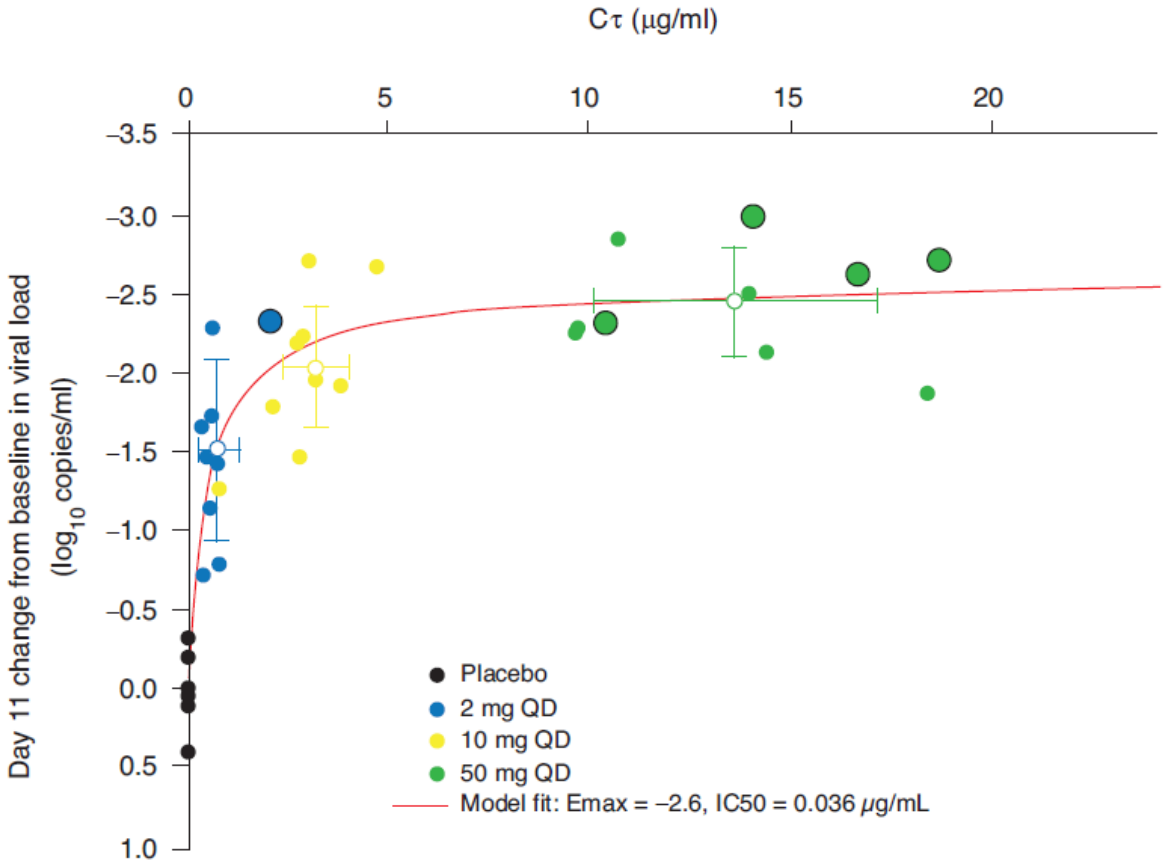

Fig. 2. Relationship of dolutegravir C_τ and reduction of plasma HIV-1 RNA on day 11 from baseline with E_{max} model. Patients with viral load less than 50 copies/ml are represented by black-bordered circles; open circles with lines denote mean ± standard deviation. C_τ, concentration at the end of the dosing interval; IC50, 50% inhibitory concentration; QD, once daily.

Exemple de méthodologie

Results: Thirty-five patients ($n = 9$ for DTG 2 and 10 mg, $n = 10$ for DTG 50 mg, and $n = 7$ for placebo) were enrolled. Baseline characteristics were similar across dose groups. Significant reductions in plasma HIV-1 RNA from baseline to day 11 were observed for all DTG dose groups compared with placebo ($P < 0.001$), with a mean decrease of 1.51–2.46 $\log_{10}$ copies/ml. In addition, a well characterized dose–response relationship was observed for viral load decrease. Most patients (seven of 10, 70%) receiving DTG 50 mg achieved plasma HIV-1 RNA less than 50 copies/ml. The pharmacokinetic variability was low (coefficient of variation, range 25–50%). Plasma HIV-1 RNA reduction was best predicted by C_τ using an E_{max} model. The most common adverse events were diarrhea, fatigue, and headache; the majority of adverse events were mild or moderate in severity.

