MÉDECINE
Santé
Université Paris Cité

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Actualités sur les antirétroviraux et formulations pédiatriques

Pr Albert Faye

Hôpital Robert Debré, Paris

7e Journée Périnatalité et Infection par le VIH

Conflits d’intérêt

- Aucun

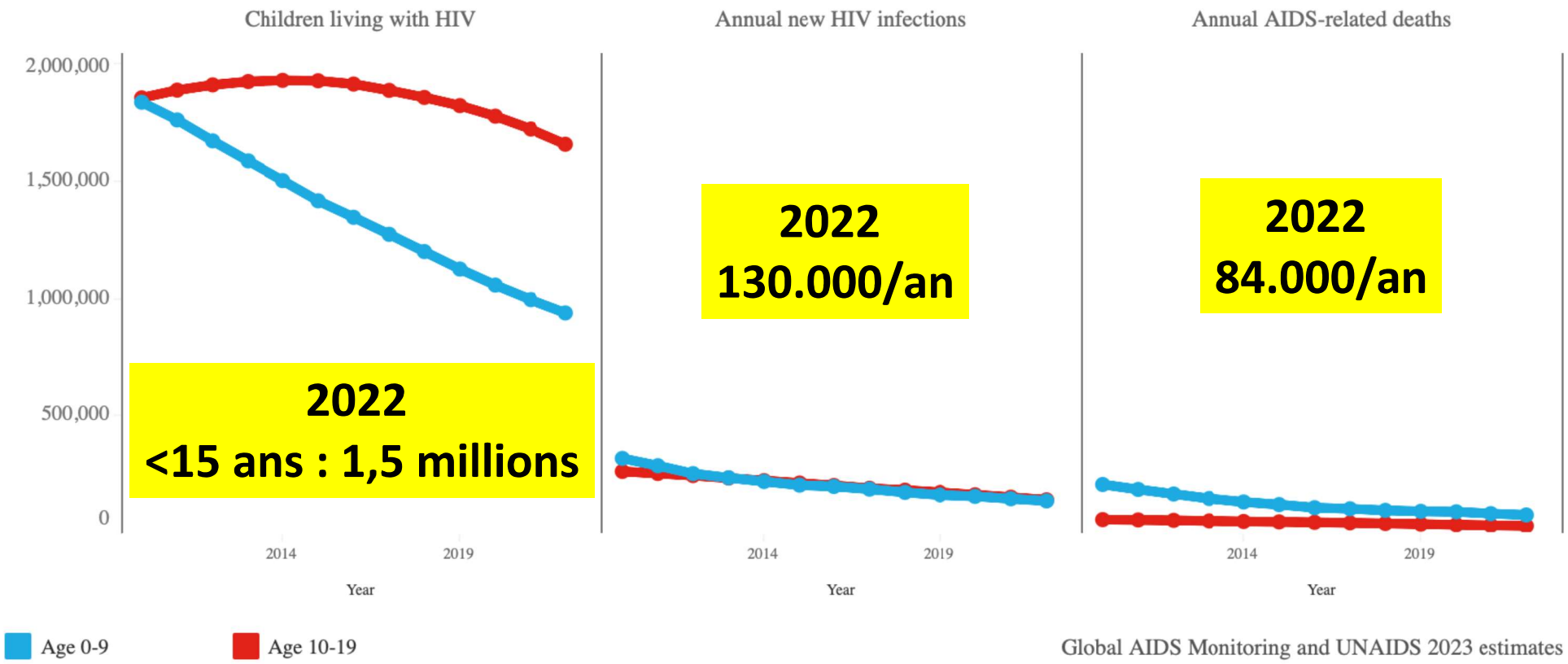
Les points abordés

- Introduction
- Il y a t'il progrès dans la couverture ARV pédiatrique dans le monde ?
- Quelles problématiques de développement des ARV chez l'enfant ?
- Où en est-on des nouvelles recommandations HAS ?
- Quelles perspectives thérapeutiques chez l'enfant ?
- Conclusion

Introduction

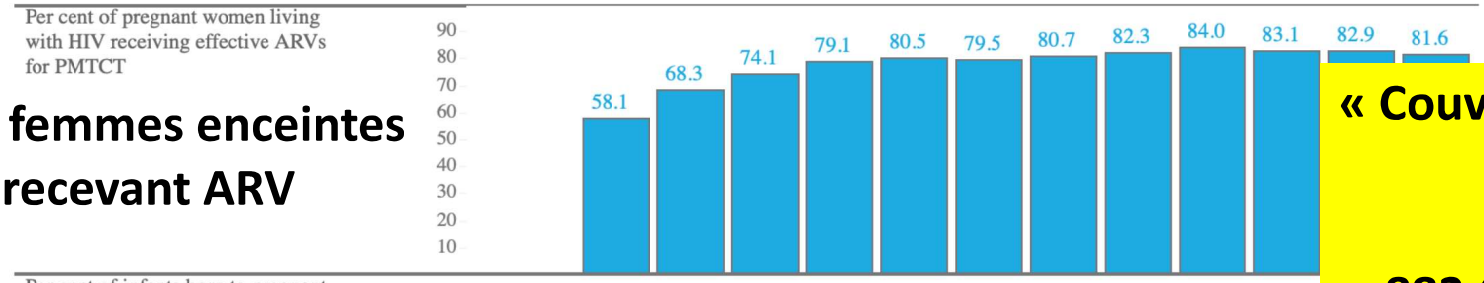
- Evolution accélérée des ARV adultes ces 5-10 dernières années «boostée» par les anti-intégrases et les injectables «Long Acting » (LA)
- Relatif échec des Plans d'Investigation Pédiatriques obligatoires pour les firmes => pas de progrès majeurs en pédiatrie…
- Quelques avancées sur les anti-intégrases chez l'enfant => large place dans les recommandations nationales et internationales

