

What is Cabergoline (Dostinex) and when do you use it?




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Objectives



- 1. Mechanism and efficacy of Cabergoline for lactation suppression**
- 2. Side effects and safety profile**
- 3. Important points for counseling patients**



BREASTFEEDING

THE GOAL

By 2025, increase to at least 50% the rate of exclusive breastfeeding in the first six months

WHY IT MATTERS

- 1** **2** **3** **4** **5** **6**

Most children are **not** getting the **best** nutrition from breastfeeding
- Exclusive breastfeeding is the **best** nutrition for babies
- Protection: Exclusive breastfeeding **reduces** the risk of **life-threatening** illnesses
- It **reduces** the risk of **obesity & non-communicable diseases** later in life

RECOMMENDED ACTIONS

LIMIT FORMULA MARKETING

WHAT: Limit advertising and promotion of formula

HOW: Regulate advertising and promotion of formula

SUPPORT PAID LEAVE

WHAT: Support mothers to breastfeed by providing paid leave

HOW: Encourage governments to provide paid leave

STRENGTHEN HEALTH SYSTEMS

WHAT: Strengthen health systems to support breastfeeding


HOW: Train health workers to support breastfeeding

SUPPORT MOTHERS

WHAT: Support mothers to breastfeed by providing resources

HOW: Encourage governments to provide resources


Globally, only **41%** of infants are exclusively breastfed





SCOPE OF THE PROBLEM

Suboptimal breastfeeding contributes to more than **800,000** infant deaths

Countries lose more than **\$300 billion** annually because of low breastfeeding rates



Hypothalamus

- decrease release of PIF = increase in prolactin
- decrease release of GnRH = decrease in FSH and LH

Magnocellular nuclei of hypothalamus (synthesizes oxytocin)

Posterior pituitary (stores and releases oxytocin)

Anterior pituitary

Prolactin

Oxytocin

Milk synthesis by mammary alveolar cells

Contraction of the myoepithelial basket cells produces milk ejection.

Suckling of the baby stimulates neural receptors in the nipple.

Afferent neurons

Prolactin - secreted from the anterior pituitary

2

Background

- Spontaneous cessation of lactation: 15 days
 - Complications: secretion, pain, engorgement, mastitis

Table II. Symptoms of lactation suppression in postpartum women who do not breast-feed* among placebo groups in clinical trials of pharmacologic lactation suppression methods†

	<i>Milk leakage</i>	<i>Engorgement</i>	<i>Breast pain</i>
Onset	Days 1-3 ²¹	Days 1-3 ²¹ Days 2-3 ¹²	Days 1-3 ²¹ Days 2-3 ¹²
Peak days	Days 3-4 ^{14, 17} ; days 3-5 ²¹	Days 2-4 ⁷ Day 4 ⁷ Days 3-4 ^{14, 17} Days 3-5 ²¹	Day 3 ⁷ Days 3-4 ^{14, 17} Days 3-5 ²¹
Degree of severity			
Moderate	22%-49% ^{14, 15, 20}	21%-66% ^{9, 10, 13-15, 17, 18, 20}	29%-68% ^{10, 12-17, 19, 20}
Severe	17%-47% ^{8, 11, 14, 15, 20}	1%-56% ^{7, 8, 11, 14, 15, 18, 20}	10% to 49% ^{8, 10-12, 14-16, 20}
Variability in definitions			
Moderate	Mild to moderate ¹⁵	Tender and congested, ⁹ firm, ^{10, 17, 18} mild to moderate, ¹⁵ or moderate or severe ¹³	Moderate or severe, ¹³ mild to moderate, ¹⁵ tender or tender to palpation, ¹⁷ painful lactation ¹⁹
Severe		Hard, painful, reddened ⁷ or rock hard ¹⁸	