Exemple de méthodologie

Vos conclusions?

Exemple de méthodologie

Conclusion: Dolutegravir demonstrated potent antiviral activity, good short-term tolerability, low pharmacokinetic variability, and a predictable pharmacokinetics/ pharmacodynamics relationship, which support once-daily dosing without a pharmacokinetic booster in integrase-naive patients in future studies.

Les études de phase IIa

Proof of concept

- Preuve de concept
- Ce n'est **pas une étude pivot**
- Nombre limité de sujets sélectionnés
- Peu de doses différentes testées
- Efficacité évaluée sur des biomarqueurs notamment
- **Pas toujours de groupe contrôle**

Possibilité de passer en étude pivot (phase IIb)

Bridging studies

- **Confirmer chez les patients, la bonne tolérance** observée chez le volontaire sain
- Etude pour confirmer l'efficacité ou la tolérance sur des **populations particulières** (obèses, IR, sujets âgés, ethnies, …)

Les études de phase IIa

Choix des doses : déterminées sur les résultats des 1ères études (critères : tolérance, activité, pharmacocinétique)

Choix du nombre de doses : plus réduit / phase 1 (études plus lourdes)

Choix de la durée de traitement : fonction de la pathologie, suffisante pour montrer une activité, éventuellement limitée par la durée des études de toxicité

Les études de phase IIa

Choix des paramètres d'activité et de tolérance (critères de substitution…)

Problème potentiel : différence de tolérance entre volontaires sains et patients (psychotropes…)

Concept de « bridging study » : évaluation préliminaire de la tolérance dans la population cible avant la recherche d'activité

Les études de phase IIa

Essais non comparatifs (Ethique et statistique)

- **Minimiser le nombre de patients** inclus
- Comparaison à un **taux d'efficacité de référence**
- **Etape non définitive**

Les études de phase IIa

Biais:

- **Effet Hawthorne**: savoir que l'on participe à une expérience augmente la motivation
- **Effet placebo**
- **Régression à la moyenne**

Pour confirmer l'efficacité thérapeutique: nécessité d'un groupe contrôle… Passage en phase IIb/III

Les études de phase IIb: l'exemple

Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial

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Exemple de méthodologie

Methods In a phase 2b, multicentre, dose-ranging study, treatment-naive adults were randomly assigned (1:1:1:1) to receive 10 mg, 25 mg, or 50 mg dolutegravir or 600 mg efavirenz. Dose but not drug allocation was masked. Randomisation was by a central integrated voice-response system according to a computer-generated code. Study drugs were given with either tenofovir plus emtricitabine or abacavir plus lamivudine. Our study was done at 34 sites in France, Germany, Italy, Russia, Spain, and the USA beginning on July 9, 2009. Eligible participants were seropositive for HIV-1, aged 18 years or older, and had plasma HIV RNA viral loads of at least 1000 copies per mL and CD4 counts of at least 200 cells per µL. Our primary endpoint was the proportion of participants with viral load of less than 50 copies per mL at week 16 and we present data to week 48. Analyses were done on the basis of allocation group and included all participants who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00951015.

Exemple de méthodologie

	10 mg dolutegravir (n=53)	25 mg dolutegravir (n=51)	50 mg dolutegravir (n=51)	600 mg efavirenz (n=50)	Total (n=205)
Age (years), median (range)	32 (21–61)	38 (20–64)	37 (22–55)	40 (20–79)	37 (20–79)
Number of men	42 (79%)	46 (90%)	45 (88%)	44 (88%)	177 (86%)
Ethnic origin					
Black	7 (13%)	6 (12%)	8 (16%)	4 (8%)	25 (12%)
White	41 (77%)	42 (82%)	38 (75%)	43 (86%)	164 (80%)
Other*	5 (9%)	3 (6%)	5 (10%)	3 (6%)	16 (8%)
Baseline viral load (HIV-1 RNA)					
Number with >100 000 copies per mL	11 (21%)	10 (20%)	12 (24%)	11 (22%)	44 (21%)
Mean concentration, $\log_{10}$ copies per mL (SD; range)	4·4 (0·66; 3·3–6·2)	4·4 (0·68; 2·9–5·6)	4·6 (0·68; 2·9–6·0)	4·5 (0·68; 3·2–6·0)	4·5 (0·68; 2·9–6·2)
Baseline CD4 count (cells per µL)					
Mean	309	334	327	328	324
Median	289	330	305	308	305
CDC category A or B	53 (100%)	50 (98%)	51 (100%)	49 (98%)	203 (99%)
Background NRTI selection					
Tenofovir plus emtricitabine	36 (68%)	34 (67%)	34 (67%)	34 (68%)	138 (67%)
Abacavir plus lamivudine	17 (32%)	17 (33%)	17 (33%)	16 (32%)	67 (33%)