Rappel : Infection à VIH chez l'enfant 2010-2022

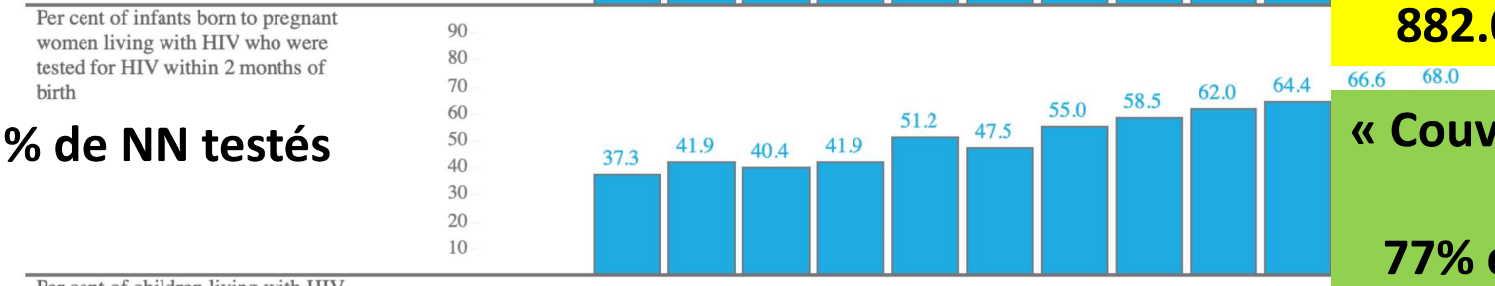


Evolution de la « cascade » du traitement de l'enfant : des résultats mitigés

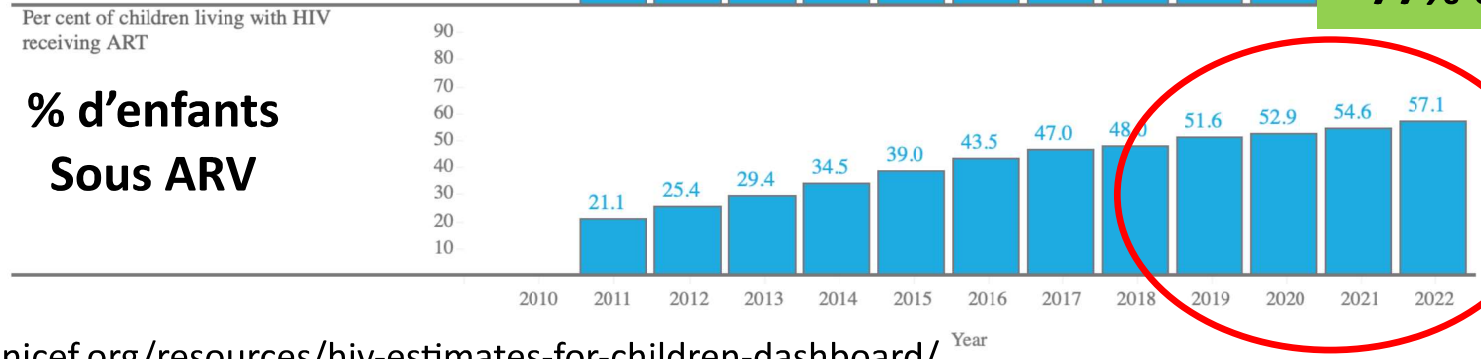
% de femmes enceintes recevant ARV



% de NN testés



% d'enfants Sous ARV

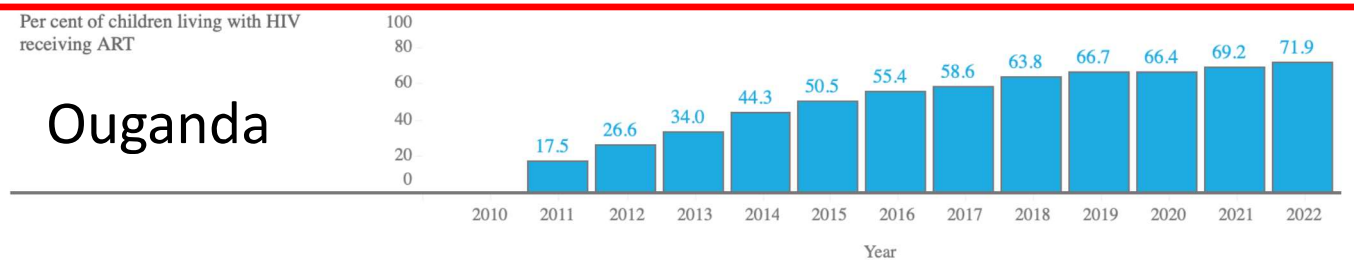


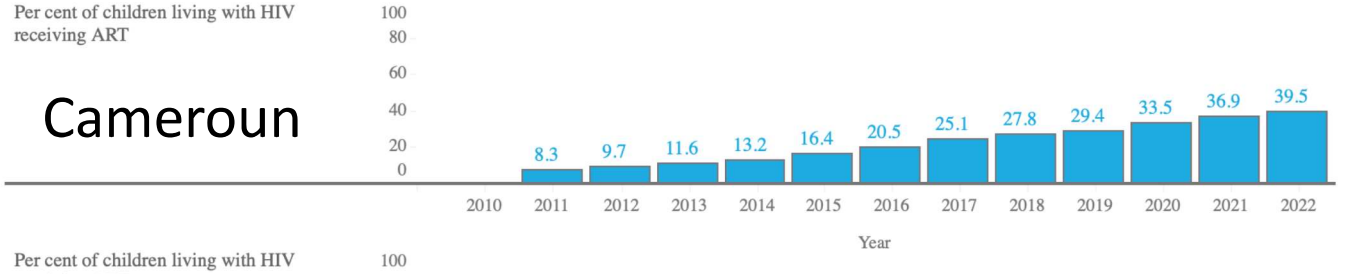
« Couverture ARV » 2022
57,1%
882.000 enfants

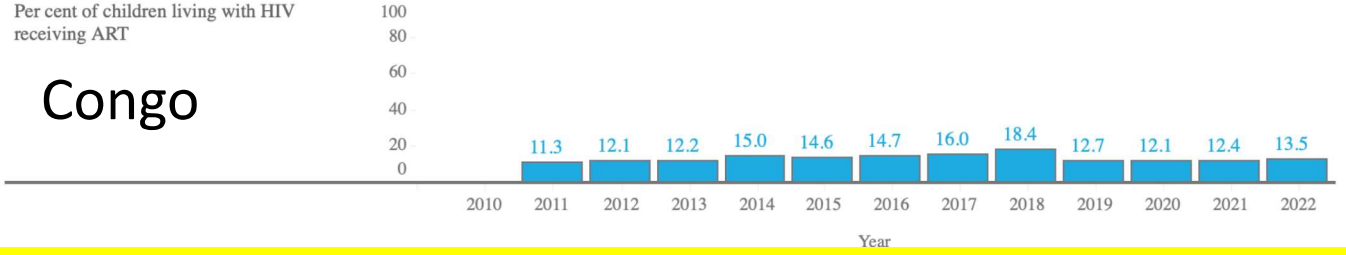
« Couverture ARV » 2022
77% chez l'adulte

https://data.unicef.org/resources/hiv-estimates-for-children-dashboard/

De grandes disparités de la couverture ARV en fonction des pays…







France >95%

Objectif 95% en 2023 loin d'être acquis pour l'enfant …

https://data.unicef.org/resources/hiv-estimates-for-children-dashboard/

Problématiques du développement des ARV chez l'enfant

- Succès de la PTME => Marché « réduit » pour les firmes !...
- Effort des firmes sur les « Long Acting » (LA) = > réduction des investissements
- Intérêt du «lobbying» OMS : Paediatric Drug Optimization for HIV (PADO-HIV) group => recommandations du développement de molécules/stratégies pédiatriques
  - ex. dolutégravir 10 mg en cp dispersible (dés 3kg et 4 semaines) demande en 2014…mais …Recommandation OMS en 2020

i-base
0808 800 6013

ARV chart
2022/23

June 2022

Antiretroviral drugs 2022/23 www.i-Base.info

Drug names		Recommended adult dose *	Total daily pills
Entry inhibitors			
maraviroc * (Celsentri)		150 mg or 300 mg or 600 mg, as directed, depending on other ARVs in the combination.	1 or 2 or 4
fostemsavir (Rukobia)		600 mg tablet, twice-daily.	2
bNAbs (broadly neutralising monoclonal antibody) - an immune-based treatment			
ibalizumab (Trogarzo)	not to scale 	150 mg/mL given as single IV infusion every two weeks.	will depend on other meds being used
Single nukes (NRTIs)			
lamivudine (3TC) ++ (Epivir [pictured] or generic)		1 x 300 mg (shown) or 2 x 150 mg, (taken as a once-daily or twice-daily dose).	1 if 300 mg 2 if 150 mg
abacavir ++ (Ziagen [pictured] or generic)		2 x 300 mg tablets (taken as a once-daily or twice-daily dose).	2
emtricitabine (FTC) (Emtriva)		1 x 200 mg capsule, once-daily.	1
tenofovir DF * ++ (Viread [pictured] or generic)		1 x 300 mg tablet, once-daily.	1
Fixed dose combinations	0 5 10 15 20 mm *Approximate to actual size.*		
Atripla (efavirenz + emtricitabine + tenofovir DF)		One tablet, once-daily. Take at night and not with a high fat meal. See info on separate drugs.	1
Biktarvy (bictegravir + TAF + emtricitabine)		One tablet, once-daily. Take with or without food. See info on separate drugs.	1
Eviplera (rilpivirine + emtricitabine + tenofovir DF)		One tablet, once-daily, with food (400 kcal). See separate drug info.	1
Odefsey (rilpivirine + emtricitabine + TAF)		One tablet, once-daily, take with food. See info on separate drugs.	1
Triumeq (dolutegravir + abacavir + lamivudine)		One tablet, once-daily. Take with or without food. See info on separate drugs.	1
Genvoya (elvitegravir + cobicistat + emtricitabine + TAF)		One tablet, once-daily. Take with food. See info on separate drugs.	1
Stribild (elvitegravir + cobicistat + emtricitabine + tenofovir DF)		One tablet, once-daily, take with food. See info on separate drugs.	1
Symtuza (carunavir + cobicistat + emtricitabine + TAF)		One tablet, once-daily, take with food. See info on separate drugs.	1
Delstrigo (doravirine + lamivudine + tenofovir DF)		One tablet, once-daily, with or without food. See info on each drug.	1
Dovato (dolutegravir + lamivudine)		One tablet, once-daily, with or without food. See info on each drug.	1
Juluca (dolutegravir + rilpivirine)		One tablet, once-daily, take with food. See info on separate drugs.	1
Dual nukes: nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)			
tenofovir DF 300 mg + emtricitabine 200 mg Truvada [pictured] or generic) ++		One tablet, once-daily.	1
TAF (10 mg white or 25 mg blue) + emtricitabine (200 mg), Descovy		One tablet, once-daily.	1
abacavir 600 mg + lamivudine 300 mg (Kivexa or generic) ++		One tablet, once-daily.	1
Injectable ART (cabotegravir/rilpivirine long-acting injections (CAB/RPV-LA) and single nukes			
See back page for info on injectable ART. Also for single nukes (which are rarely used).			