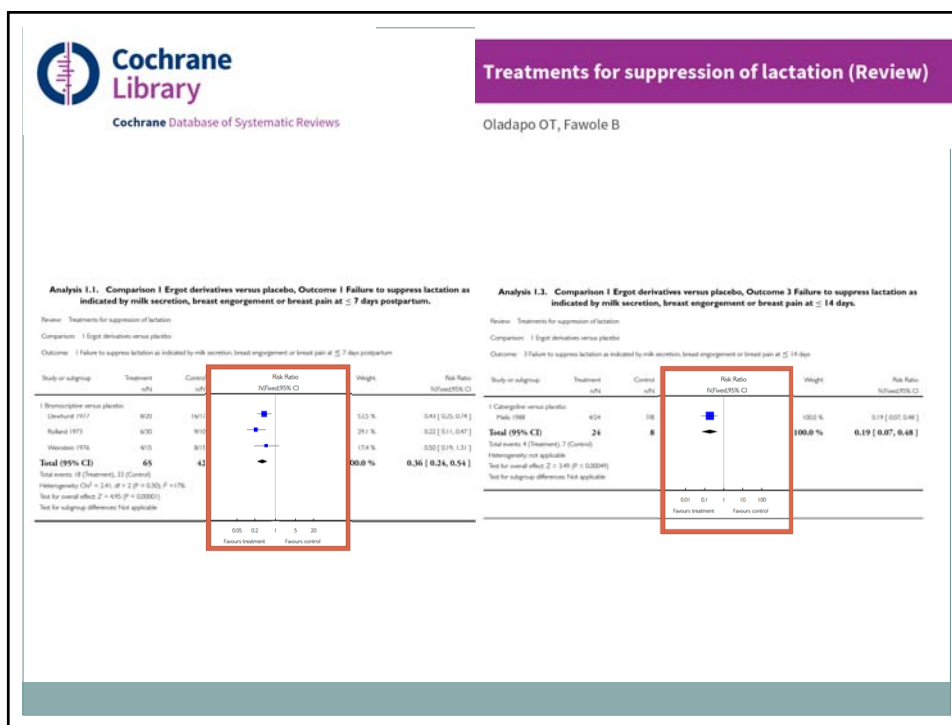
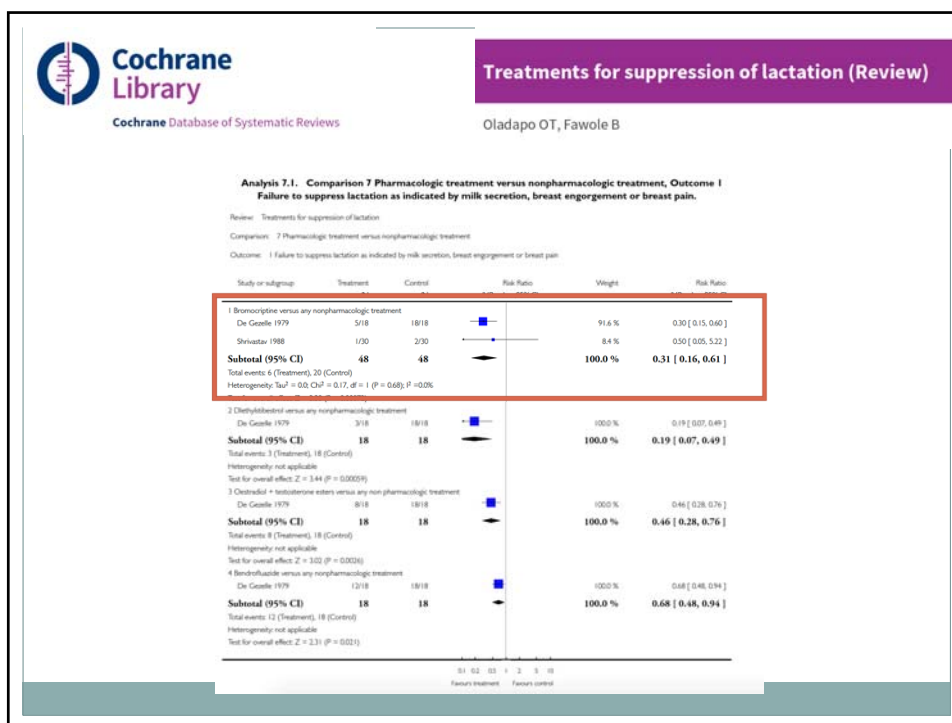
*Includes studies of women who were instructed to use a brassiere or binder to suppress lactation^{7, 14-20}; of these, 4 studies included women who were also instructed to use ice packs^{14-16, 18} and 7 included women who were also advised to use analgesics for pain.^{7, 14-16, 18-20}