Data are n (%) unless otherwise stated. CDC=US Centers for Disease Control and Prevention. NRTI=nucleoside reverse transcriptase inhibitor. *Includes Asian, Native American, Native Alaskan, Native Hawaiian, or other Pacific Islander. Overall, 16% of participants reported Hispanic ethnicity.

Table 1: **Baseline characteristics**

Exemple de méthodologie

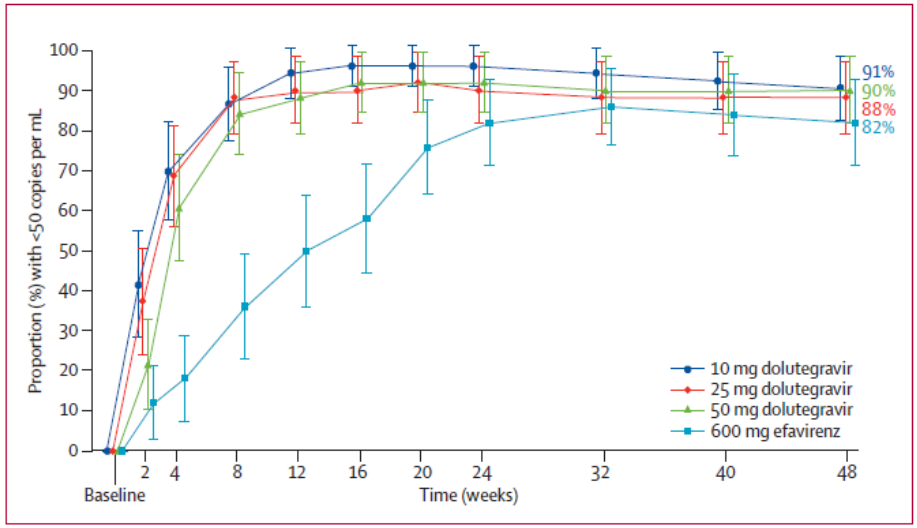

Figure 2: **Proportion of participants with viral load less than 50 copies per mL**
Viral load measured as HIV-1 RNA copies per mL. Endpoint established with time to loss of virological response algorithm. 95% CIs derived with the normal approximation.

	10 mg dolutegravir (n=53)	25 mg dolutegravir (n=51)	50 mg dolutegravir (n=51)	600 mg efavirenz (n=50)
Overall number of responders at week 16	51 (96%)	47 (92%)	46 (90%)	30 (60%)
Overall number of responders at week 48	48 (91%)	45 (88%)	46 (90%)	41 (82%)
Non-response (virological reason) by week 48				
Rebound or protocol-defined virological failure	4 (8%)	3 (6%)	2 (4%)*	3 (6%)
Never suppressed by week 48	0	0	1 (2%)	1 (2%)
Non-response (non-virological reasons) by week 48				
Discontinuation because of adverse event	0	1 (2%)	0	4 (8%)
Protocol deviation or non-permitted change in ART	1 (2%)	2 (4%)	1 (2%)	0
Lost to follow-up or participant discontinued	0	0	1 (2%)	1 (2%)
By baseline viral load (HIV-1 RNA)				
Non-response (virological reason)				
≤100 000 copies per mL subgroup (n=161)	3	2	0	2
>100 000 copies per mL subgroup (n=44)	1	1	3*	2
By background NRTI selection				
Non-response (virological reason)				
Tenofovir plus emtricitabine (n=138)	2	0	1	3
Abacavir plus lamivudine (n=67)	2	3	2*	1

Data are n (%). ART=antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor. *Includes one participant who discontinued the study drug because of Burkitt's lymphoma and therefore had detectable viral load at the time of discontinuation.