Different doses or formulations might be used - always check doses with your pharmacist.
Generic versions might be a different colour and shape. § EU approval pending.

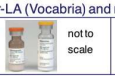
NNRTIs: non-nucleoside reverse transcriptase inhibitors (non-nukes)

efavirenz 600 mg or 200 mg (Sustiva, [pictured] or generic) ++		1 x 600 tablet (or 3 x 200 caps) once-daily; at night, not with high fat meal.	1 tablet (or 3 capsules)
nevirapine PR 400 mg (Viramune [pictured] or generic ++		1 x 400 mg once a day. Take with or without food.	1 x 400 mg
etravirine (100 mg or 200 mg) (Intelence)		2 x 100 mg OR 1 x 200 mg, twice daily, take with food. Dispersible in water.	2 or 4
rilpivirine (Edurant)		1 x 25 mg tablet, once-daily, take with main meal (500 kcal).	1
doravirine (Pifeltro)		1 x 100 mg tablet, once-daily, take with or without food.	1

INIs or INSTIs: integrase inhibitors

raltegravir 400 mg (pink) & 600 mg (yellow) (Isentress)		1 x 400 mg, twice-daily OR 2 x 600 mg tablet, once-daily. Take with or without food.	2
dolutegravir (Tivicay) *		1 x 50 mg tablet, once-daily (or 1 x 50 mg twice -daily). With food if twice-daily but with or without otherwise.	1 or 2
elvitegravir and bictegravir are only in combination pills – see Stribild, Genvoya and Biktarvy.			1

Injectable long-acting cabotegravir-LA (Vocabria) and rilpivirine - LA (Rekambys)

Cabotegravir + rilpivirine-LA (Vocabria + Rekambys)	not to scale 	Two injections into muscle (in the buttocks) every two months. Oral pills might be used for the first month.	none

b/PI: boosted protease inhibitors

atazanavir * (Reyataz)		1 x 300 mg cap + booster, once-daily. Take with food. 150 mg and 200 mg capsules also available.	1 (+ 1 booster)
darunavir 600 mg (orange) & 800 mg (red), (Prezista) * ++		1 x 800 mg + booster once-daily (OR 1 x 600 mg + 100 mg booster twice-daily with resistance). Take with food.	1 or 2 (+ 1 or 2 boosters)
atazanavir/cobicistat (Evotaz)		1 tablet, once-daily. Take with food.	1
darunavir/cobicistat (Rezolsta)		1 tablet, once-daily. Take with food.	1
PK (pharmacokinetic) boosters			
cobicistat (/c) (Tybost)		150 mg tablet, once daily. Used to boost atazanavir, darunavir and elvitegravir.	depends on boosted drug
ritonavir (/r) * ++ (Norvir)		100 mg tablets used at different doses to boost other PIs.	depends on PI

Environ 35 présentations « adultes » différentes dont 11 « Single Treatment Tablet » (STR)

Depuis les dernières recommandations 2018 peu de grandes nouveautés chez l'enfant …

- Cp 10 et 25 mg de **dolutégravir** en 2018 puis 5 mg orodispersibles => AMM 4 semaines et > 3 kg en 2021
- Age de l'AMM abaissé pour plusieurs ARV :
  - **Bictegravir/tenofovir alafenamide/emtricitabine** : 2 ans et poids 14 à 25 kg (nouvelle forme galénique 30mg/120mg/15mg – avec barre de sécabilité mais toujours pas arrivée en France… décret imminent…)
  - Elvitégravir/cobicistat/tenofovir alafenamide/emtricitabine : 6 ans et > 25kg, Doravirine : 12 ans, Etravirine et maraviroc peuvent : 2 ans
- Molécules autorisées par la FDA mais pas AMM : rilpivirine LP + cabotégravir LP injectable chez l'ado. de plus de 35 kg

Pas d'évolution actuelle dans les recommandations d'initiation

Tout enfant infecté par le VIH-1 doit recevoir un traitement antirétroviral le plus tôt possible (grade A) :

- Ce traitement doit être débuté au mieux dans les jours suivant le diagnostic. Selon les cas, le traitement pourra être initié sans délai, ou différé d'une à deux semaines le temps d'avoir les résultats du bilan initial.
- Toutes les mesures d'accompagnement et d'aide à l'adhésion au traitement jugées nécessaires (soutien socio-administratif et psychologique de la famille, consultation d'éducation thérapeutique, infirmière à domicile voire hospitalisation courte ou en long séjour de l'enfant) doivent être immédiatement mises en œuvre pour la réussite du traitement.
- Il est recommandé que le délai d'initiation soit porté à un minimum de 4 semaines en cas d'infection neuroméningée à *Cryptococcus sp*. ou à *Mycobacterium tuberculosis complex*.

Reco. HAS 2023 non validée

Rappel recommandations 2018

Age		<3 ans	3-6 ans	6-12 ans	≥ 12 ans
Traitement préférentiel	Association d'INTI	ABC + 3TC (ou FTC)			ABC*+3TC ou FTC+TAF (≥35 kg) ‡
	3ème agent	LPV/r	DRV/r	DRV/r ou ATV/r ou DTG	DTG ou EVG/cobi (≥35 kg) ou RPV‡* (≥35 kg) ou DRV/r ou ATV/r
Alternatives	Association d'INTI	3TC (ou FTC) + ZDV ABC* + ZDV (intérêt chez le nourrisson et/ou l'enfant dont l'observance est incertaine)			
	3ème agent (**par ordre de préférence**)	NVP** ou RAL***	LPV/r EFV ou NVP** ou RAL***		RAL*** EFV ou LPV/r

ZDV = zidovudine; ABC = abacavir; 3TC = lamivudine; FTC = emtricitabine; LPV/r = lopinavir/ritonavir; ATV = atazanavir/ritonavir; DRV = darunavir/ritonavir; TAF : tenofovir Alafenamide; NVP = nevirapine; RAL = raltegravir; EFV = efavirenz; DTG = dolutegravir; EVG = elvitegravir; cobi = cobicistat; ATV = atazanavir. RPV=rilpivirine

Proposition dans les nouvelles recommandations

Non validé

Age		<4 semaines	1mois - 2ans	2 - 12 ans	≥ 12 ans
Traitement de 1ère intention	Association d'INTI	ZDV + 3TC	ABC* + 3TC	ABC* + 3TC TAF + FTC	ABC* + 3TC TDF ou TAF + 3TC ou FTC
	3ème agent	RAL ≥2kg	DTG	DTG BIC	DTG BIC
Alternatives	Association d'INTI	ZDV + 3TC (ou FTC) ABC* + ZDV (intérêt chez le nourrisson et/ou l'enfant dont l'observance est incertaine)			
	3ème agent***	LPV/r si > 42 SA et > 14 jours NVP** avant 14 jours ou si traitement d'un nouveau-né prématuré		ATZ/r DRV/r (≥3 ans) ETV LPV/r RAL	ATZ/r DOR DRV/r EVG/c RAL RPV‡

ABC: abacavir; ATV/r: atazanavir/ritonavir; BIC: bictégravir; DTG: dolutegravir; DRV/r: darunavir/ritonavir; DOR: doravirine ; ETV : etravirine; EVG/c : elvitegravir/cobicistat; FTC: emtricitabine; 3TC: lamivudine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; RAL: raltegravir; RPV: rilpivirine; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; ZDV: zidovudine.