†One study⁷ included pharmacologic and nonpharmacologic methods of lactation suppression.

Spitz AM, Lee NC, Peterson HB. Treatment for lactation suppression: little progress in one hundred years. *Am J Obstet Gynecol* 1998; 179(6 pt 1): 1485-90.

Background

- Non-pharmacological strategies
 - Firm breast support
 - Fluid restriction
 - Avoidance of tactile stimulation
 - Cabbage leaves, jasmine flower, ice packs
 - Analgesia



Background

- **Bromocriptine (Parlodel)**

- Mechanism of action:

- ✕ Dopamine agonist
- ✕ Prolactin inhibition

- Efficacy:

- ✕ Bromocriptine > placebo

3-11/yr
5.1/100,000

Mild side effects	Serious side effects
-dizziness/lightheadedness -rebound lactation -headache	-thromboembolic -cardiovascular (stroke, MI) -seizure -hallucinations -death

Severe adverse effects of bromocriptine in lactation inhibition: a pharmacovigilance survey

N Bernaud,¹ H Jantzen,² M Becker,³ C Pecriaux,⁴ A Benard-Laribière,⁵ JL Montastruc,⁶ J Descozes,⁷ T Vial,⁸ the French Network of Regional Pharmacovigilance Centres

Number of ADR classified by system organ class	n (%)
Cardiovascular disorders	74 (70.5)
Ischaemic disorders	47
Myocardial infarction	11
Stroke	34
Ischaemic stroke	18
Postpartum cerebral angiopathy	10
Other stroke**	6
Peripheral ischaemic disorders***	2
Arterial hypertension	17
Other cardiovascular disorders****	10
Nervous system disorders	15 (14.3)
Isolated seizures	4
Dizziness	6
Other nervous system disorders*****	5
Psychiatric disorders	9 (8.6)
Hallucinations or puerperal psychosis	4
Acute schizophrenic decompensation	2
Confusion	2
Mania	1
Other system organ class*****	7 (6.7)
Outcome (n = 86)	n (%)
Recovered	74 (70.5)
Recovered with sequelae	10 (9.5)
Fatal	2 (1.9)

Table 3. Distribution of non-compliant use of bromocriptine (misuse and predisposing cardiovascular factors) among women with cardiovascular ADRs

	Number of women*
Misuse	
Bromocriptine dose > 2.5 mg	6
No progressive dose increase	15
Treatment duration > 3 weeks	1
Treatment continuation despite hypertension, persisting headaches, or other neurological signs	15
Combination with alpha-sympathomimetic drug	2
Combination with vasoconstricting ergot alkaloid	1
Predisposing cardiovascular factors mentioned in the SPC	
Smoking	18
Hypertension, toxemia, postpartum or puerperal hypertension	8
Obesity	6
Predisposing cardiovascular factors not mentioned in the SPC	
Overweight	6
Dyslipidemia	3
Protein C deficiency	1
Protein S deficiency	1
Antiphospholipid antibody syndrome	1
Systemic lupus erythematosus	1
Sickle cell trait and α -thalassaemia	1
Family history of stroke	1

*More than one cause of non-compliant use can be found in the same patient.