Table 2: **Summary of study outcomes at weeks 16 and 48—overall and by baseline strata**

Exemple de méthodologie

	10 mg dolutegravir (n=53)	25 mg dolutegravir (n=51)	50 mg dolutegravir (n=51)	Subtotal (n=155)	600 mg efavirenz (n=50)
Any event	47 (89%)	41 (80%)	44 (86%)	132 (85%)	44 (88%)
Serious adverse events*	3 (6%)	1 (2%)	4 (8%)	8 (5%)	4 (8%)
Any drug-related event (all grades)†	25 (47%)	18 (35%)	23 (45%)	66 (43%)	29 (58%)
Nausea	7 (13%)	6 (12%)	6 (12%)	19 (12%)	3 (6%)
Diarrhoea	4 (8%)	3 (6%)	5 (10%)	12 (8%)	3 (6%)
Dizziness	2 (4%)	0	3 (6%)	5 (3%)	9 (18%)
Headache	2 (4%)	4 (8%)	4 (8%)	10 (6%)	1 (2%)
Fatigue	1 (2%)	3 (6%)	1 (2%)	5 (3%)	4 (8%)
Asthenia	3 (6%)	0	1 (2%)	4 (3%)	0
Insomnia	0	0	3 (6%)	3 (2%)	4 (8%)
Abnormal dreams	1 (2%)	0	0	1 (<1%)	3 (6%)
Rash	2 (4%)	0	0	2 (1%)	4 (8%)

Data are n (%). *For 10 mg dolutegravir were abscess, dysmenorrhoea, and joint dislocation; for 25 mg was headache after lumbar puncture; for 50 mg were herpes zoster, fracture (foot and wrist), pyrexia, and Burkitt's lymphoma; and for efavirenz were bronchitis, neurosyphilis, epididymitis, and suicide attempt. †Adverse events in at least 5% of participants in one or more treatment groups.

Table 3: **Adverse events**

Exemple de méthodologie

	$AUC_{(0-\tau)}$ µg.h/mL	C_{max} µg/mL	C_τ µg/mL*	Inhibitory quotient (C_t/protein-adjusted IC_{90})†
10 mg (n=15)	16·0 (40%)	1·10 (37%)	0·30 (71%)	4·7
25 mg (n=15)	23·1 (48%)	1·71 (43%)	0·54 (67%)	8·4
50 mg (n=15)	48·1 (40%)	3·40 (27%)	1·20 (62%)	19

Data are geometric means (coefficient of variance, %). $AUC_{(0-\tau)}$=area under the concentration–time curve from zero to the end of dosing interval. C_{max}=maximum observed plasma concentration. C_τ=concentration at the end of the dosing interval. IC_{90}=90% inhibitory concentration. *Total number of samples assessed for the 10 mg group were 47, for the 25 mg group were 44, and for the 50 mg group were 44. †Protein-adjusted IC_{90}=0·064 µg/mL.

Table 4: **Summary of dolutegravir pharmacokinetic parameters by dose at week 2**

Exemple de méthodologie

Findings 205 patients were randomly allocated and received at least one dose of study drug: 53, 51, and 51 to receive 10 mg, 25 mg, and 50 mg dolutegravir, respectively, and 50 to receive efavirenz. Week 16 response rates to viral loads of at most 50 copies per mL were 93% (144 of 155 participants) for all doses of dolutegravir (with little difference between dose groups) and 60% (30 of 50) for efavirenz; week 48 response rates were 90% (139 of 155) for all doses of dolutegravir and 82% (41 of 50) for efavirenz. Response rates between nucleoside reverse transcriptase inhibitor subgroups were similar. We identified three virological failures in the dolutegravir groups and one in the efavirenz group—we did not identify any integrase inhibitor mutations. We did not identify any dose-related clinical or laboratory toxic effects, with more drug-related adverse events of moderate-or-higher intensity in the efavirenz group (20%) than the dolutegravir group (8%). We did not judge that any serious adverse events were related to dolutegravir.

Exemple de méthodologie

Vos conclusions?

Exemple de méthodologie

Interpretation Dolutegravir was effective when given once daily without a pharmacokinetic booster and was well tolerated at all assessed doses. Our findings support the assessment of once daily 50 mg dolutegravir in phase 3 trials.

Les études de phase IIb

- Premiers **essais comparatifs** versus le traitement de référence et un placebo
- **Recherche de dose** sur un petit nombre de dose (3 en moyenne) + placebo + traitement de référence
- Différence avec un essai de phase III:
  - Faible quantité d'information disponible avant le début de l'essai
  - Nombre de patient plus faible
  - Critères de jugement intermédiaires +++

Questions ?