Comparable aux reco. US et Penta 2023 Sauf OK ABC avant l'âge de 4 semaines

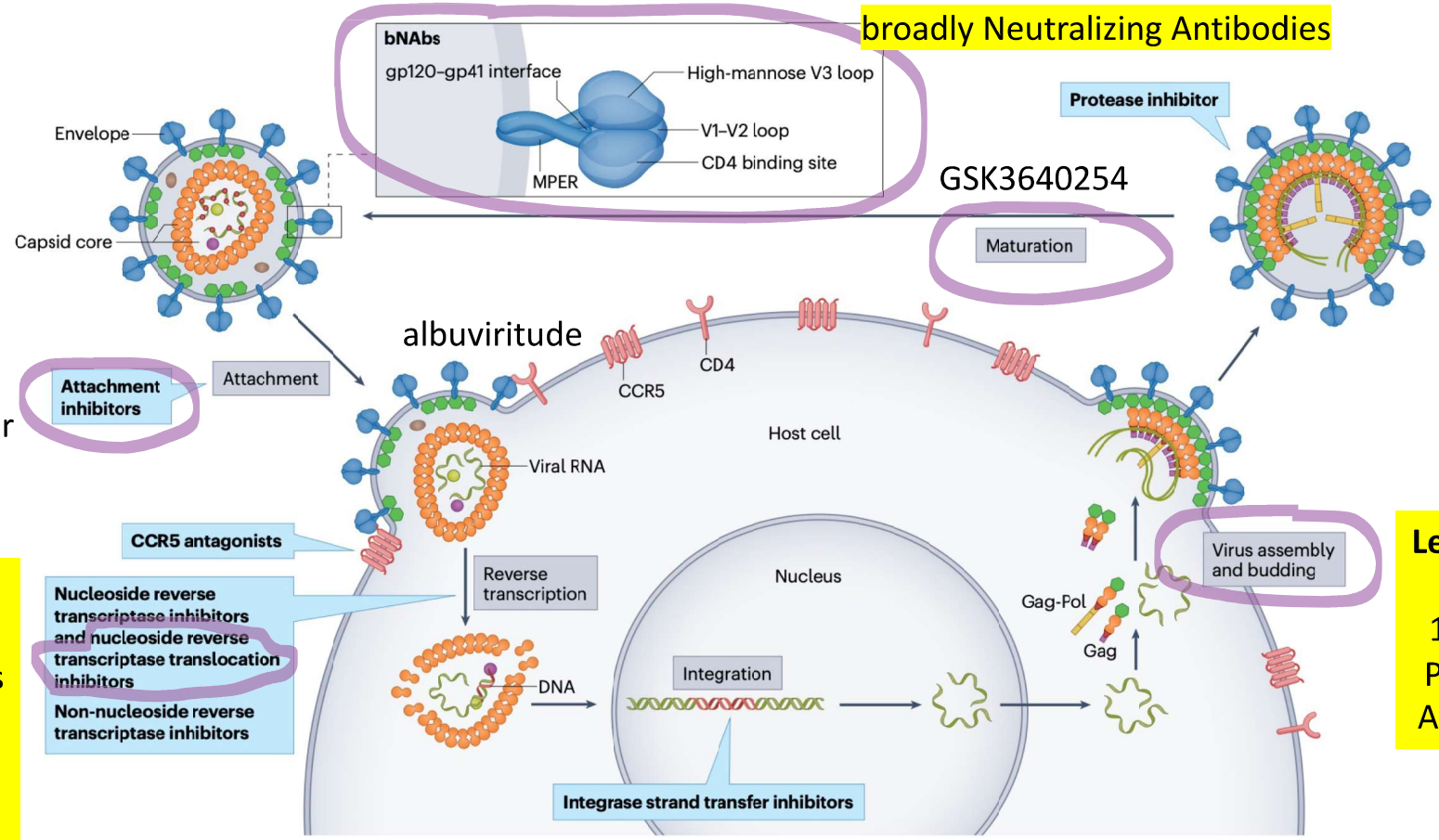
Les perspectives chez l'enfant : le tournant des « Long Acting »

- Le premier chez l'adulte Cabotégravir + Rilpivirine
- Etude de phase I/II study chez l'adolescents 12–18 ans (MOCHA, IMPAACT-2017, NCT03497676) : dose chez l'adolescent = doses adultes
- Etude phase I/II chez l'enfant 2-12 years en cours US, Brésil, Afrique et Asie) (CRAYON (Cabotegravir and Rilpivirine Long-Acting Injections in YOung ChildreN) , IMPAACT-2036)
- Inconvénient si effets secondaires persistance du traitement

Cibles des ARV «émergents »

Nature Reviews Microbiology | Volume 21 | October 2023 | 657–670

broadly Neutralizing Antibodies



Fostemsavir

Islatravir
LA voie orale
1x/sem ou mois
Phase 2
Adulte-Ado
suspendue

Lenacapavir
LA sc
1x/6 mois
Phase 2/3
Adulte-Ado

Fig. 1 | Mechanism of action for current and emerging antiretroviral (VRC07-523LS, 3BNC117, N6), the gp120–gp41 interface and the membrane

broadly Neutralizing Antibodies (bNAbs)

- Approche prometteuse en particulier combinés et en association avec des ARV « long acting »
- Réduction du réservoir - induction d'une réponse T cytotoxique puissante - retard du rebond viral *Landovitz et al, Nature Review microbiology 2023*
- Etude chez le nouveau-né à haut risque ou non dans la PTME (IMPAACT 1112, 1115 et P2008) – voie SC toutes les 12 semaines
- Tatelo Study : Etude chez l'enfant infecté âgé de 2 à 7 ans au Botswana, traités précocément et à CV contrôlée : VRC01LS + 10-1074 en IV x 1 /mois
  - PK
  - Etape 1 : poursuite bnAbs+ARV
  - Etape 2 : arrêt ARV
  - Etape 3 : arrêt bNAbs et reprise ARV

J Acquir Immune Defic Syndr • Volume 91, Number 2, October 1, 2022

Safety and Pharmacokinetics of Intravenous 10-1074 and VRC01LS in Young Children

Edmund V. Capparelli, PharmD,[a] Gbolahan Ajibola, MBBS, MPH,[b] Kenneth Maswabi, MD,[b] Molly P. Holme, MSc,[c] Kara Bennett, MS,[d] Kathleen M. Powis, MPH,[b,c,e] Sikhulile Moyo, PhD,[b] Terence Mohammed, PhD,[b] Comfort Maphorisa, MS,[b] Michael D. Hughes, PhD,[f] Kelly E. Seaton, PhD,[g] Georgia D. Tomaras, PhD,[g] Shad Mosher, PhD,[g] Alison Taylor, MIBMS,[h] Sarah O'Connell, PhD,[h] Sandeep Narpala, PhD,[h] Adrian Mcdermott, MSc, PhD,[h] Marina Caskey, MD,[i] Lucio Gama, PhD,[h] Shahin Lockman, MD, MSc,[b,c,j] Patrick Jean-Philippe, MD,[k] Joseph Makhema, MD,[b,c] Daniel R. Kuritzkes, MD,[j,l] Mathias Lichterfeld, MD,[m] and Roger L. Shapiro, MD,[b,c] for the Tatelo Study Team

Conclusions: 10-1074 and VRC01LS were safe and well-tolerated among children receiving ART. Troughs exceeded minimal targets with every 4-week administration of 10-1074 at 30 mg/kg and VRC01LS at 15 mg/kg.