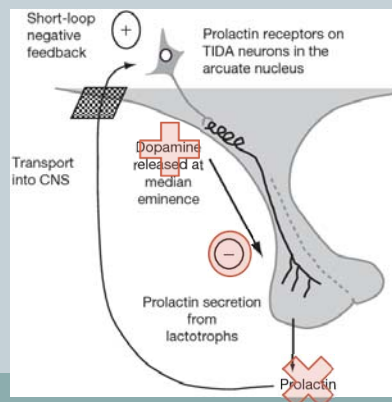


Mechanism of Action



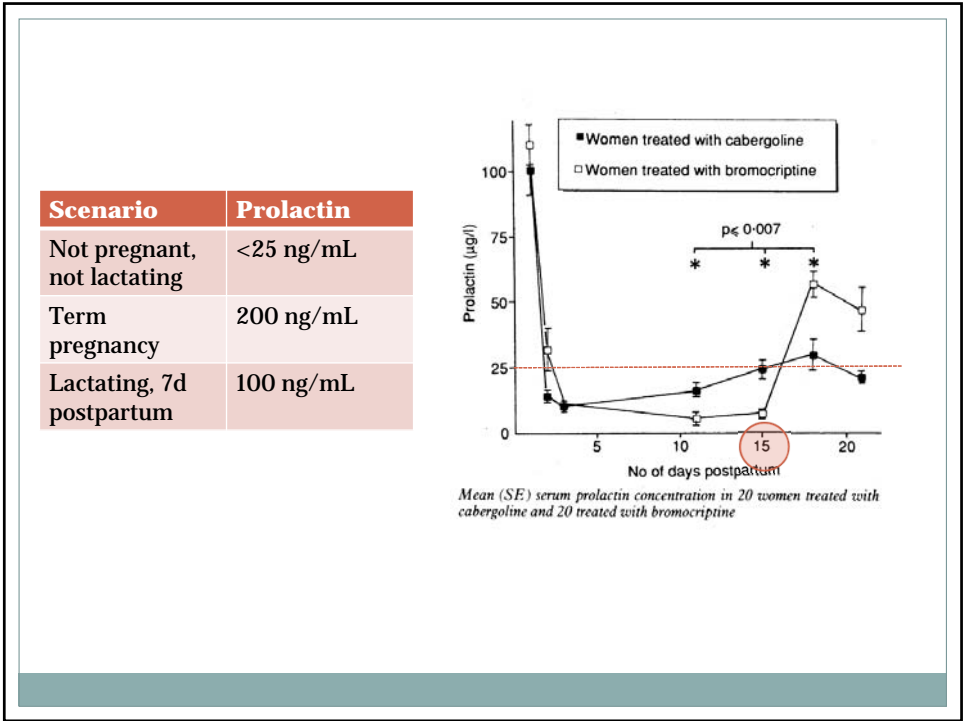
Mechanism of Action

- Dopaminergic ergot derivative
- Stimulates D2-dopamine receptors
 - Selective for pituitary lactotrophs
 - Greater affinity for D2
 - Low affinity for other receptors
- Inhibits prolactin secretion
 - No effect on other anterior pituitary hormones



Mechanism of Action

- Lactation inhibition
 - Prevent initiation of lactation
 - 1 mg single dose
- Lactation suppression
 - Stop ongoing lactation
 - 0.5 mg BID x 2 days
- Peak concentration: 2-3h
- Long elimination half-life: 63-69h
- Hepatic clearance
 - Unaltered pharmacokinetics in renal or mild/moderate hepatic disease
 - Independent of CYP P450



Efficacy

Efficacy

Single dose cabergoline versus bromocriptine in inhibition of puerperal lactation: randomised, double blind, multicentre study

European Multicentre Study Group for Cabergoline in Lactation Inhibition

- Prospective randomized double blinded parallel group multicentre study, 1989
- 136 per group
 - Cabergoline 1mg single dose
 - Bromocriptine 0.5mg BID x 14d
 - First dose within 27h of delivery
 - Exclusions: PET, IUFD, liver or renal impairment