En dehors des injectables : nouvelles perspectives d'administration des ARV

- **Implants sous-cutanés**
  - ✓Technologie déjà largement utilisé (contraception) durée prolongée possible (> 1 an)
  - ✓Possibilité de retrait si effets secondaires
  - ✓En développement : TAF+FTC, Islatravir…
  - ✓Technicité de la mise en place - retrait
- **Patchs à micro-réseaux (micro-array patches)**
  - ✓Praticité potentielle en pédiatrie +++
  - ✓Traitements utilisables nécessitant : petites doses, longue demi-vie et bonne tolérance

Modalités d'administration en fonction de l'âge

	Microarray patches (home or clinic administration)	Long-acting injectables, subcutaneous (clinic administration likely)	Long-acting injectables, intramuscular (clinic administration)	Implants (clinic administration)
Neonates (0–4 weeks) **Infants (1–12 months)**	+ Avoids oral administration challenges + Can be administered by caregivers – Possible skin sensitivities	+ Can also be used for prophylaxis in neonates + Avoids oral administration challenges + Can align with already existing clinic visits for administration + Dose can be adjusted + Regulatory pathways already exist	– Depending on volume, pain and injection site irritation might be prohibitive – Possible challenges with low birthweight neonates and infants	– Inability to frequently dose adjust as needed is probably prohibitive
Children (1–10 years)	+ Avoids oral administration challenges – Depending on size of patch and duration of exposure needed, placement might be burdensome	+ Avoids oral administration challenges and daily dosing + Pain of administration is more tolerable than intramuscular injections + Regulatory pathways already exist + Could align with immunisations	+ Avoids oral administration challenges + Dosing might align with already existing clinic visits + Regulatory pathways already exist – Monthly injections might not be acceptable	? Depending on dosing, and length of action, administration might be possible in some children
Adolescents (10–18 years)	– Probable need for large patch with frequent redosing ? Possibility of using multiple patches	+ Pain of administration is more tolerable than intramuscular injections + Regulatory pathways already exist + High acceptability in previous surveys	+ Can allow for less frequent dosing + Overcomes adherence challenges in adolescents	+ No dose adjustments needed + Aligns with less frequent clinic visits and multi-month dosing + Overcomes adherence challenges in adolescents

***gure:* Advantages and disadvantages of new drug delivery technologies for different paediatric populations**

Penazzato et al, Lancet HIV 2022

Panel 1: PADO-HIV 5 priority list

PADO-HIV 5 priority list: medium term, 3–5 years

- Dolutegravir/lamivudine/abacavir (5/30/60 mg dispersible)
- Ritonavir–boosted darunavir (20/120 mg)
- Lamivudine/emtricitabine combined with tenofovir alafenamide, with or without dolutegravir
- Cabotegravir for postnatal prophylaxis

PADO-HIV 5 watch list (products of potential interest for paediatric treatment in the longer term)

- Islatravir
- Broadly neutralising antibodies
- Microarray patches (with potent antiretroviral identified after appropriate matching)
- Lenacapavir

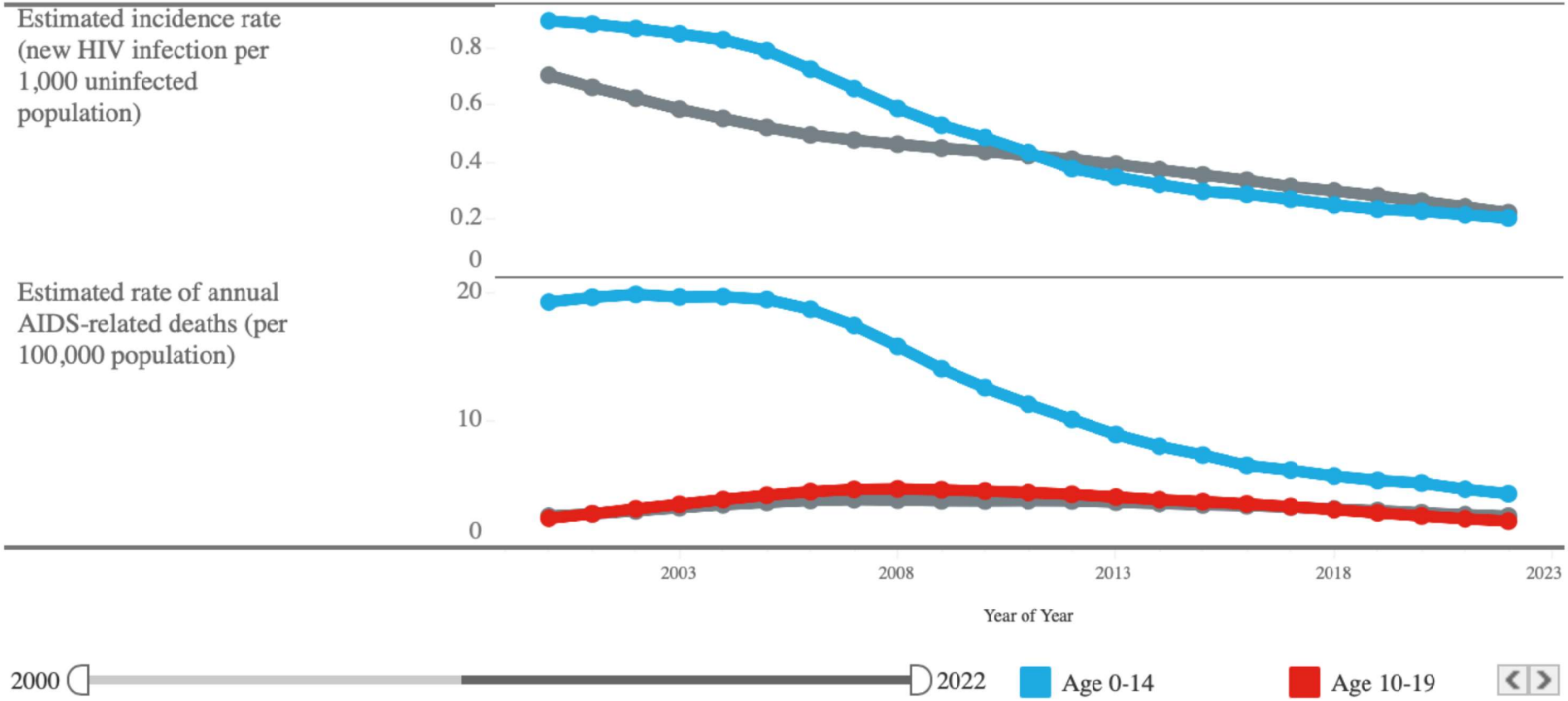
PADO-HIV=Paediatric Drug Optimization for HIV.

Penazzato et al, Lancet HIV 2022

Conclusion

- Couverture et traitements émergents : persistance d'une différence **trop importante** adulte-enfant
- Poursuivre le « lobbying »…
- Des perspectives intéressantes sur les **modalités d'administration** => alléger le poids du traitement journalier pour les enfants et leurs parents
- **Développement majeur des bNAbs** : la pédiatrie est bien placée => peut-être 1ère étape des bases du « HIV cure »…

Evolution mondiale de l'infection à VIH chez l'enfant 2003-2022



En résumé…en 2022…

UNAIDS

In 2022, 76% [65–89%] of all people living with HIV were accessing treatment.

- 77% [65–90%] of adults aged 15 years and older living with HIV had access to treatment, as did 57% [44–78%] of children aged 0–14 years.

Objectif 95% en 2023 loin d'être acquis pour l'enfant …

- A phase 1 trial to investigate the safety, tolerability, and dosing of a liquid suspension of dolutegravir is currently in development (IMPAACT-2023). This study will also allow for assessment of the 5 mg dispersible dolutegravir tablet if initial data with the liquid formulation are
- acceptable. However, it was agreed that a parallel study to investigate the pharmacokinetics of the generic 10 mg scored dispersible dolutegravir tablet in neonates would be complementary and would help fast-track the safe use of the most widely available formulation in this population.
- As we mentioned previously, novel candidates that hold promise for neonatal prophylaxis and potentially treatment include oral islatravir and bNAbs. Although an optimal combination of bNAbs has not yet been identified, studies of several bNAbs in neonates have shown them to be safe and tolerable, and other studies are underway. Formu- lations containing islatravir might also have potential for neonatal treatment in the long-term, if and when the drug development programme is resumed.

Priorités moyen et long terme de développement des ARV de l'enfant

- Comme chez l'adulte : bonne tolérance et possibilité d'administration moins fréquente !
- Nouvelles cibles ARV
- Anticorps monoclonaux
- Nouvelles modalités/technologies d'administration :
  - Patches
  - ARV injectables en sc « long acting »
  - ARV injectables en IM « long acting »
  - Implants

Nouveaux ARV

- Lenacapavir : inhibiteur de la capside du VIH « long acting » en SC
  - Phase 2 and 3 d'injections une fois/6 mois chez des adultes naïfs (CALIBRATE, NCT04143594) et des adolescents et adultes prétraités (CAPELLA, NCT04150068)
- Islatravir = inhibiteur de la translocation « long acting » par voir orale (une fois/j, semaine ou mois) – phase 2 chez l'adulte et chez l'adolescent avec doravirine > 12 ans mais arrêt temporaire car observation de baisse des CD4
- Autres en cours : MK-8507 non nuc « long-acting », fostemsavir inhibiteur de l'attachement à la GP-120; GSK3640254, inhibiteur de la maturation du VIH-1; ABX464, ARV se fixant sur cap-binding complex, albuviritude inhibiteur de fusion.

JAMA
THE JOURNAL of the American Medical Association
May 6 1983 Vol 249, No. 17

Immune Deficiency Syndrome in Children

James Oleske, MD, MPH; Anthony Minnefor, MD; Roger Cooper, Jr, MD; Kathleen Thomas, MD; Antonio dela Cruz, MD; Houman Ahdieh; Isabel Guerrero, MD; Vijay V. Joshi, MD; Franklin Desposito, MD

• The present epidemic of acquired immuno deficiency syndrome (AIDS) was originally described in homosexual men and subsequently in intravenous drug abusers, Haitians, and hemophiliacs. Profound defects in cell-mediated immunity (CMI) are associated with Kaposi's sarcoma and a variety of serious opportunistic infections. Recently, we and others have encountered a group of children with an otherwise unexplained immune deficiency syndrome and infections of the type found in adults with AIDS. In this report, we describe eight children from the Newark, NJ, metropolitan area born into families with recognized risks for AIDS. These patients have had recurrent febrile illnesses, failure to thrive, hypergammaglobulinemia, and depressed CMI. Four of these children have died. Our experience suggests that children living in high-risk households are susceptible to AIDS and that sexual contact, drug abuse, or exposure to blood products is not necessary for disease transmission.

(*JAMA* 1983;249:2345-2349)

THE ACQUIRED immune deficiency syndrome (AIDS) is a now-familiar entity initially described in male homosexuals and intravenous (IV) drug abusers. Subsequently, the condition has been reported in Haitians and hemophiliacs. Patients suffer from a profound defect in cell-mediated immunity (CMI) and have an increased risk for the development of Kaposi's sarcoma and a variety of serious opportunistic infections. Although the mortality rate (25%) among more recently diagnosed patients is less than that in earlier reports, ultimately 70% may succumb; as outcome is uncertain, with potentially high mortality among current "survivors." The cause of the syndrome remains unknown. Data are accumulating, however, that suggest that a transmissible agent is responsible for the immune dysfunction and that certain malignant neoplasms and opportunistic infections then develop thereafter.

See also pp 2350, 2370, and 2375.

Until recently, AIDS seemed to be limited to adults, predominantly in those with aberrant life-styles or exposure to blood products. It seems, however, that the epidemiology of AIDS may now have taken an ominous new turn, with otherwise "normal" infants and children as additional victims.

In this article, we report our experience with eight children with unexplained immunodeficiencies, some of whom had the opportunistic infections and fit the working definition of AIDS developed by the Centers for Disease Control (CDC).

PATIENTS AND METHODS

Since 1979, eight children from the Newark, NJ, metropolitan area have been found to have a disease complex compatible with AIDS. Laboratory and epidemiologic studies were done on these eight children and their family members, and hospital records and biopsy and autopsy reports were reviewed. The four surviving children have had more extensive immunologic studies than the earlier four fatal cases.

Cellular immune assays were performed on mononuclear cells obtained from peripheral blood samples from seven of these children and 11 family members by Ficoll-Hypaque density centrifugation. Studies included determination of T cells by E rosetting; B cells by surface markers; blastogenic response to mitogens, including phytohemagglutinin, concanavalin A, and pokeweed mitogen; and enumeration of OKT₄ helper cell and OKT₈ suppressor cells using Ortho-Mune monoclonal antibodies.

The eight patients had undergone extensive evaluations during their initial and subsequent hospitalizations. All were examined for underlying malignancies, hemoglobinopathy, and cystic fibrosis. With the exception of patient 6, all had urine, throat, CSF, and stool cultures for viruses in human fibroblasts and monkey kidney cells. Biopsy specimens from the lung and

From the Departments of Pediatrics (Drs Oleske, Thomas, Joshi, and Desposito) and Preventive Medicine (Drs Oleske and Minnefor), University of Medicine and Dentistry of New Jersey–New Jersey Medical School; the St Michael's Medical Center, Newark, NJ (Drs Oleske, dela Cruz, Cooper, and Ahdieh); the St Joseph's Hospital and Medical Center, Paterson, NJ (Dr Minnefor); and the New Jersey Department of Health, Trenton (Dr Guerrero).

Reprint requests to University of Medicine and Dentistry of New Jersey, 100 Bergen St, Newark, NJ 07103 (Dr Oleske).

Acquired Immunodeficiency With Reversed T_4/T_8 Ratios in Infants Born to Promiscuous and Drug-Addicted Mothers

Arye Rubinstein, MD; Marc Sicklick, MD; Asha Gupta, MD; Larry Bernstein, MD; Norman Klein, MD; Ethan Rubinstein, MD; Ilya Spigland, MD; Lazar Fruchter, MD; Nathan Litman, MD; Hassoon Lee, MD; Melvin Hollander, MD

• A new syndrome of acquired immunodeficiency has been identified in seven children who were small for gestational age at birth and subsequently have exhibited failure to thrive, lymphadenopathy, parotitis, hepatosplenomegaly, interstitial pneumonia, and recurrent infections. All have a profound cell-mediated immunodeficiency with reversed T_4/T_8 ratios. Six are hypergammaglobulinemic and one has low IgG levels. The mothers of five of the seven children are sexually promiscuous and/or drug addicts. Three mothers have an immunodeficiency similar to that found in their infants. One of them died at age 33 years with a diagnosis of acquired immunodeficiency syndrome. In five of the children and in three of their mothers, there is evidence of a persistent Epstein-Barr virus (EBV) infection. We speculate that a perinatal or in utero transmission of EBV can induce an "infectious immunodeficiency." The clinical, histopathologic, and immunologic features resemble those described in adult homosexuals and drug addicts.

(*JAMA* 1983;249:2350-2356)

AN OUTBREAK of acquired immunodeficiency and Kaposi's sarcoma in homosexuals has recently been described in the New York City area and in Los Angeles and San Francisco. In most patients, a profound abnormality in cell-mediated immunity with a reversed T_4/T_8 cell ratio, as well as opportunistic infections and/or Kaposi's sarcoma, were noted.

See also pp 2345, 2370, and 2375.

A similar acquired immunodeficiency has been reported in drug addicts, Haitians, and hemophiliacs. The epidemic proportions of the syndrome suggest an infectious origin. It has been postulated that the infectious agent is transmitted via body fluids such as sperm, saliva, and urine, and is probably present in the blood pool.

We report a similar immunodeficiency in seven infants, five of whom were born to sexually promiscuous and/or drug-addicted women. A T-cell deficiency with inverted T_4/T_8 ratios has been verified in all the children and in three mothers. These findings suggest the possibility of horizontal or vertical transmission of an infectious agent leading to an acquired immunodeficiency.

REPORT OF CASES

CASE 1.—A black boy, 3 years 7 months old, was referred to us at 3 years of age for evaluation of an interstitial pneumonia, generalized lymphadenopathy, and a history of recurrent infections. His five older siblings were healthy. He had a younger brother, born after seven months' gestation, who had recurrent infections from birth to his death at age 7 months of pneumonia. Patient 1 was small for gestational age. His mother had a history of drug abuse and prostitution. At birth, he was noted to be in respiratory distress. On discharge, the infant was briefly cared for by his mother, but was placed in a foster-care home at age 3 months because of neglect and child abuse.

At 4 months of age, he was hospitalized with fever and cough. Clinically he had generalized lymphadenopathy and hepato-

From the Departments of Pediatrics and Microbiology and Immunology, Division of Clinical Allergy and Immunology (Drs A. Rubinstein, Sicklick, Gupta, Bernstein, Klein, E. Rubinstein, Spigland, Fruchter, and Litman), Albert Einstein College of Medicine, Bronx, NY; the Department of Pediatrics, Jewish Hospital and Medical Center, Brooklyn, NY (Dr Lee), and the Department of Pediatrics, Misericordia Hospital Medical Center, Bronx, NY (Dr Hollander).