Efficacy

TABLE 1—Rating scale for measures of efficacy of treatment with cabergoline or bromocriptine in inhibiting lactation

Intensity of sign/symptom	Spontaneous milk secretion	Breast pain	Breast engorgement
Mild	A few drops for ≤3 days	Easily bearable	Tenderness only on palpation
Moderate	A few drops for >3 days or copious secretion for <3 days	Tolerable with difficulty	Bearable hardening and spontaneous tenderness
Abundant or severe	Copious secretion for >3 days	Analgesic drugs required	Hardening and tenderness interfering with normal daily activity

N = 136 per group	Complete response	Partial response	Overall response	Failure	Rebound
Cabergoline	106 (78%)	21 (69%)	127 (93%)	9 (7%)	5 (3%)
Bromocriptine	94 (69%)	33 (24%)	127 (93%)	9 (7%)	23 (17%)

Safety Profile

Incidence of Reported Adverse Events During the 4-Week, Double-Blind, Placebo-Controlled Trial

Adverse Event*	Cabergoline (n=168) 0.125 to 1 mg two times a week	Placebo (n=20)
	Number (percent)	
Gastrointestinal		
Nausea	45 (27)	4 (20)
Constipation	16 (10)	0
Abdominal pain	9 (5)	1 (5)
Dyspepsia	4 (2)	0
Vomiting	4 (2)	0
Central and Peripheral Nervous System		
Headache	43 (26)	5 (25)
Dizziness	25 (15)	1 (5)
Paresthesia	2 (1)	0
Vertigo	2 (1)	0
Body As a Whole		
Asthenia	15 (9)	2 (10)
Fatigue	12 (7)	0
Hot flashes	2 (1)	1 (5)
Psychiatric		
Somnolence	9 (5)	1 (5)
Depression	5 (3)	1 (5)
Nervousness	4 (2)	0
Autonomic Nervous System		
Postural hypotension	6 (4)	0
Reproductive – Female		
Breast pain	2 (1)	0
Dysmenorrhea	2 (1)	0
Vision		
Abnormal vision	2 (1)	0

* Reported at $\geq 1\%$ for cabergoline

Safety Profile

- **Contraindications:**

- Uncontrolled hypertension
- History of pulmonary, pericardial, retroperitoneal fibrotic disorders
- History of cardiac valvulopathy
- Known hypersensitivity

- **Precautions:**

- PET, gHTN
- Doses >1mg
- Cardiovascular disease
- Raynaud's syndrome

Safety Profile

- **Drug interactions**

- Ergot derivatives
 - ✦ Theoretical risk of additive toxicity
- Clarithromycin and Itraconazole
 - ✦ Inhibit P-gp transporter
 - ✦ Increase levels of cabergoline >> toxicity
- Metoclopramide and Phenothiazine
 - ✦ D2 antagonist >> decrease efficacy

REVIEW ARTICLE

Safety of Cabergoline for Postpartum Lactation Inhibition or Suppression: A Systematic Review

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Safety Profile

- Systematic review: 1985-2018
- Criteria: cabergoline use for postpartum lactation inhibition or suppression in women aged 15-50
- 695 articles, 25 included
 - 8 RCT
 - 9 Cohort
 - 6 Case study/series
 - 2 Pharmacovigilance database
- Bias assessment: most were classified as 'fair' or 'poor'

Safety Profile

- 757 women
- 108 adverse events in 96 women (14.2%)
 - Dizziness 4.6%
 - Headache 4%
 - Nausea or vomiting 2.5%
 - Short-lived, self-resolving, dose dependent
 - 6 studies: no adverse events
- No serious adverse events
- 3 studies included women with HTN
 - Adverse events not reported

CO - 045

Safety of cabergoline in lactation inhibition during the puerperal period

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Introduction: Cabergoline, an ergoline derivative, is a long-acting dopamine receptor (D2) agonist with a low affinity for other dopamine, adrenergic, and serotonin receptors. It is used to suppress puerperal lactation for medical reasons (eg: in utero fetal death, HIV infection...). Safety profile includes gastrointestinal (constipation, nausea) and neurological (dizziness, headache) non serious adverse drug reactions (ADRs). In France, its use has recently increased after the safety warning regarding neurovascular and cardiovascular ADRs associated with bromocriptine in this indication. Our goal was to assess the safety profile of cabergoline for puerperal lactation suppression from the WHO pharmacovigilance database, Vigibase[®].