Reprint requests to Division of Clinical Allergy and Immunology, Albert Einstein College of Medicine, 1300 Morris Park Ave, Room F426, Bronx, NY 10461 (Dr A. Rubinstein).

SUCCESS IN TRANSLATIONAL MEDICINE

Twenty-Five Years of Translational Medicine in Antiretroviral Therapy: Promises to Keep

Samuel Broder*

Published 7 July 2010; Volume 2 Issue 39 39ps33

" (…) The daunting and often self-imposed "requirement" of total viral eradication fostered skepticism about the nascent experimental antiretroviral therapy programs

This skepticism in turn strengthened the belief that the best course to treat patients with AIDS was to provide supportive care, while attempting to manage opportunistic infections and neoplasms".

Une **divergence** Nord Sud des recommandations de prophylaxie MF 1

« …we will support programs that administer single dose of Nevirapine to the mother… »

President BUSH, 2002

ANC TODAY
ONLINE VOICE OF THE AFRICAN NATIONAL CONGRESS

Dec 2004

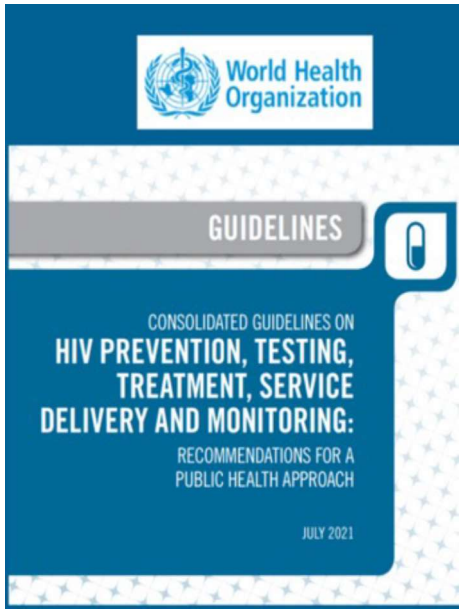
Nevirapine, drugs & African guinea pigs

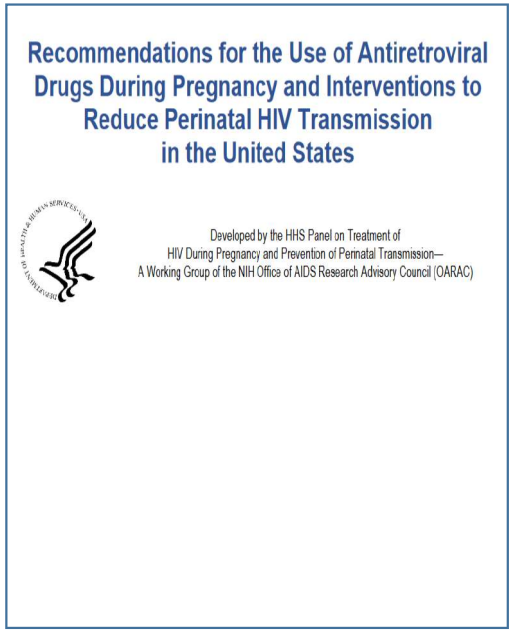
« …a conspiracy with a pharmaceutical company to tell lies to promote the sales of nevirapine in Africa, with absolutely no consideration of the health impact of those lies on the lives of millions of Africans. »

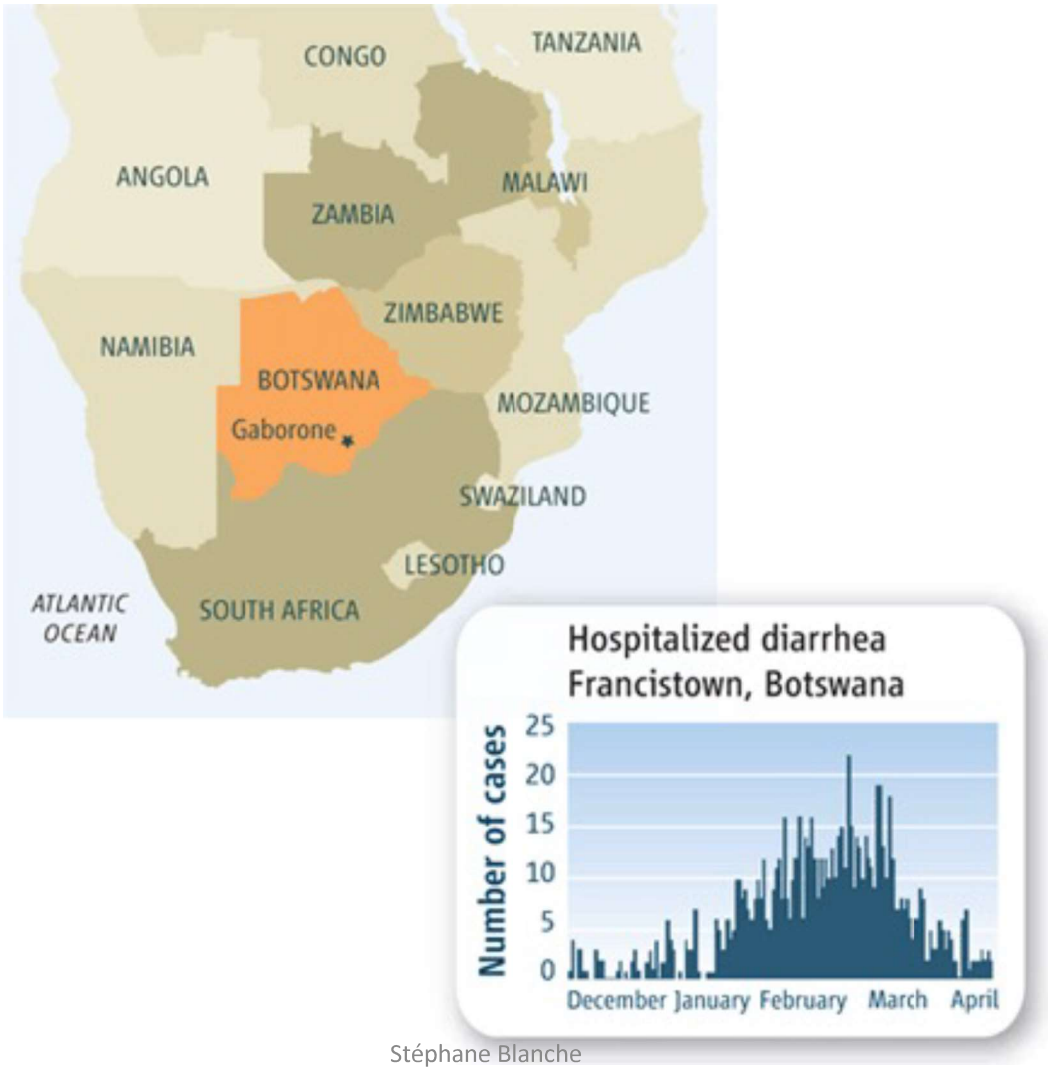
« This was not a thoughtful and reasonable decision but a crime against humanity… »

Jesse Jackson Dec 16,2004

Une **convergence** Nord Sud des recommandations de prophylaxie MF 2

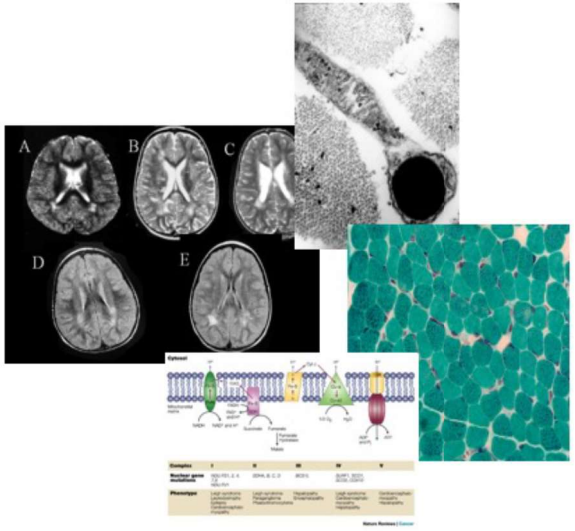






Stéphane Blanche

Stéphane Blanche



Stéphane Blanche

BMJ. 1999 Dec 11; 319(7224): 1522.