Material and methods: We review the Individual Case Safety Reports (ICSR) from Vigibase[®]. We extracted ICSRs related to cabergoline as a substance, in female patients between 14 and 50 year-old. Thereafter, inclusion criteria were (i) cabergoline coded as "suspect" and (ii) lactation inhibition (and related terms) as indication. We excluded ICSRs that included several drugs. ADRs were classified according to MedDRA dictionary.

Results: A total of 715 ICSRs have been extracted from Vigibase[®], including 346 without the cabergoline indication reported. Finally, 72 ICSRs have been included in the study, corresponding to 175 ADRs. 29 (40.3%) ICSRs were serious and the seriousness criterion was not specified in 16 ICSRs (22.2%). ADRs were mainly represented by nervous system and neurovascular affections (n = 59; 33.7%), gastro-intestinal affections (n = 24; 13.7%) and, general disorders (n = 23; 13.1%). Regarding the 59 neurological adverse events, reported for 36 (50%) patients, they were serious in half of the cases, including two cases of reversible cerebral vasoconstriction syndrome (RCVS) associated with cerebral bleeding or posterior reversible encephalopathy syndrome, one case of grand mal seizure and one case of transient blindness. Noteworthy, one ICSR included a life threatening pulmonary embolism, and one death has been reported, not related to cabergoline.

Discussion/Conclusion: Cabergoline related ADRs are increasingly reported within WHO pharmacovigilance database, in relation with its increasing use around the world. About one third of the reported ADRs involves neurologic or neurovascular affections, including two serious RVCS. No cardiovascular serious effects have been reported. Due to the relatively small number of cases of ADRs currently analyzed, vigilance is still needed.

Safety Profile

- Six cases in psychiatric population
- 3/6
 - Cabergoline initiated AFTER DIAGNOSIS of postpartum psychosis
 - No adverse outcomes
 - No exacerbation of psychiatric outcomes
- 3/6
 - Cabergoline initiated for lactation inhibition
 - × (1) Hx disorganized schizophrenia, no meds, @2mos
 - × (2) Hx psychosis, on meds >> schizoaffective disorder, @24h
 - × (3) No previous diagnosis, @15mos
 - Psychotic symptoms two days AFTER TREATMENT
 - Symptoms resolved with discontinuation of cabergoline and antipsychotic medications
- No drug interactions

Table 2. Summary of reported adverse events with cabergoline use for lactation inhibition or suppression in case studies/series and pharmacovigilance studies

Author, year	Intervention	Headache	Dizziness	Nausea or vomiting	Abdominal or epigastric pain	Breast pain or tension	Psychiatric	Other	Total events (% of exposed)	Total exposed to intervention ^a
Cabergoline versus bromocriptine										
Giorda, 1991	CAB	1	3	1	0	0	0	0	5 (27.8%)	18
	BC	2	2	3	0	0	0	Amiaurosis (1)	8 (44.4%)	18
Rolland, 1991	CAB	7	8	2	3	0	0	Vertigo (1), palpitation (1), drowsiness (1), epistaxis (1), transient hemianopia (1)	25 (18.4%)	136
	BC	6	17	13	1	0	0	Vertigo (2), symptomatic hypotension (1), facial paralysis (1), precordial pain (1), fever (1), vaginal hemorrhage (1)	44 (32.4%)	136
Vermeesch, 1996	CAB	0	0	0	0	0	0	0	0	100
	BC	2	0	0	0	0	0	0	2 (0.6%)	100

- 3 studies
- Adverse events:
 - Bromocriptine 20%
 - Cabergoline 11.8%
- Longer duration of symptoms in bromocriptine group

Safety Profile

- **Conclusions:**

- Adverse events generally benign, tolerable and self-resolving
- Cabergoline is better tolerated than bromocriptine
- Caution is needed given pharmacovigilance data
- Caution should be exercised in patients with psychiatric disorders

Counselling

Counselling

- **Who:**

- >16wks GA
- Requesting lactation inhibition or suppression
 - ✦ Stillbirth, NND, adoption, HIV+, PPCM, chemotherapy, neonatal galactosemia, maternal choice

- **Why:**

- Moderate-severe symptoms including pain, risk of mastitis with engorgement, emotionally triggering
- Non-pharmacologic may not be effective

Counselling

- **What:**

- Inhibition: 1 mg single dose within 24-48h of delivery
- Suppression: 0.5 mg BID x 2 days

- **When:**

- If desire to not feed is known >> ideally <48h

Counselling

- **Efficacy:**

	d3	d15	
Complete		78%	-minimum pain, mild tenderness, few drops of milk <3d
Partial	90%	93% 15%	-moderate pain, bearable hardening/tenderness of breasts, few drops of milk >3d or copious amounts <3d
Failure	7%	7%	-analgesia for pain, engorgement interfering with daily activity, copious secretions >3d
Rebound	3%	3%	

Counselling

- **Side effects:**

- <5%
 - ✦ Dizziness/lightheadedness
 - ✦ Nausea/vomiting
- Self-limiting
- Severe AE: rare

RETURN TO HOSPITAL:

- chest pain
- shortness of breath
- severe headache
- seizure
- hallucination/delusions

Counselling

Contraindications	Precautions
<ul style="list-style-type: none"> -Uncontrolled hypertension -History of fibrotic disorders -History of cardiac valvulopathy -Known hypersensitivity -Hepatic insufficiency 	<ul style="list-style-type: none"> -PET or gHTN -Doses >1mg -Cardiovascular disease -Smoking -Raynaud's syndrome -Psychiatric conditions with predisposition for psychosis -Ergot derivatives -Clarithromycin/ Itraconazole

Women Living with HIV

- SOGC GL #310
 - Breastfeeding is not recommended regardless of cART or VL
 - ✦ Potential transmission of both cell-free and cell-associated DNA
 - Symptoms of engorgement
 - ✦ Acetaminophen, ibuprofen and cold compresses
 - The co-administration of bromocriptine and cabergoline is CI with protease inhibitors

Original research article

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Evaluation of cabergoline for lactation inhibition in women living with HIV


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Table 2. Reported adverse events during the postpartum period in women living with HIV after taking a single oral dose of cabergoline 1 mg.

	Day 2 postpartum (n = 67), n (%)	Day 14 postpartum (n = 58), n (%)
Headache	4(6.0)	14(24.1)
Dizziness	1(1.6.4)	8(13.8)
Nausea and vomiting	3(4.5)	5(8.6)
Hand or foot numbness	4(6.0)	8(13.8)
Hand or foot pain	2(3.0)	4(6.9)
Any adverse effects	20(29.8)	24(41.4)

Adverse effects	d2	d14	P value
PI (N=29)	35.3%	42.9%	0.203
Integrase inhibitor (N=30)	64.7%	56.7%	0.309

- No significant association between specific ARV medication and adverse effects
- No evidence of clinically significant drug interaction and concomitant use is not a CI



Two women are sitting on a grey couch, each holding and breastfeeding a baby. The woman on the left is wearing a red top and has her baby in a red outfit. The woman on the right is wearing a striped top and has her baby in a white outfit. They are both smiling and looking at their babies.

- Options are available for patients requesting lactation inhibition or suppression
- Individualized care is important

Photo: Lark & Lux