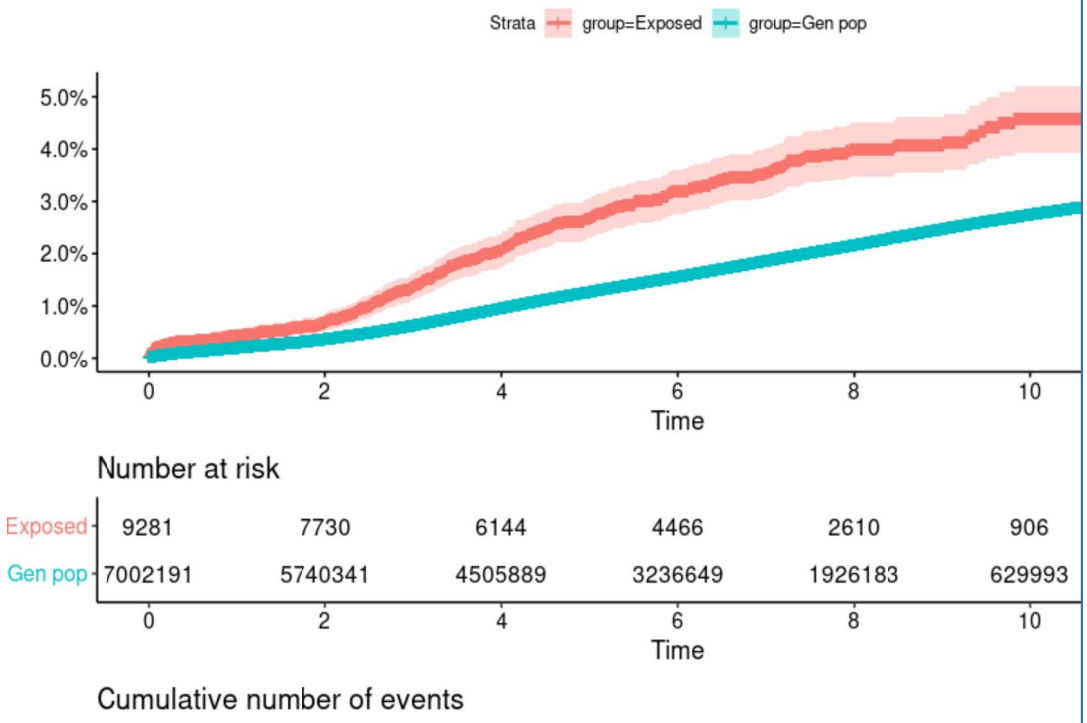
Mbeki claims that AZT is dangerous

Risque de toxicité *versus* risque d'infection

1994: 0.5% vs 20%

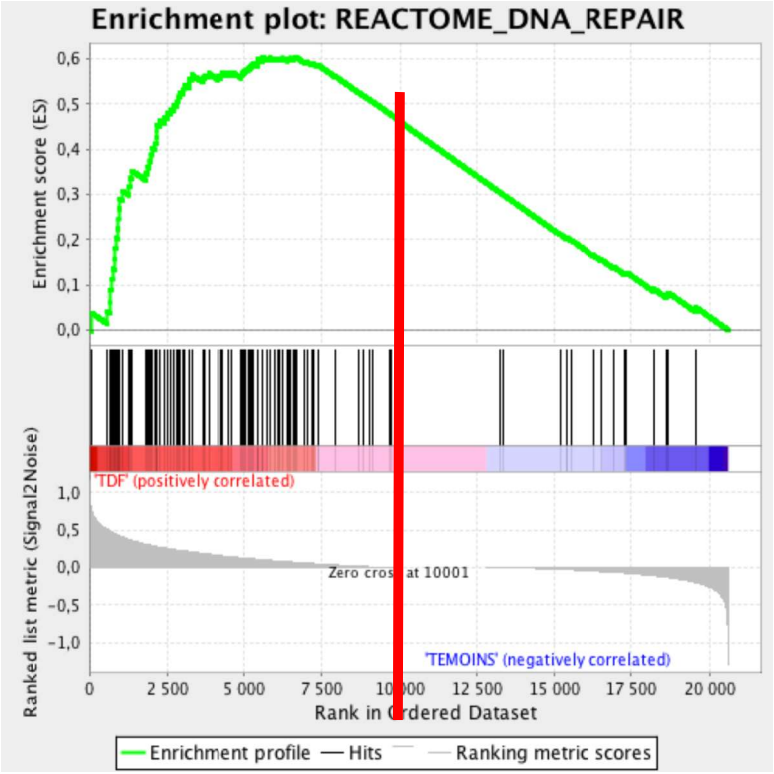
2023: 0.5% vs 0%

Des outils épidémiologiques



Mathis COLLIER

Des outils biologiques

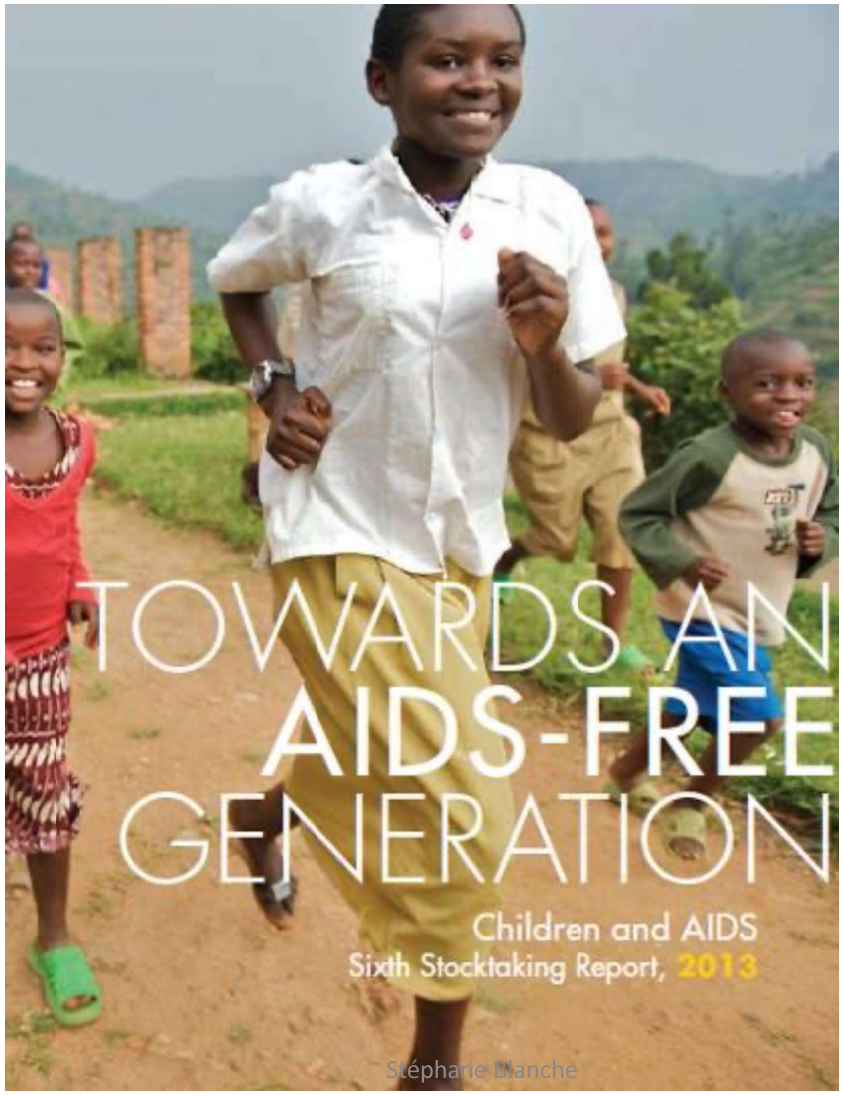


Emmanuelle SIX

PERINATALITE ET INFECTION PAR LE VIH
7ème journée
de la maternité Port-Royal
et de la FHU Préma

Vendredi 24 Novembre 2023

Remerciements à
E. Pannier, O. Launay, J. Sibiude, L. Mandelbrot


TOWARDS AN
AIDS-FREE
GENERATION
Children and AIDS
Sixth Stocktaking Report, 2013
Stéphane Blanche